Journal of Chemical Research
www.scilet.com
2007 Issue No. 12
ISSN 0308-2342 JRPSDC

Contents

RESEARCH PAPERS

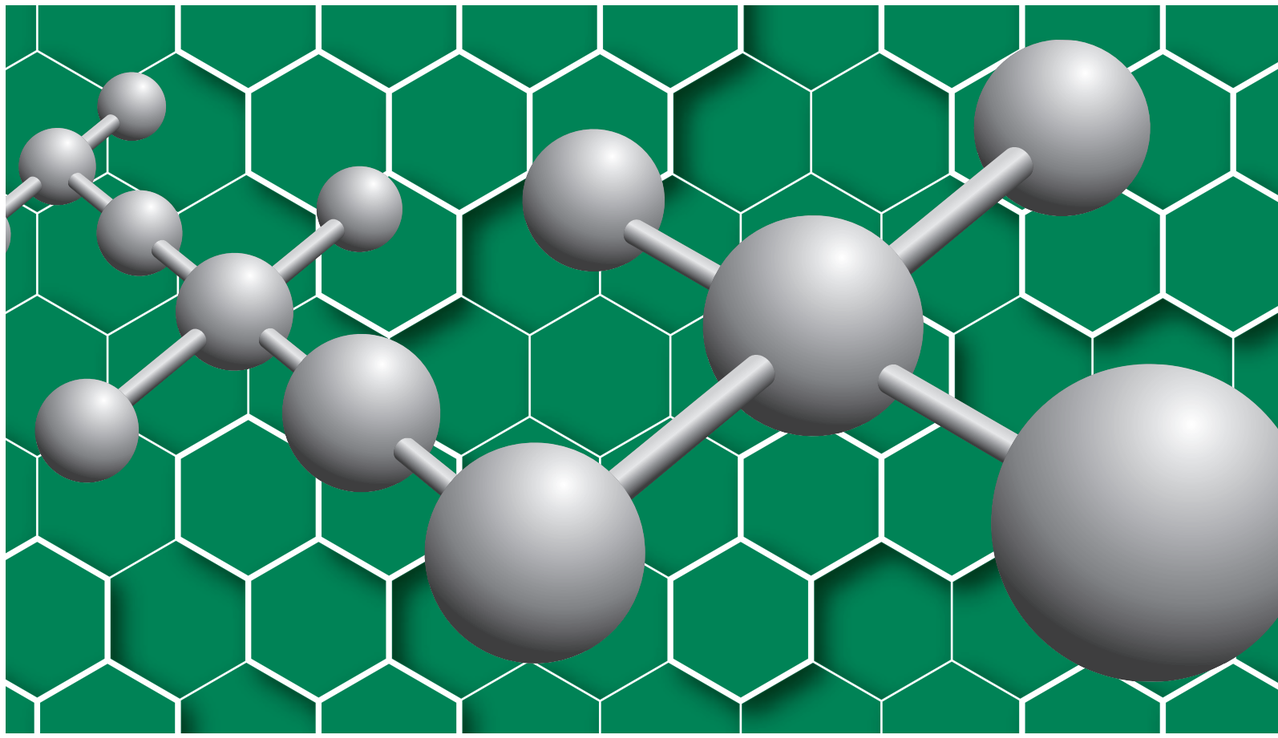
0308-2342(2007)12;1-0

This journal is covered by the following secondary information sources: *Chemical Abstracts*, *Current Contents*, *Current Abstracts of Chemistry/Index Chemicus*, *Current Chemical Reactions*, *Current Bibliography on Science and Technology*, *Science Citation Index*, *Bulletin Signalétique*, *Referativnyi Zhurnal* and *ChemInform*

Journal of Chemical Research 2007 Issue 12 December Pages 677–740

Journal of Chemical Research

2007 Issue 12 December Pages 677-740



Reviews and Research Papers from all branches of Chemistry

ISSN 0308-2342

www.scilet.com

Journal of Chemical Research

www.turpin-distribution.com/Tops/JournalInfo/Sci/jcrpub.htm **www.scilet.com**

Founded by:

Gesellschaft Deutscher Chemiker
The Royal Society of Chemistry
Société Française de Chimie

Original Supporting Societies:

American Chemical Society
The Chemical Institute of Canada
DECHEMA
Gesellschaft Österreichischer Chemiker
Koninklijke Nederlandse Chemische Vereniging
Koninklijke Vlaamse Chemische Vereniging
Norsk Kjemisk Selskap
Polskie Towarzystwo Chemiczne
Real Sociedad Española de Química
The Royal Australian Chemical Institute
Sociedade Brasileira de Química
Società Chimica Italiana
Société Chimique de Belgique
Société de Chimie physique
The South African Chemical Institute
Suomen Kemian Seura – Kemiska Sällskapet i Finland
Svenska Kemistsamfunder

How to use this journal

Journal of Chemical Research publishes RESEARCH PAPERS, and REVIEWS of all papers accepted for publication in both printed and in microfiche form.

How to contribute to this journal

Journal of Chemical Research publishes papers reporting experimental or theoretical work in all fields of chemistry. Authors intending to contribute to this journal should first consult a copy of the Instructions for Authors from the website www.scilet.com, published in Issue 1 of each year or obtainable from the Production Manager. E-mail: jcr@scilet.com

Articles should be sent to jcr@scilet.com

The senior author receives a copy of the journal in which the paper appears. Reprints or additional copies of the journal may be ordered.

How to subscribe to this journal

The annual subscription 2008 to *Journal of Chemical Research* is £900 or $1800. Internet only access is £800 or $1600 ordered through custserve@turpin-distribution.com. Additional copies of the journal may be obtained at substantially reduced rates. Personal subscriptions are available and free on-line access for those whose institution's library is a subscriber. In such cases the journal is delivered to a private address.

Journal of Chemical Research is distributed by Turpin Distribution Services Ltd, Stratton Business Park, Pegasus Drive, Biggleswade, Bedfordshire SG18 8QB, UK Tel +44(0)1767 604800; Fax +44(0)1767 601640, E-mail: custserve@turpin-distribution.com

Publisher: Science Reviews 2000 Ltd
PO Box 314, St Albans, Herts AL1 4ZG, UK. E-mail: jcr@scilet.com
1060 Plymouth Ct,Chicago, Illinois 60605, USA.
E-mail: scirev@ameritech.net

Setting up online access:

Online access avaliable via www.ingentaconnect.com/content/stl/jcr

1. Register at www.ingentaconnect.com
2. Request access to JCR quoting your subscription reference number
3. You will be notified by E-mail once your online access has been activated

If you have any problems setting up your online access please contact help@ingenta.com

Journal of Chemical Research

2007 Issue No. 12

ISSN 0308-2342 JRPSDC

This journal is covered by the following secondary information sources: *Chemical Abstracts*, *Current Contents*, *Current Abstracts of Chemistry/Index Chemicus*, *Current Chemical Reactions*, *Current Bibliography on Science and Technology*, *Science Citation Index*, *Bulletin Signalétique*, *Referativnyi Zhurnal* and *ChemInform*

Contents

RESEARCH PAPERS

Reviews

Short reviews are published in Journal of Chemical Research. These are normally commissioned, but authors who are interested in contributing such a review should make contact with one of the Editors. Reviews should be between 2,000 and 5,000 words in length, and authors will be remunerated at a rate of £40 ($60) per printed page.

The previous topics were:

J. Eames and N. Weerasooriya, Recent Studies on the regioselective C-protonation of enol derivatives using carbonyl-containing proton donors. *J. Chem. Research (S),* 2001, 2-8.

J.R. Hanson, A.J.M. Sanchez and C. Uyanik, Applications of tetracyanoethylene as a π-acid catalyst. *J. Chem. Research* (*S)*, 2001, 121-123.

K. Hemming, Recent developments in the synthesis, chemistry, and applications of the fully unsaturated 1,2,4-oxadiazoles. *J. Chem. Research* (*S*), 2001, 209-216.

A.G. Davies, The generation of organic radical cations: a guide to current practice for EPR spectroscopic studies. *J. Chem. Research (S),* 2001, 253-261.

D.J. Evans, Metal-sulfur chemistry with a view to modelling the active sites of some enzymes of environmental importance. *J. Chem. Research (S),* 2001, 297-303.

L.J. Twyman and A.S.H. King, Catalysis using peripherally functionalized dendrimers *J. Chem. Research (S)*, 2002, 43-59.

R.L. Richards and M.C. Durrant, Copper complexes with N-donor ligands as models of the active centres of nitrite reductase and related enzymes. *J. Chem. Research (S)*, 2002, 95-98.

T. Thiemann and K.G. Dongol, Thiophene S-oxides. *J. Chem. Research (S),* 2002, 303-308.

R.A. Henderson, Protonation mechanisms of nickel complexes relevant to industrial and biological catalysis. *J. Chem. Research (S),* 407-411.

W. Levason and G. Reid, Early transition metal complexes of polydentate and marcrocyclic thio- and seleno-ethers. *J. Chem. Research (S)*, 2002, 1-5.

J.R. Hanson, Directing effects in the hydroboration of steroidal alkenes. *J. Chem. Research*, 2004, 1-5.

Z.V. Todres, Recent advances in the study of mechanochromic transitions of organic compounds. *J. Chem. Research*, 2004, 89-93.

S. Ghosh, Recent research and development in synthetic polymer-based drug delivery systems. *J. Chem. Research*, 2004, 241-246.

A.G. Davies, Difunctional distannoxanes. *J. Chem. Research,* 2004, 241-246

J.A.R. Salvador and J.R. Hanson, Solid phase oxidation of steroidal alkenes with potassium permanganate and metal salts. *J. Chem. Research*, 2004, 513-516

K. Hemming and C. Loukou, Synthetic approaches to 1,2,5-benzothiadiazepine 1,1-dioxides: sulphonamide analogues of 1,4-benzodiazepines. *J. Chem. Research*, 2005, 1-12.

J.R. Hanson, General dienol:benzene rearrangement of ring A of the steroids. *J. Chem. Research,* 2005, 141-146.

N.L. Lancaster, Organic reactivity in ionic liquids: some mechanistic insights into nucleophiloic substitution reactions. *J. Chem. Research*, 2005, 413-417.

A.G. Davies, Recent advances in the chemistry of the organotin hydrides. *J. Chem. Research*, 2006, 141-148.

Synthesis and cytotoxicity of analogues of the marine secondary metabolite, 2-deoxylapachol

Suthananda N. Sunassee[a], Albert W.W. van Wyk[a], Omolaja Osoniyi[b], Denver T. Hendricks[b] and Michael T. Davies-Coleman[a]*

[a]*Department of Chemistry, Rhodes University, Grahamstown, 6140, South Africa*

[b]*Division of Medical Biochemistry, University of Cape Town, Rondebosch, South Africa*

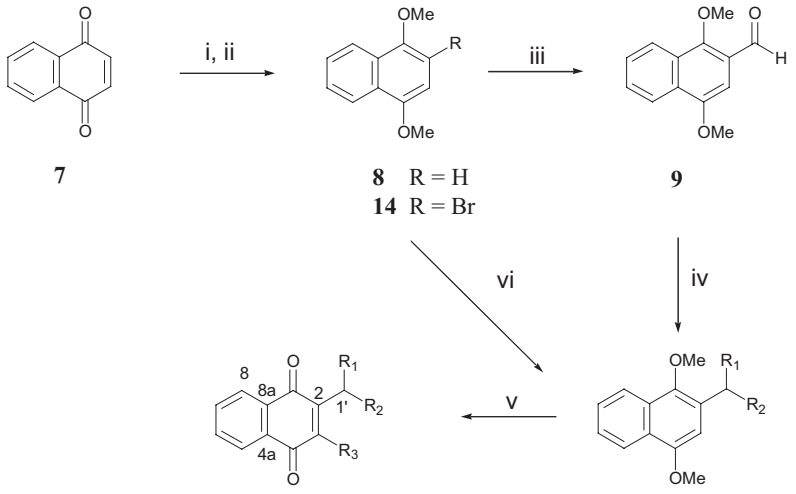
The syntheses of four 2-substituted 1,4 naphthoquinones, related to the marine natural product 2-deoxylapachol, are reported. All four synthetic compounds were cytotoxic to WHCO1 oesophageal cancer cells.

Keywords: 2-deoxylapachol, 1,4-naphthoquinones, oesophageal cancer

Lapachol (**1**), originally isolated from the heartwood of the Brazilian tree *Tabebuia avellanedae* commonly known as "pau d'arco", has been used clinically in Brazil for the treatment of adenocarcinoma and squamous carcinomas.[1] Squamous cell oesophageal cancer (SCOC) is common in the poor rural and peri-urban populations of South Africa, with studies in Soweto, near Johannesburg, revealing that residents there have a five-fold higher risk of developing this particular cancer than the world average.[2] The limitations of current chemotherapeutic interventions against SCOC *e.g.* cisplatin[3] coupled with the prevalence of this disease in South Africa, has prompted us to search for new potential anti-oesophageal cancer agents amongst the secondary metabolites produced by marine organisms[4] and to investigate, where possible, the cytotoxicity of synthetic analogues related to selected marine natural products.

The marine secondary metabolite 2-deoxylapachol (**2**), isolated from extracts of a New Zealand brown alga *Landsburgia quercifolia*, was also reported to be cytotoxic to cancer cells (IC_{50} of 2.7 μM against P338 leukaemia cells).[5] To the best of our knowledge **2** has not been screened against SCOC. Accordingly, we report here the cytotoxicity of this compound and four synthetic analogues (**3**–**6**) to the oesophageal cancer cell line WHCO1. The synthesis of **3**–**6** forms part of an ongoing structure activity relationship (SAR) study in which we have investigated first, the effect on the cytotoxic properties of lapachol type compounds when the hydroxyl substituent at C-2 in **1** is effectively relocated to the benzylic position of the side chain in **2** to give the 2-deoxylapachol analogue, 2-(1-hydroxy-3-methyl-2-butenyl)-1,4-naphthoquinone (**3**). The effect on cytotoxicity of further elaboration of the hydroxylated side-chain in **3** was also investigated by either shortening the side-chain *e.g.* 2-(1-hydroxyethyl)-1,4-naphthoquinone (**4**) and 2-(1-hydroxy-2-propenyl)-1,4-naphthoquinone (**5**) or extending the side-chain by the addition of a phenyl substituent *e.g.* 2-(1-hydroxy-1-phenylmethyl)-1,4-naphthoquinone (**6**).

Our synthetic approach to **3-6** is summarised in Scheme 1. Reductive methylation of 1,4 naphthoquinone (**7**) yielded 1,4-dimethoxynaphthalene (**8**)[6] which was subjected to standard Vilsmeier Haack formylation to afford 1,4-dimethoxy-2-naphthalenecarbaldehyde (**9**). The Grignard addition of



7

8 R = H
14 R = Br

9

1 R_1 = H, R_2 = CH=C$(CH_3)_2$, R_3 = OH
2 R_1 = R_3 = H, R_2 = CH=C$(CH_3)_2$
3 R_1 = OH, R_2 = CH=C$(CH_3)_2$, R_3 = H
4 R_1 = OH, R_2 = CH_3, R_3 = H
5 R_1 = OH, R_2 = CH=CH_2, R_3 = H
6 R_1 = OH, R_2 = Ph, R_3 = H

10 R_1 = OH, R_2 = CH=C$(CH_3)_2$
11 R_1 = OH, R_2 = CH_3
12 R_1 = OH, R_2 = CH=CH2
13 R_1 = OH, R_2 = Ph
15 R_1 = H, R_2 = CH=C$(CH_3)_2$

Scheme 1 i, $Na_2S_2O_4$, TEAB, THF, RT; ii, KOH, Me_2SO_4, RT, overnight (81%); iii, $POCl_3$, DMF, $CHCl_3$, reflux, 96 h (91%); iv, R – MgBr, THF, –10°C – RT, overnight (83–100%); v, CAN (2–3 equiv.), H_2O, MeCN (77–94%); vi, Mg, I_2, THF, reflux, 1 h, then $BrCH_2CH=C(CH_3)_2$, Li_2CuCl_4, THF, –10°C – RT, overnight (67%).

* Correspondent. E-mail: M.Davies-Coleman@ru.ac.za

isobutenylmagnesium bromide (prepared *in situ*)[7] to **9** gave **10**. Compounds **11–13** were accessed in similar fashion by the addition of methyl, vinyl and phenylmagnesium bromides respectively to **9**. Cerium ammonium nitrate (CAN) demethylation of **10–13** proceeded smoothly to yield the corresponding naphthoquinones **3–6**. Interestingly, **4** has been synthesised previously in five steps from **7** *via* a circuitous Fries rearrangement[8] and more directly by the addition of acetaldehyde to the Grignard reagent prepared from 2-bromo-1,4-dimethoxynaphthalene (**14**) and magnesium.[9] Although **6** has also been used as a precursor in the synthesis of 2-benzyl-1,4-naphthoquinones no details of this compound's preparation were provided.[10] Compounds **3** and **5** have not been synthesised before.

In order to compare the cytotoxicity of **3–6** with that of **2** it was deemed necessary to prepare sufficient **2** for screening against the WHCO1 cell line. Two methods exist for the preparation of this compound *i.e*. either *via* radical prenylation of **7** with 4-methyl-3-pentenoic acid[11-13] or by the addition of prenyltriflurosilane to **7** in the presence of the Lewis acid $FeCl_3.6H_2O$.[13,14] We were, however, able to prepare **2** by the addition of excess Grignard reagent prepared from **14** to 1-bromo-3-methyl-2-butene in THF/Li_2CuCl_4 to afford 1,4-dimethoxy-2-(3-methyl-2-butenyl)-naphthalene (**15**) which on CAN deprotection in the usual manner, gave **2**.

Compounds **3–6** exhibited good activity (IC_{50} 5.1, 6.4, 4.1 and 1.5 μM respectively) against the WHCO1 oesophageal cancer cell line when compared to the cytotoxicity of 2-deoxylapachol (IC_{50} 14.8 μM) and the commonly used SCOC chemotherapeutic agent cisplatin (IC_{50} 13 μM)[15] against the same cell line. Interestingly, the dimethyl ethers **10–15** were not cytotoxic to WHCO1 cells. A recent study of the cellular mechanism of the anti-oesophageal cancer activity of series of prenylated toluquinones (originally isolated from the endemic South African opisthobranch mollusc *Leminda millecra*) has revealed that these compounds mediate cell death by triggering the production of reactive oxygen species (ROS) leading to the activation of signaling pathways (cJun and p38) which ultimately induces apoptosis.[16] The possibility that compounds **2–6** may initiate apoptosis in oesophageal cancer cells by a similar mechanism is currently under investigation.

Experimental

General procedure

^1H and ^{13}C NMR spectra were recorded on either a Bruker 400 MHz or 600 MHz Avance NMR spectrometer in $CDCl_3$ and were referenced to residual protonated solvent at δ 7.25 and 77.0 respectively. HRFABMS data were acquired on a Micromass 70-70E spectrometer and the LREI mass spectra (70 eV) were obtained on a Finnegan-Matt GCQ mass spectrometer. Melting points were determined using a Reichert hot-stage microscope and are uncorrected. Normal phase semi-preparative HPLC separations were performed on a Whatman Magnum 9 Partisil 10 column with an eluent flow rate of 4 ml min^{-1} and eluting fractions detected using a Waters R401 differential refractometer.

Grignard synthesis of 2-deoxylapachol **2:** A few drops of a solution of 2-bromo-1,4-dimethoxynaphthalene (**14**)[17] (0.250 g, 0.94 mmol) in dry THF (1 ml) was added to a suspension of Mg turnings (0.036 g, 1.4 mmol) and iodine in dry THF (2 ml). The mixture was gently warmed to initiate reflux, upon which the rest of the solution of **14** was added very slowly over 5 min. The resulting mixture was refluxed (1 h) before being cooled to –10°C. The supernatant containing excess 1,4-dimethoxynaphthalenylmagnesium bromide (*ca* 8 equiv.) was transferred *via* cannula to a solution of 1-bromo-3-methyl-2-butene (0.017 g, 0.12 mmol), Li_2CuCl_4 (1 ml, 0.1 mmol) and dry THF (2 ml) at –10°C. The reaction mixture was slowly warmed to RT and left to stir overnight, quenched with water (5 ml) and extracted with CH_2Cl_2 (3 × 3 ml). The combined organic phases were washed with 10% HCl (5 ml), H_2O (5 ml) and sat. brine (5 ml), dried over $MgSO_4$ and concentrated *in vacuo* to yield a dark brown oil (0.20 g). NP HPLC of the oil in 96:4 hexane/EtOAc yielded **15** as a dark yellow oil (0.020 g, 0.08 mmol, 67%), ^1H and ^{13}C NMR data consistent with published values;[5] HRFABMS *m/z*: calcd for $C_{17}H_{21}O_2$ $[M + H]^+$ 257.1542; found 257.1541.

Oxidative demethylation of **15**: A solution of cerium ammonium nitrate (CAN) (0.065 g, 0.12 mmol) in water (0.1 ml) was added dropwise to a solution of **15** (0.015 g, 0.06 mmol) in MeCN (1.5 ml) at 0°C. The mixture was stirred (15 mins) at 0°C, diluted with water (2 ml) and extracted with ether (3 × 2 ml). The combined organic extracts were washed with water (5 ml), sat. brine (5 ml), dried over $MgSO_4$ and the solvent evaporated *in vacuo* to give **2** as a brown oil (0.0125 g, 0.06 mmol, 92%). ^1H and ^{13}C NMR data consistent with published values;[5] HRFABMS *m/z*: calcd for $C_{15}H_{15}O_2$ $[M + H]^+$ 227.1072; found 227.1072.

Reductive methylation of 1,4-naphthoquinone **7**:[6] Tetraethylammonium bromide (TEAB, 0.5 g) was added to a solution of the quinone **7** (2.0 g, 12.6 mmol) in THF (30 ml) and water (12 ml). Aqueous sodium dithionite (13.16 g, 75.6 mmol) was added and the mixture stirred at RT for 20 min. An aqueous KOH (16.32 g, 291 mmol) solution was added to the reaction mixture and, after 5 min, dimethyl sulfate (36.70 g, 291 mmol) was added dropwise. The solution was allowed to stir (16 h) before the reaction was quenched with water (30 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The combined organic fractions were washed with water (20 ml) and sat. brine (10 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a reddish oil (2.63 g). Flash chromatography of the crude product in pure hexane afforded **8** (1.91 g, 10.1 mmol, 81%) as a white crystalline solid, m.p. 87–88°C, lit.[17] 84–86°C; ^1H and ^{13}C NMR data consistent with published values.[17]

Vilsmeier-Haack formylation of **8:**[18] A solution of **8** (0.50 g, 2.7 mmol) in chloroform (10 ml) was added to a mixture of phosphoryl chloride (4.72 g, 31 mmol) and *N*,*N*-dimethylformamide (2.25 g, 31 mmol). The resulting solution was refluxed (96 h) before the reaction was carefully quenched with cold water. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 ml) and the combined organic fractions washed with water (1 × 10 ml) and sat. brine (1 × 10 ml), dried over Na_2SO_4 and concentrated under reduced pressure to give a reddish brown solid (0.66 g). Recrystallisation from hexane afforded **9** (0.53 g, 91%) as a yellow solid, m.p. 122–123°C, lit.[19] 119.5–120°C; ^1H NMR data consistent with published values;[19] δ_C (100 MHz, $CDCl_3$) 189.6 (s), 157.0 (s), 152.3 (s), 130.3 (s), 128.9 (d), 128.5 (s), 127.3 (d), 124.7 (s), 123.0 (d), 122.9 (d), 98.3 (d), 65.8 (q), 55.8 (q).

Preparation of 2-(1-hydroxy-3-methyl-2-butenyl)-1,4-dimethoxy-naphthalene **10**: A solution of isobutenylmagnesium bromide (1.5 g, 11.1 mmol) was prepared *in situ* as described previously,[7] and added dropwise *via cannula* to a stirred solution of **9** (0.255 g, 1.2 mmol) in dry THF (10 ml) at –10°C. The resulting solution was stirred (2 h) at –10°C and then gradually warmed to RT. The mixture was stirred further (1 h) before being quenched with sat. NH_4Cl (10 ml) and extracted with Et_2O (3 × 5 ml). The combined organic extracts were washed with water (2 × 10 ml) and sat. brine (1 × 10 ml), dried over $MgSO_4$ and concentrated under vacuum to yield a brown oil (0.407 g). NP HPLC (6:4 hexane/EtOAc) of the crude product afforded **10** (0.202 g, 0.74 mmol, 62%) as a pale yellow oil, ν_{max} cm^{-1} 3407, 1371, 1092, 846, 770; δ_H (600 MHz, $CDCl_3$) 8.21 (1H, d, *J* = 8.5 Hz), 8.01 (1H, d, *J* = 8.5 Hz), 7.52 (1H, t, *J* = 7.5 Hz), 7.45 (1H, t, *J* = 7.5 Hz), 6.92 (1H, s), 6.02 (1H, d, *J* = 8.9 Hz), 5.53 (1H, d, *J* = 8.9 Hz), 4.0 (3H, s, OMe), 3.9 (3H, s, OMe), 1.88 (3H, s), 1.76 (3H, s). δ_C (150 MHz, $CDCl_3$) 152.3 (s), 145.8 (s), 135.9 (s), 131.8 (s), 128.3 (s), 127.0 (s), 126.6 (d), 126.1 (d), 125.3 (d), 122.4 (d), 121.9 (d), 101.6 (d), 65.6 (d), 62.5 (q), 55.7 (q), 25.9 (q), 18.4 (q); HRFABMS *m/z*: calcd for $C_{17}H_{21}O_3$ $[M + H]^+$ 273.1491; found 273.1490.

Oxidative demethylation of **10**: Compound **10** (0.065 g, 0.24 mmol) was demethylated with CAN (0.262 g, 0.48 mmol), *vide supra*, to give a dark brown oil (0.056 g). NP HPLC (1:1 hexane/EtOAc) of this oil afforded **3** as a dark yellow oil (0.013 g, 0.05 mmol, 23%), ν_{max} cm^{-1} 3416, 1662, 843, 775; δ_H (600 MHz, $CDCl_3$) 8.06 (2H, m), 7.73 (2H, m), 6.99 (1H, s), 5.57 (1H, d, *J* = 8.6 Hz), 5.25 (1H, d, *J* = 8.6 Hz), 1.83 (3H, s), 1.76 (3H, s); δ_C (150 MHz, $CDCl_3$) 185.6 (s), 185.5 (s), 150.9 (s), 138.7 (s), 134.0 (d), 133.8 (d), 133.2 (d), 132.3 (s), 132.0 (s), 126.5 (d), 126.2 (d), 123.8 (d), 66.5 (d), 25.9 (q), 18.6 (q); calcd for $C_{15}H_{14}O_3$ $[M]^+$ 242.1196; found 242.1196.

General procedure A

Preparation of compounds **11–13**

The respective Grignard reagents (3 equiv.) were added to a stirred solution of **9** (0.10 g, 0.46 mmol) in dry THF (3 ml) at –10°C. The resulting solution was stirred (1 h) at –10°C and then gradually allowed to reach RT. The mixture was stirred for a further 16 h at RT

before being quenched with sat. NH_4Cl (10 ml) and extracted with $CHCl_3$ (3 × 3 ml). The combined organic extracts were washed with water (2 × 5 ml) and sat. brine (1 × 5 ml), dried over Na_2SO_4 and concentrated under vacuum. NP HPLC (1:1 hexane/EtOAc) of the crude products afforded the respective 1,4-dimethoxy-2-hydroxy-naphthalene products (**11–13**).

2-(1-hydroxyethyl)-1,4-dimethoxynaphthalene **11**:[8] (0.107 g, 0.46 mmol, 100%) white crystalline solid, m.p. 104–105°C; lit.[20] 101–103°C; ν_{max} cm^{-1} 3401, 1598, 770; δ_H (400 MHz, $CDCl_3$) 8.21 (1H, d, *J* = 8.5 Hz), 8.0 (1H, d, *J* = 8.5 Hz), 7.52 (1H, t, *J* = 7.5 Hz), 7.46 (1H, m), 6.90 (1H, s), 5.46 (1H, q, *J* = 6.4 Hz), 3.98 (3H, s, OMe), 3.90 (3H, s, OMe), 1.56 (3H, d, *J* = 6.4 Hz). δ_C (100 MHz, $CDCl_3$) 152.4 (s), 145.5 (s), 133.1 (s), 128.3 (s), 126.6 (d), 126.1 (s), 125.4 (d), 122.4 (d), 121.8 (d), 101.0 (d), 64.7 (d), 62.7 (q), 55.6 (q), 24.3 (q); calcd for $C_{14}H_{17}O_3$ $[M + H]^+$ 233.1178; found 233.1177.

2-(1-hydroxy-2-propenyl)-1,4-dimethoxynaphthalene **12**: (0.092 g, 0.38 mmol, 83%); Pale yellow oil; ν_{max} cm^{-1} 3397, 1370, 770; δ_H (400 MHz, $CDCl_3$) 8.21 (1H, d, *J* = 8.3 Hz), 8.02 (1H, d, *J* = 8.3 Hz), 7.53 (1H, m), 7.47 (1H, m), 6.78 (1H, s), 6.15 (1H, ddd, *J* = 17.6, 10.4, 5.2 Hz), 5.77 (1H, br d, *J* = 4.9 Hz), 5.41 (1H, d, *J* = 17.1 Hz), 5.23 (1H, d, *J* = 10.5 Hz), 3.96 (3H, s, OMe), 3.90 (3H, s, OMe); δ_C (100 MHz, $CDCl_3$) 152.3 (s), 146.4 (s), 140.0 (d), 130.1 (s), 128.4 (s), 126.7 (d), 126.3 (s), 125.6 (d), 122.4 (d), 122.0 (d), 114.9 (t), 101.8 (d), 69.7 (d), 62.9 (q), 55.6 (q); calcd for $C_{15}H_{17}O_3$ $[M + H]^+$ 245.1178; found 245.1177.

2-(1-hydroxy-1-phenylmethyl)-1,4-dimethoxynaphthalene **13**: (0.125 g, 0.43 mmol, 93%) white crystalline solid; m.p. 123–125°C; ν_{max} cm^{-1} 3407, 1370, 770, 702; δ_H (600 MHz, $CDCl_3$) 8.22 (1H, d, *J* = 8.4 Hz), 8.02 (1H, d, *J* = 8.4 Hz), 7.52 (2H, t, *J* = 7.6 Hz), 7.47 (2H, m), 7.45 (2H, d, *J* = 8.1 Hz), 7.32 (2H, t, *J* = 7.6 Hz), 7.24 (1H, t, *J* = 7.3 Hz), 6.80 (1H, s), 6.36 (1H, s), 3.92 (3H, s, OMe), 3.80 (3H, s, OMe); δ_C (150 MHz, $CDCl_3$) 152.2 (s), 146.5 (s), 143.7 (s), 131.4 (s), 128.3 (d), 127.3 (d), 126.7 (d), 126.4 (d), 126.3 (s), 125.6 (d), 122.5 (d), 122.0 (d), 102.4 (d), 71.0 (d), 62.6 (q), 55.6 (q); calcd for $C_{19}H_{19}O_3$ $[M + H]^+$ 295.1134; found 245.1133.

General procedure B

CAN demethylation of compounds **10–13**

Separate solutions of compounds **11–13** in acetonitrile and water were oxidised with a solution of CAN (2–3 equiv.) in water, as previously described for the preparation of **2**, and purified by NP HPLC (1 : 1 hexane/EtOAc) to yield the respective 2-hydroxy-1,4-naphthoquinone products **4–6**.

2-(1-hydroxyethyl)-1,4-naphthoquinone **4**:[8] (0.035 g, 0.17 mmol, 77%) yellow powder; 86–87°C; lit.[20] 87-88°C; ν_{max} cm^{-1} 3430, 1662, 720; δ_H (400 MHz, $CDCl_3$) 8.02 (2H, m), 7.70 (2H, m), 6.99 (1H, s), 5.00 (1H, q, *J* = 6.4 Hz), 1.48 (3H, d, *J* = 6.43 Hz). δ_C (100 MHz, $CDCl_3$) 185.4 (s), 185.3 (s), 153.0 (s), 134.0 (d), 133.8 (d), 132.7 (d), 132.1 (s), 131.8 (s), 126.4 (d), 126.1 (d), 65.0 (d), 22.6 (q); calcd for $C_{12}H_{11}O_3$ $[M + H]^+$ 203.0708; found 203.0709.

2-(1-hydroxy-allyl)-1,4-naphthoquinone **5**: **(**0.031 g, 0.14 mmol, 70%) brown oil; ν_{max} cm^{-1} 3419, 1662, 1594, 754; δ_H (600 MHz, $CDCl_3$) 8.05 (2H, m), 7.72 (2H, m), 7.0 (1H, s), 6.00 (1H, ddd, *J* = 16.7, 10.4, 5.8 Hz), 5.46 (1H, d, *J* = 17.2 Hz), 5.36 (1H, br d, *J* = 4.2 Hz), 5.27 (1H, d, *J* = 10.4 Hz); δ_C (150 MHz, $CDCl_3$) 185.2 (s), 185.1 (s), 150.0 (s), 137.0 (d), 134.0 (d), 133.8 (d), 133.6 (d), 132.1 (s), 131.8 (s), 126.4 (d), 126.2 (d), 117.3 (t), 69.8 (d); calcd for $C_{13}H_{11}O_3$ $[M + H]^+$ 215.0708; found 215.0709.

2-(1-hydroxy-1-phenylmethyl)-1,4-naphthoquinone **6**: (0.041 g, 0.16 mmol, 94%) brown oil, ν_{max} cm^{-1} 3427, 1662, 726, 700; δ_H (600 MHz, $CDCl_3$) 8.00 (1H, d, *J* = 7.4 Hz), 7.96 (1H, d, *J* = 7.4 Hz), 7.67 (2H, m), 7.42 (2H, d, *J* = 7.5 Hz), 7.31 (2H, t, *J* = 7.5 Hz), 7.24 (1H, m), 7.05 (1H, s), 5.90 (1H, s); δ_C (150 MHz, $CDCl_3$) 185.3 (s), 184.9 (s), 151.0 (s), 140.3 (s), 134.0 (d), 133.8 (d), 133.5 (d), 132.1 (s), 131.9 (s), 128.7 (d), 128.7 (d), 128.4 (d), 126.9 (d), 126.9 (d), 126.5 (d), 126.1 (d), 70.8 (d).

Cell culture

Cells were routinely maintained at 37°C and 5% CO_2. WHCO1 cells were maintained in DMEM, supplemented with 10% fetal calf serum, 100 U/ml penicillin and 100 µg/ml streptomycin.

MTT assay

IC_{50} determinations were carried out using the MTT kit from Roche (Cat #1465007), according to manufacturer's instructions. Briefly, 1500 cells were seeded per well in 96 well plates. Cells were incubated (24 h), after which aqueous DMSO solutions of each compound (10 µl, with a constant final concentration of DMSO = 0.1%) were plated at various concentrations. After 48 h incubation, observations were made, and MTT (10 µl) solution added to each well. After a further 4 h incubation, solubilisation solution (100 µl) was added to each well, and plates were incubated overnight. Plates were read at 595 nm on an Anthos microplate reader.

Rhodes University, the University of Cape Town, the South African National Research Foundation (NRF), the South African Network for Coastal and Oceanographic Research (SANCOR) and Rhodes University are thanked for their financial support. SNS gratefully acknowledges student support in the form of a DAAD Third Country Scholarship.

Received 30 November 2007; accepted 13 December 2007
Paper 07/4967 doi: 10.3184/030823407X270437

References

1 S. Subramanian, M.M.C. Ferreira and M. Trsic, *Structural Chem.*, 1998, **9**, 47.
2 N. Mqoqi, P. Kellett, J. Madhoo and F. Sitas (2003). National Cancer Registry of South Africa. Incidence and geographical distribution of histologically diagnosed cancer in South Africa, 1996-1997. South African Institute for Medical Research, Johannesburg.
3. A. Pickens and M.B. Orringer, *Ann. Thorac. Surg.,* 2003, **76**, 1367.
4. C.E. Whibley, R.A. Keyzers, A.G. Soper, M.T. Davies-Coleman, T. Samaai and D.T. Hendricks, *Annls N.Y. Acad. Sci.,* 2005, **1056**, 405.
5 N.B. Perry, J.W. Blunt and M.H.G. Munro, *J. Nat. Prod.,* 1991, **54**, 978.
6 G.A. Kraus and T. On Man, *Synth. Commun.*, 1986, **16**, 1037.
7 Y. Chen and W. Chang, *J. Org. Chem.*, 1996, **61**, 2536.
8 T. Nquyen Van, B. Kesteleyn and N. De Kimpe, *Tetrahedron*, 2001, **57**, 4213.
9 K. Kobayashi, M. Uchida, T. Uneda, K. Yoneda, M. Tanmatsu, O. Morikawa and H. Konishi, *J. Chem. Soc., Perkin Trans. 1,* 2001, 2977.
10 A. Tsai, Y. Wu and C. Chuang, *Tetrahedron*, 2001, **57**, 7829.
11 N. Ragoussis, *Tetrahedron Lett.*, 1987, **28**, 93.
12 N. Jacobsen and K. Torssell, *Acta. Chem. Scan.*, 1973, **27**, 3211-3216.
13 S. Claessens, B. Kesteleyn, T. Nguyen Van and N. De Kimpe, *Tetrahedron*, 2006, **62**, 8419.
14 E. Hagiwara, Y. Hatanaka, K. Gohda and T. Hiyama, *Tetrahedron Lett.*, 1995, **36**, 2773.
15 J. Rajput, J.R. Moss, A.T Hutton, D.T. Hendricks, C.E. Arendse and C. Imrie, *J. Organomet. Chem.,* 2004, **689**, 1553.
16 C.E. Whibley, K.L. McPhail, R.A. Keyzers, M.F. Maritz, V.D. Leaner, M.T. Davies-Coleman and D.T. Hendricks, *Mol. Cancer Ther.,* 2007, **6**, 2535.
17 P.A. Evans and T.A. Brandt, *J. Org. Chem.*, 1997, **62**, 5321.
18 Y. Tanoue, A. Terada and Y. Matsumoto, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 2736.
19 H. Uno, *J. Org. Chem.*, 1986, **51**, 350.
20 R.G.F. Giles, I.R. Green, V.I. Hugo, P.R.K. Mitchell and S.C. Yorke, *J. Chem. Soc. Perkin Trans 1*, 1983, 2309.

Ring contraction of N-acetyl-2-aryl-1,2,3,4-tetrahydro-4-quinolones with [hydroxy(tosyloxy)iodo]benzene to *trans* methyl N-acetyl-2-aryl-2,3-dihydroindol-3-carboxylates

Ashok Kumar, Sunil Kumar, Rakesh K. Gupta and Devinder Kumar*

Department of Chemistry, Guru Jambheshwar University of Science and Technology, Hisar-125001, Haryana, India

The ring contraction of N-acetyl-2-aryl-1,2,3,4-tetrahydro-4-quinolones with [hydroxy(tosyloxy)iodo]benzene to *trans* methyl N-acetyl-2-aryl-2,3-dihydroindol-3-carboxylates in trimethylorthoformate in good yield is described.

Keywords: [hydroxy(tosyloxy)iodo]benzene, 4-quinolones, 2,3-dihydroindoles

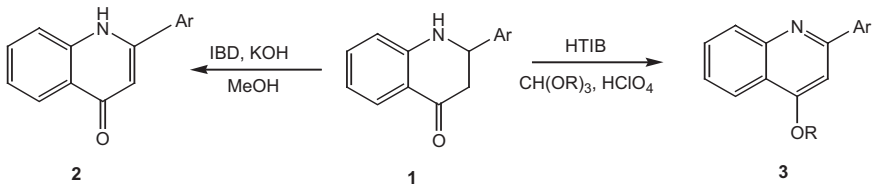
Hypervalent iodine reagents have been widely used in organic synthesis over the past few years.[1] These reagents have been found to be excellent substitutes for metal-containing oxidising agents, such as lead(IV), thallium(III) and mercury(II) salts. Oxidation of quinolones with hypervalent iodine reagents, particularly iodobenzene diacetate (IBD) and [(hydroxytosyloxy)iodo] benzene (HTIB) have been shown to afford different products depending upon the reaction conditions[2,3] (Scheme 1).

Oxidation of 2-aryl-1,2,3,4-tetrahydro-4-quinolones (**1**) with IBD under basic conditions in methanol gave 2-aryl-4-quinolones (**2**) via dehydrogenation[2] whilst treatment of compound **1** with HTIB under acidic conditions in trialkyl orthoformate resulted in the naturally occurring 4-alkoxy-2-arylquinoline (**3**) alkaloids.[3] These compounds have also been obtained by oxidation with iodine-methanol.[4] Further, oxidation of 2-methyl-4-quinolones using HTIB afforded 2-methyl-3-iodo-4-phenoxyquinolines with the intermediacy of isolable α-phenyliodonio tosylates and novel monocarbonyl iodonium ylides.[5] In continuation of our earlier work on oxidation of quinolones by hypervalent iodine,[2,5] the oxidative ring contraction of N-acetyl-2-aryl-1,2,3,4-tetrahydro-4-quinolones to *trans* methyl N-acetyl-2-aryl-2,3-dihydroindol-3-carboxylates in trimethylorthoformate (TMOF) using HTIB is described.

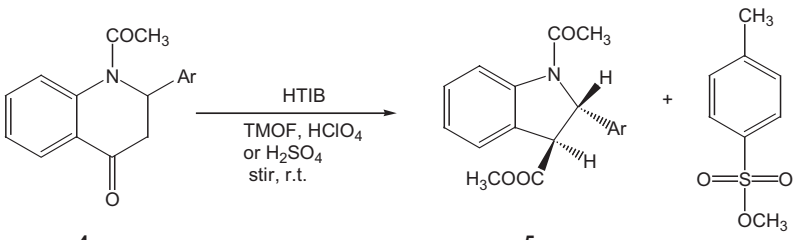
The 2,3-dihydroindole ring is present in many naturally occurring compounds including biologically active alkaloids.[6,7] 2,3-Dihydroindoles have also been found to behave as selective monoamine oxidase inhibitors[8] and as non-peptide angiotensin II receptor antagonists.[9] 2,3-Dihydroindoles are also potential intermediates for the synthesis of other indoles.[10]

Results and discussion

The reaction of N-acetyl-2-aryl-1,2,3,4-tetrahydro-4-quinolones (**4**) with HTIB was examined in trimethyl orthoformate (TMOF) in the presence of a few drops of either $HClO_4$ or H_2SO_4 at room temperature. The stereoselective ring-contracted products which were formed were identified as *trans* methyl N-acetyl-2-aryl-2,3-dihydroindol-3-carboxylates (**5**). A side product, methyl *p*-toluenesulfonate (**6**), was also isolated (Scheme 2) in small quantity. The structures of **5a–e** and **6**[11] were established by physical and spectroscopic techniques (IR, ^1H and ^{13}C NMR). The characteristic feature in the ^1H NMR spectrum of compounds **5a–e** was the doublet (or broad singlet) of C_3–H at δ 3.79–3.97 (J = 1.8 Hz, broad singlet of C_2–H at δ 5.73–5.99 and downfield signal of C_7–H at δ 8.24–8.43 (probably due to its deshieding by N-acetyl group). The *trans* stereochemistry of dihydroindole ring in **5a–e** was established by comparing the coupling



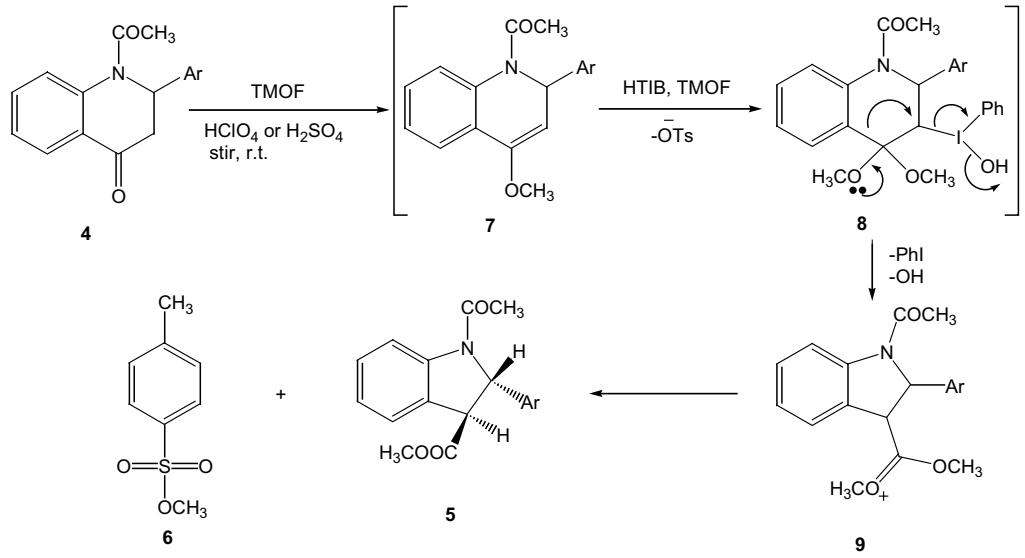
Scheme 1



4, **5**; a, Ar = C_6H_5
b, Ar = C_6H_5Br (p)
c, Ar = C_6H_5OMe (p)
d, Ar = $C_6H_5NO_2$ (p)
e, Ar = C_6H_5Cl (p)

Scheme 2

* Correspondent. E-mail: dk_ic@yahoo.com



Scheme 3

constant between C_2–H and C_3–H with that of reported *cis* and *trans* 2,3-dihydroindoles.[12] The coupling constant between C_2–H and C_3–H of *cis* 2,3-dihydroindoles where nitrogen is protected with nitrosyl or arylsulfonyl is 8–9 Hz, whereas that of *trans* isomer is < 4 Hz. The less coupling constant (1.8 Hz) in **5a–e** is perhaps due to π–π interaction between N-acetyl and C_2-aryl groups, thus significantly altering the C_2–H/C_3–H dihedral angle.[13]

The probable mechanism involves the ketalisation of **4** with TMOF in presence of either $HClO_4$ or H_2SO_4 to afford intermediate enol ether **7**. The electrophilic attack of HTIB on the double bond of enol ether **7** furnished the iodine (III) complex, **8**. Reductive elimination of iodobenzene from **8** with simultaneous migration of aryl residue from C_4 to C_3 position gave intermediate carbocation **9** which on hydrolysis afforded the ring contracted product **5** alongwith **6.** The migration of aryl residue is preferred over C_2 aryl ring probably because of greater stability of the carbocation formed. Compound **5** was formed by ring contraction of compound **4** under the reaction conditions while side product **6** was formed probably due to condensation of methanol and *p*-toluenesulfonic acid formed *in situ*.

The present approach for the synthesis of *trans* methyl N-acetyl-2-aryl-2,3-dihydroindol-3-carboxylates is simple. This method avoids the use of toxic thallium salts for a similar type of reaction of N-acetyl-2-aryl-1,2,3,4-tetrahydro-4-quinolones (**4**) that results in a mixture of *trans* methyl N-acetyl-2-aryl-2,3-dihydroindol-3-carboxylates (**5**) and 4-methoxy-2-arylquinolines.[14] It should be noted that compound **4a** has also been reported to produce 3-phenylquinoline using HTIB under microwave irradiation instead of a ring contracted product.[15]

Experimental

FTIR spectra were obtained in KBr/neat film on Perkin Elmer Spectrum RX1 instruments and are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance II 400 MHz and 100 MHz NMR Spectrometer, respectively in $CDCl_3$; shifts are expressed as ppm with respect to TMS. Elemental analysis was carried out on Perkin Elmer 2400 instrument. 2-Aminochalcone, 2-aryl-1,2,3,4-tetrahydro-4-quinolones, N-acetyl-2-aryl-1,2,3,4-tetrahydro-4-quinolones were synthesised using known methods.[14,16]

General procedure

To a solution of N-acetyl-2-aryl-1,2,3,4-tetrahydro-4-quinolones (**4**, 2 mmol) in freshly distilled trimethylorthoformate (15 ml), was added 1–2 drops of either $HClO_4$ (70%) or conc. H_2SO_4 and stirred for 15–30 min. at room temperature (30°C). HTIB (753 mg, 2.2 mmol) was added in small amounts and the resulting solution was further stirred for 1 h. After completion of the reaction, as monitored by TLC, the reaction mixture was extracted with dichloromethane (3 x 15 ml), washed with saturated aq. sodium bicarbonate solution followed by water. The combined extract was dried over anhydrous Na_2SO_4. Removal of excess of solvent afforded gummy mass which was chromatographed over a neutral alumina column using hexane: ethyl acetate (9:1) as eluent to afford **5a–e** and **6**.

Compound **5a** (Ar = Ph): Oil,[14] yield 68%. IR: 2953 (C–H), 1738 (C=O), 1652 (C=O), 1494, 1385, 1280, 1265, 1029, 756 cm^{-1}. NMR: δ_H 2.05 (s, 3H, $COCH_3$), 3.76 (s, 3H, $COOCH_3$), 3.97 (d, 1H, J = 1.8 Hz, C_3–H), 5.85 (brs, 1H, C_2–H), 7.06–7.10 (m, 1H, C_5–H), 7.17–7.19 (m, 2H, C_4–H and C_6–H), 7.25–7.37 (m, 5H, C_6H_5), 8.34 (1H, d, J = 7.88 Hz, C_7–H); δ_C 24.1, 52.8, 55.7, 65.6, 117.2, 124.1, 125.0, 125.8, 126.0, 128.2, 129.3, 129.4, 141.3, 142.9, 169.5, 171.1.

Compound **5b** (Ar =C_6H_5Br-*p*): Oil, yield 73%. IR: 2923 (C–H), 1736 (C=O), 1661 (C=O), 1504, 1392, 1277, 1026, 759 cm^{-1}. NMR: δ_H 2.03 (s, 3H, $COCH_3$), 3.70 (s, 3H, $COOCH_3$), 3.85 (brs, 1H, C_3–H), 5.74 (brs, 1H, C_2–H), 7.00–7.04 (m, 3H, C_4–H, C_5–H and C_6–H), 7.28 (d, 2H, J = 7.70 Hz, $C_{2'}$–H and $C_{6'}$–H), 7.37 (d, 2H, J = 7.70 Hz, $C_{3'}$–H and $C_{5'}$–H), 8.24 (d, 1H, J = 7.60 Hz, C_7–H); δ_C 24.2, 53.0, 55.6, 65.0, 117.3, 122.2, 124.4, 125.7, 125.9, 126.9, 129.5, 132.5, 140.4, 142.8, 169.3, 171.0. Anal. Calcd. for $C_{18}H_{16}BrNO_3$: C, 57.8; H, 4.3; N, 3.7. Found: C, 57.9; H, 4.21; N, 3.6.

Compound **5c** (Ar =C_6H_5OMe-*p*): Oil,[14] yield 65%. IR: 2970 (C–H), 1735 (C=O), 1650 (C=O), 1501, 1369, 1095, 1122, 1033, 753 cm^{-1}. NMR: δ_H 2.37 (s, 3H, $COCH_3$), 3.66 (s, 6H, $COOCH_3$ and OCH_3), 3.79 (brs, 1H, C_3–H), 5.73 (brs, 1H, C_2–H), 6.88 (d, 2H, J = 7.80 Hz, $C_{3'}$–H and $C_{5'}$–H) 7.01–7.10 (m, 3H, C_4–H, C_5–H, and C_6–H), 7.49 (d, 2H, J = 7.80 Hz, $C_{2'}$ –H and $C_{6'}$–H), 8.29 (1H, d, J = 8.28 Hz, C_7–H).

Compound **5d** (Ar =$C_6H_5NO_2$-*p*): Oil, yield 71%. IR: 2950 (C–H), 1739 (C=O), 1660 (C=O), 1597, 1538, 1480, 1390, 1210, 867, 760 cm^{-1}. NMR: δ_H ($CDCl_3$) 2.04 (s, 3H, $COCH_3$), 3.82 (s, 3H, $COOCH_3$), 3.95 (brs, 1H, C_3–H), 5.99 (brs, 1H, C_2–H), 7.11 (m, 1H, C_5–H), 7.36–7.41 (m, 4H, C_4–H, C_6–H, $C_{3'}$–H and $C_{5'}$–H), 8.19 (d, 2H, J = 7.84 Hz, $C_{2'}$–H and $C_{6'}$–H), 8.32 (d, 1H, J = 7.16 Hz, C_7–H); δ_C 24.1, 53.1, 55.3, 64.9, 117.3, 124.6, 125.2, 126.0, 126.2, 129.7, 132.5, 142.5, 147.7, 148.3, 168.9, 170.0. Anal. Calcd. for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.7; N, 8.2. Found: C, 63.7; H, 4.65; N, 8.1.

Compound **5e** (Ar =C_6H_5Cl-*p*): White solid, m.p. 52–53°C (lit.,[14] m.p. 52–53°C), yield 72%. IR: 2950 (C–H), 1735 (C=O), 1651 (C=O), 1492, 1387, 1280, 1260, 1032, 760, 557 cm^{-1}. NMR: δ_H 2.05 (s, 3H, $COCH_3$), 3.76 (s, 3H, $COOCH_3$), 3.97 (d, 1H, J = 1.8 Hz, C_3–H), 5.81 (brs, 1H, C_2–H), 7.05–7.11 (m, 3H, $C_{2'}$–H, $C_{6'}$–H and C_5–H), 7.26–7.41 (m, 4H, $C_{3'}$–H, $C_{5'}$–H, C_4–H and C_6–H), 8.43 (1H, d, J = 8.10 Hz, C_7–H).

Compound **6**: Oil (lit.,[11] m.p. 25–28°C), IR:2921 (C–H), 1529, 1369, 1195, 1038, 771, 680, 563 cm^{-1}. NMR: δ_H 2.45 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 7.35 (dd, 2H, J = 8.44 and 0.40 Hz, C_3–H and C_5–H), 7.77 (dd, 2H, J = 8.44 and 1.70 Hz, C_2–H and C_6–H); δ_C 21.6,

56.2, 128.0, 129.8, 132.0, 144.9. Anal. Calcd. for $C_8H_{10}O_3S$: C, 51.6; H, 5.41. Found: C, 51.7; H, 5.3.

The authors are grateful to UGC and CSIR, New Delhi for providing financial assistance and Mr. Avtar Singh, SAIF, Chandigarh for recording the NMR spectra.

Received 15 November 2007; accepted 13 December 2007
Paper 07/4940 doi: 10.3184/030823407X270329

References

1 (a) P.J. Stang and V.V. Zhdankin, *Chem. Rev.*, 2002, **102**, 2523; (b) R.M. Moriarty, *J. Org. Chem.*, 2005, **70**, 2893; (c) T. Worth, *Angew. Chem. Int. Ed.*, 2005, **44**, 3656; (d) L.F. Silva, Jr, *Molecules*, 2006, **11**, 421; (e) G.F. Koser, *Adv. Heterocycl. Chem*., 2004, **86**, 225.
2 O. Prakash, D. Kumar, R.K. Saini and S.P. Singh, *Synth. Commun.*, 1994, **24**, 2167.
3 R.S. Varma and D. Kumar, *Tetrahedron Lett.*, 1998, **39**, 9113.
4 M.J. Mphahlele, F.K. Mogamisi, M. Tsanwani, S.M. Hlatshwayo and K.M. Mampa, *J. Chem. Res. (S)*, 1999, 706.
5 O. Prakash, D. Kumar, R.K. Saini and S.P. Singh, *Tetrahedron Lett.*, 1994, **35**, 4211.
6 A.M. Nasser and W.E. Court, *J. Ethanopharmacol.*, 1984, **11**, 99.
7 G. Buchi and T. Kamikawa, *J. Org. Chem.*, 1977, **42**, 4153.
8 L. Florvall, Y. Kumar, A.L. Ask, I. Fagervall, L. Renyi and S.B. Ross, *J. Med. Chem.*, 1986, **29**, 1406.
9 D.S. Dhanoa, S.W. Bagley, R.S.L. Chang, V.J. Lotti, T.B. Chen, S.D. Kivlighn, G.J. Zingaro, P.K.S. Siegl, A.A. Patchett and W.J. Greenlee, *J. Med. Chem.*, 1993, **36**, 4230.
10 (a) B. Witulski and T. Stengel, *Angew. Chem. Int. Ed.*, 1999, **38**, 2426; (b) W.H. Cheung, S.L. Zheng, W.Y. Yu, G.C. Zhou and C.M. Che, *Org. Lett.*, 2003, **5**, 2535; (c) M. Beller, C. Breindl, T.H. Riermeler and A. Tillack, *J. Org. Chem.,* 2001, **66**, 1403; (d) G.W. Gribble, *J. Chem. Soc. Perkin Trans. 1*, 2000, 1045; (e) D.P. Curran, C.H.T. Chen, S.J. Geib and A.J.B. Lapierre, *Tetrahedron*, 2004, **60**, 4413.
11 Aldrich Chemical Catalogue, 2007.
12 C.C. McComas, E.J. Gilbert and V. Vranken*, J. Org. Chem.,* 1997, **62**, 8600.
13 T.A. Engler, W. Chai and K.O. LaTessa, *J. Org. Chem.,* 1996, **61**, 9297.
14 O.V. Singh, M. Muthukrishnan and M. Sundaravdvelu, *Synth. Commun.,* 2006, **36**, 943.
15 T. Patonay, A. Levai, E. Riman and R.S. Varma, Arkivoc, 2004, (vii), 183.
16 J.A. Donnelly and D.F. Farrel, *J. Org. Chem.,* 1990, **55**, 1757; *Tetrahedron,* 1990, **46**, 885.

Synthesis of N-urethane protected β-amino alcohols employing *N*-(protected-α-aminoacyl)benzotriazoles

Vommina V. Sureshbabu*, N.S. Sudarshan, L. Muralidhar and N. Narendra

Peptide Research Laboratory, Department of Studies in Chemistry, Central College Campus, Bangalore University, Dr. B. R. Ambedkar Veedhi, Bangalore 560 001, India

A simple and racemisation-free synthesis of *N*-urethane protected α-amino/peptidyl alcohols by the reduction of the corresponding easily accessible *N*-acylbenzotriazoles is described. The method is practical, straightforward, fast and efficient for the synthesis of amino/peptidyl alcohols. All the alcohols made were isolated in high yields and purity.

Keywords: β-aminoalcohols, *N*-protecting groups, amino acids, benzotriazoles, sodium borohydride, reduction

N-Protected amino alcohols and peptidyl alcohols are important synthetic intermediates,[1] especially useful in the synthesis of amino/peptidyl aldehydes which have diverse synthetic as well as biological applications.[2,3] Several peptides including enkephalins have been shown to exhibit better biological activity upon reduction of the terminal carboxylic group into the corresponding alcohol.[4] The N-protected amino alcohols are also used in the synthesis of peptides possessing reduced peptide bonds[5] and in the preparation of stereochemically defined methylene-oxydipeptides.[6] They are also key intermediates in the synthesis of vicinal diamines, ureidopeptides,[7] oxazolidinones, peptidosulfinamides, and peptidosulfonamides.[8] Moreover, oligopeptidyl carbamates[9] as well as peptidyl carbonates are assembled starting from β-aminoalcohol building blocks.

The aminoalcohols are widely prepared by borane-mediated reduction of N-protected amino acids.[3] They are also synthesised by the reduction of the corresponding alkyl esters or active esters[10] with $NaBH_4$. Kokotos[11a] and Rodriguez *et al*.[11b] have reported the chemoselective reduction of mixed carboxylic anhydrides generated by the reaction of N-protected amino acid with ethyl chloroformate or isobutyl chloroformate in presence of a base. Similarly, urethane-protected *N*-carboxyanhydrides (UNCAs)[12] and various acid fluorides[13] are also reduced into alcohols using $NaBH_4$. On the other hand, there are several reports describing the use of reducing agents such as $LiAlH_4$,[14] DIBAL,[15] *etc.,* for such reductions.

Katritzky *et al*. have accomplished pioneering work on the synthesis of stable *N*-acylbenzotriazoles and they demonstrated their wide range of applications in organic synthesis.[16] In peptide chemistry, *N*-acylbenzotriazole derivatives of amino acids have been used to acylate unprotected amino acids under aqueous reaction conditions to obtain peptide acids,[17] prepare N-protected α-amino acid azides,[18] hydroxamic acids and peptide heterocycles such as oxadiazoles.[19] The utility of *N*-acylbenzotriazoles as activated precursors for the synthesis of aminoalcohols is to the best of our knowledge yet to be demonstrated.

The present work describes the simple and selective reduction of *N*-t-butoxycarbonyl (Boc)/benzyloxycarbonyl (Z)/9-fluorenylmethoxycarbonyl (Fmoc)/1,1-dioxobenzo-thiophen-2-ylmethyloxycarbonyl (Bsmoc) amino acid-derived acylbenzotriazoles using $NaBH_4$ to form the corresponding alcohols. During peptide synthesis, the amino group is usually protected with any one of the urethane type groups, Boc, Z, Fmoc and Bsmoc which differ from one another in their deprotection conditions. Boc and Z groups are deprotected using acidolysis whereas Fmoc and Bsmoc groups are deprotected using an organic base. We herein describe a general route for the reduction of α-amino acids carrying with all four commonly employed amine protecting groups.

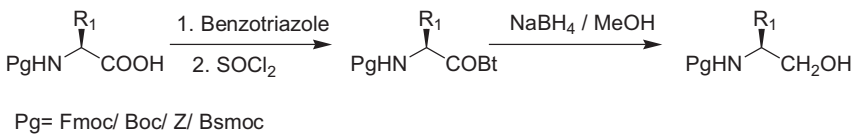
Results and discussion

N-Protected amino acylbenzotriazoles are accessible in excellent yields by reacting the corresponding amino acid or peptide acid with a solution of benzotriazole pretreated with $SOCl_2$.[17] In a typical procedure, the *N*-acylbenzotriazoles were treated with $NaBH_4$ in MeOH at room temperature to accomplish their conversion to the corresponding alcohol. The reduction was found to be very fast, being complete within 2 min. In many cases, the product separated out as a solid after the reaction. Consequently, the reaction mixture was diluted with water and the products were filtered and isolated. A regular aqueous workup method was also followed to isolate the products which could not be precipitated out from the reaction mixture (Scheme 1).

All the protected amino alcohols were obtained in excellent yield (95–99%). In the case of bifunctional amino acids the side chain protecting group such as tertiary butyl ester of Asp/Glu, a benzyl ether linkage on Ser/Thr remained unaffected during reduction. In order to demonstrate the versatility of this protocol, a series of Fmoc, Boc, Z and Bsmoc protected amino acids were converted into the corresponding alcohols (Table 1).

The protocol was then extended to the synthesis of N-protected peptide alcohols. The peptide acids were synthesised by coupling with *O,N*-bis-trimethylsilyl amino acid with mixed anhydride of N-protected amino acid.[20] They were then converted into the corresponding acylbenzotriazole derivatives and further reduced to the corresponding alcohols using $NaBH_4$ following the same procedure (Scheme 2).

The reaction was also tested for racemisation by recording the ^1H NMR spectra of compounds **4** and **5** (Table 1) synthesised via the present protocol. Compound **4** contained a doublet at δ 1.163, 1.180 while its epimer **5** showed the



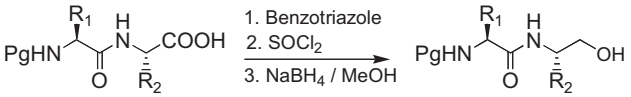
Pg= Fmoc/ Boc/ Z/ Bsmoc

Scheme 1 Synthesis of *N*-protected β-aminoalcohols from *N*-(Pg-α-aminoacyl)benzotriazoles.

* Correspondent. Email: haricch@rediffmail.com

Table 1 Preparation of *N*-protected amino and peptide alcohols

Compd	Protected amino or peptide alcohol	Yield/%	M.p./°C	$[\alpha]^{24}_D$ (c = 1, $CHCl_3$)	ES-MS $(M + 1)^+$
1	Fmoc-Leu-ol	94	131	–20.8	340
2	Fmoc-Asp(O^{t}Bu)-ol	90	97	–6.5	398
3	Fmoc-Phg-Phe-ol	91	137	–24.6	507
4	Fmoc-L-Phg-Ala-ol	89	126	–20.6	431
5	Fmoc-D-Phg-Ala-ol	91	128	+21.1	431
6	Boc-Phe-ol	89	94	–21.6	252
7	Boc-Thr(Bzl)-ol	90	oil	+12.0	308
8	Boc-Ser(Bzl)-ol	86	58	+12.1	296
9	Boc-Asp(OBzl)-Ala-ol	81	80	–11.6	381
10	Z-Phe-ol	94	88	–12.1	286
11	Z-Asp(ol)OBzl	82	gum	–29.1	344
12	Z-Glu(OMe)-ol	91	69	–18.2	282
13	Z-Ala-Ala-ol	86	144	–29.4	281
14	Bsmoc-Ala-ol	70	gum	–5.45	298
15	Bsmoc-Phe-ol	72	gum	–30.1	374



Pg= Fmoc / Boc / Z / Bsmoc

Scheme 2 Synthesis of alcohols from *N*-(Pg-α-aminopeptidyl)benzotriazoles.

peaks at δ 1.179, 1.196. The equimolar mixture of **4** and **5,** intentionally mixed**,** had two doublets at the different values δ 1.161, 1.174, 1.181, 1.194. This clearly demonstrated that the method described to make β-amino alcohols is racemisation-free.

In conclusion, we have developed an efficient method for the conversion of N-urethane protected amino acids/peptide acids into the corresponding β-amino alcohols using *N*-acylbenzotriazoles. The reduction is rapid, high yielding and proceeds with no side reactions or racemisation. Common side chain protecting groups remain unaffected. The present method is advantageous as it utilises acylbenzotriazoles which are easy to make and stable to store as C-activated precursors. Further, since the benzotriazoles of all common N-protecting groups can be prepared as shelf stable solids in good yield, the current method becomes a general protocol for reduction of N-urethane protected amino acids and peptide acids.

Experimental

Melting points were determined by the capillary method. IR spectra were recorded on a Nicolet model impact 400D FT-IR spectrometer (KBr pellets). Specific rotations were recorded on a Rudolf Research Autopol IV automatic polarimeter. NMR spectra were measured on a Bruker AMX 400 MHz spectrometer. ES-MS spectra were obtained from an ES-MS (HP 1100 series, MSD single quadrupole) instrument. Elemental analyses were recorded using Perkin Elmer Analyser and the samples were dried under vacuum before analysis. The TLC analysis was carried out on precoated silica gel plates using the solvent system ethyl acetate: hexane (35: 65 v/v). All the solvents were freshly distilled prior to use.

General procedure for the preparation of N-Fmoc/Boc/Z/Bsmoc-β-amino alcohols

To the *N*-(Fmoc/Boc/Z/Bsmoc-α-aminoacyl)benzotriazole (10 mmol) in methanol was added 6.0 mmol (0.22 g) of $NaBH_4$ and the mixture was stirred at room temperature for 2–5 min. Upon completion of the reaction, as evident by TLC, the reaction mixture was diluted with excess of water. On precipitation of the product, which is common with Fmoc-protected alcohols, the product was filtered, washed with 10% citric acid, water and dried. In other cases, the product was extracted into ethyl acetate. The organic layer was washed with 10% citric acid followed by water and brine, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to obtain the compound as a white solid. The melting points of the products are listed in Table 1.

Fmoc-Leu-ol (**1**): NMR ($CDCl_3$): δ_H 0.93 (d, 6H, *J* = 5.4 Hz), 1.33 (m, 2H), 1.63 (m, 1H), 2.34 (br s, 1H), 3.55 (br m, 2H), 3.77 (m, 1H), 4.19 (t, 1H, *J* = 6.6 Hz), 4.41 (m, 2H), 5.08 (d, 1H, *J* = 8.8 Hz), 7.27–7.40 (m, 4H), 7.56 (d, 2H), 7.77 (d, 2H); δ_C 22.0, 23.0, 24.6, 40.3, 47.2, 51.2, 65.5, 66.4, 119.8, 124.9, 126.9, 127.6, 141.2, 143.8, 156.7. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31, H, 7.42, N, 4.13, Found, C, 74.30, H, 7.38, N, 4.09%.

Fmoc-Phg-Phe-ol (**3**): ^{1}H NMR (*δ,* $CDCl_3$): 2.07 (s, 1H), 2.87 (d, 2H, *J* = 6.4 Hz), 3.60 (m, 2H), 3.96 (m, 1H), 4.16 (t, 1H, *J* = 6.80 Hz), 4.4 (m, 3H), 5.91 (s, 1H), 7.10–7.40 (m, 14H), 7.56 (m, 2H), 7.77 (d, 2H, *J* = 7.6 Hz): δ_C 37.3, 47.2, 54.1, 64.0, 66.7, 68.5, 120.0, 124.7, 125.0, 126.2, 126.5, 126.9, 127.0, 127.2, 128.2, 130.8, 132.7, 139.1, 141.5, 143.9, 156.4, 166.7. Anal. Calcd for $C_{32}H_{30}N_2O_4$: C, 75.87, H, 5.97, N, 5.53, Found, C, 75.81, H, 5.98, N, 5.50%.

Boc-Ser(Bzl)-ol (**8**): NMR ($CDCl_3$): δ_H 1.40 (s, 9H), 3.50–3.95 (m, 5H), 4.48 (s, 2H), 7.35 (s, 5H); δ_C 28.2, 59.4, 65.4, 67.1, 73.7, 81.1, 128.1, 128.0, 128.1, 128.3, 138.1, 156.1. Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03, H, 8.24, N, 4.98, Found, C, 64.00, H, 8.30, N, 4.94%.

Z-Phe-ol (**10**): NMR ($CDCl_3$): δ_H 2.91 (d, 2H), 2.80 (br, H), 3.55 (m, 2H), 3.71 (br, 1H), 5.05 (s, 2H), 5.61 (s, 1H), 7.30 (s, 5H), 7.35 (s, 5H); δ_C 37.2, 54.1, 62.6, 64.0, 127.2, 127.57, 127.75, 128.10, 128.5, 136.5, 136.9, 156.6. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56, H, 6.71, N, 4.91, Found, C, 71.50, H, 6.77, N, 4.99%.

Bsmoc-Ala-ol (**14**): NMR ($CDCl_3$): δ_H 1.25 (3H, d, *J* = 7.2 Hz), 3.32 (1H, m), 3.71 (2H, d, *J* = 6.9 Hz), 5.10 (2H, s), 5.54 (1H, s), 7.15 (1H, s), 7.34 (1H, d, *J* = 7.0 Hz), 7.49 (2H, m), 7.71 (1H, d, *J* = 7.2 Hz); δ_C 17.4, 47.1, 66.3, 67.2, 121.3, 125.8, 126.3, 127.8, 130.6, 134.1, 137.0, 156.9. Anal. Calcd for $C_{13}H_{15}NO_5S$: C, 52.51, H, 5.09, N, 4.71, Found, C, 52.79, H, 5.10, N, 4.80%.

Bsmoc-Phe-ol (**15**): NMR ($CDCl_3$): δ_H 2.93 (2H, d, *J* = 4.9 Hz), 3.48 (2H, d(d)), 3.87 (1H, m), 5.1 (2H, s), 7.15 (1H, s), 7.33 (1H, d, *J* = 6.9 Hz), 7.49 (2H, m), 7.71 (1H, d, *J* = 7.1 Hz); δ_C 37.9, 47.3, 52.7, 66.9, 121.3, 125.8, 126.3, 127.8, 128.5, 128.6, 129.8, 130.6, 134.1, 137.0, 139.6, 140.6, 156.9. Anal. Calcd for $C_{19}H_{19}NO_5S$: C, 61.11, H, 5.13, N, 3.75, Found, C, 61.19, H, 5.18, N, 3.81%.

Received 27 August 2007; accepted 23 December 2007
Paper 07/4808 doi: 10.3184/030823407X272985

References

1 (a) J.-M. Cassal, A. Furst and W. Meier, *Helv. Chim. Acta,* 1976, **59**, 1917; (b) S. Thaisrivongs, D.T. Pals, W.M. Kati, S.R. Turner, L.M. Thomosco and W. Watt, *J. Med. Chem.,* 1986, **29**, 2080; (c) R.H. Schlessinger and E.J. Iwanowicz, *Tetrahedron Lett.,* 1987, **28**, 2083.
2 (a) R. Thompson, *Methods Enzymol.,* 1977, **46**, 220; (b) R.P. Sharma, M.G. Gore and M. Akhtar, *J. Chem. Soc., Chem. Commun,* 1979, 875.
3 C.F. Stanfield, J.E. Parker and P. Kanellis, *J. Org. Chem.,* 1981, **46**, 4797.
4 J. Pless, W. Bauer, F. Cordinaux, A. Closse, D. Hauser, R. Huguenia, D. Roemer, H.-H. Buescher and R.C. Hill, *Helv. Chim. Acta,* 1979, **62**, 398.
5 J. Martinez, J.P. Bali, M. Rodriguez, B. Castro, R. Magous, J. Laur and M.F. Lignon, *J. Med. Chem.,* 1985, **28**, 1874.
6 R.E. Ten Brink, *J. Org. Chem.,* 1987, **52**, 418.
7 (a) A. Boeijen, J.V. Ameijde and R.M.J. Liskamp, *J. Org. Chem.,* 2001, **66**, 8454; (b) G. Guichard, V. Sometey, C. Didierjean, A. Aubry, J.P. Briand and M. Rodriguez, *J. Org. Chem.,*1999, **64**, 8702.
8 M.C.F. Monnee, M.F. Marijne, A.J. Brouwer and R.M.J. Liskamp, *Tetrahedron Lett.,* 2000, **41**, 7991.

9 C.Y. Cho, R.S. Youngquist, S.J. Paikoff, M.H. Beresini, A.R. Hebert, L.T. Berleau, C.W. Liu, D.E. Wenner, T. Keough and P.G. Schultz, *J. Am. Chem. Soc.,* 1998, **120**, 7706.
10 (a) K. Soai, H. Oyamada and M. Takase, *Bull. Chem. Soc. Jpn,* 1984, **57**, 2327; (b) Y. Hamada, M. Shibata, T. Sugiura, S. Kato and T. Shioiri, *J. Org. Chem.,* 1987, **52**, 1252; (c) J. Nitakawa and T. Shiba, *Chem.. Lett.,* 1979, 981.
11 (a) G. Kokotos, *Synthesis*, 1990, 299; (b) M. Rodriguez, M. Llinares, S. Doulut, A. Heitz and J. Martinez, *Tetrahedron Lett.,* 1991, **32**, 923.
12 J.-A. Fehrentz, J.-C. Califano, M. Amblard, A. Lottet and J. Martinez, *Tetrahedron Lett.,* 1994, **35**, 569.
13 G. Kokotos and C. Noula, *J. Org. Chem.*, 1996, **61**, 6994.
14 P. Karrer and M. Suter, *Helv. Chim. Acta,* 1948, **32**, 1156.
15 A. Ito, R. Takahashi and Y. Baba, *Chem. Pharm. Bull.,* 1975, **23**, 3081.
16 A.R. Katritzky, X. Lan, J.Z. Yang and O.V. Denisko, *Chem. Rev.*, 1998, **98**, 409.
17 A.R. Katritzky, P. Angrish, D. Hur and K. Suzuki, *Synthesis*, 2005, **3**, 397.
18 A.R. Katritzky, K. Widyan and K. Kirichenko, *J. Org. Chem.,* 2007, **72**, 5802.
19 (a) A.R. Katritzky, N. Kirichenko and B.U. Rogovoy, *Synthesis*, 2003, 2777; (b) A.R. Katritzky, A.A. Shestopalov and K. Suzuki, *Arkivoc* 2005, vii, 36.
20S.J. Tantry and V.V. Sureshbabu, *Indian J. Chem.,* 2004, **43B**, 1282

Friedel–Crafts allylation of 2-(benzyloxy)-3,4,5-trimethoxytoluene catalysed by a metal trifluoromethanesulfonic salt: synthesis of coenzyme Q10

Yun-Feng Zheng[a], Jing-Du Lin[a], Cheng-Ping Li[b] and Jing-Hua Li[a]*

[a]*College of Pharmaceutical Sciences, Zhejiang University of Technology, 310032, P. R. China*

[b]*College of Biology and Environmental Engineering, Zhejiang Shuren University, 310015, P. R. China*

In the presence of a catalytic amount of scandium triflate, 2-benzyloxy-3,4,5-trimethoxytoluene reacted with allylic derivatives **4**, giving the key intermediate **3** (R = benzyl) which was used for preparing coenzyme Q10, in moderate to high yields.

Keywords: 2-(benzyloxy)-3,4,5-trimethoxytoluene, metal triflate, Friedel–Crafts allylation, coenzyme Q10

Coenzyme Q10 (**1**, also called ubiquinone), was discovered in 1957,[1] and shown to function in mitochondria in the formation of ATP. It has been found to be beneficial for a variety of conditions,[2,3] such as heart disease and Parkinson's disease.

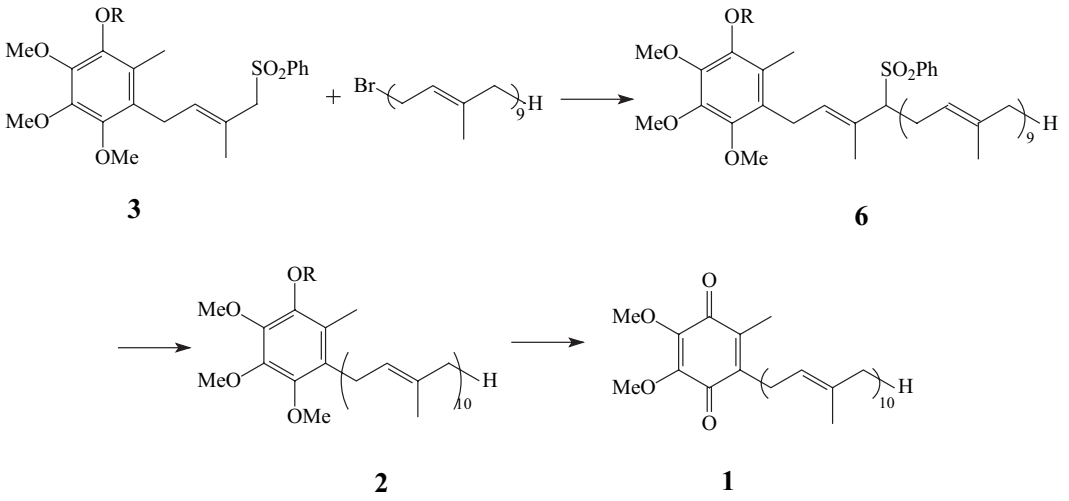
Because of those important effects, there have been extensive synthetic efforts directed at this natural product.[4-12] The key issue was the coupling of the quinone core generally derived from inexpensive trimethoxytoluene and the polyprenyl side chain derived from expensive solanesol. An ideal synthesis would seek to not only minimise the extent to which intermediates based on solanesol are manipulated *en route* to Coenzyme Q10 but also improve its overall yield. Recently, a new process for preparing Q10 (Scheme 1, R = Me) was reported.[13] Although the final step, oxidation of **2** (R = Me) with $(NH_4)_2Ce(NO_3)_6$, gave Q10 in low yield, the whole process is an improvement.

Scheme 1 shows that **3** is a key compound in the synthesis of coenzyme Q-10 (**1**). Fujita[14] reported a method for the preparation of **3** (R = Me) *via* copper-mediated coupling of (E)-4-Chloro-2-methyl-1-phenylsulfonyl-2-butene with the Grignard reagent of 2,3,4,5-tetramethoxytolyl bromide. Compared to Fujita's method, Friedel–Crafts reaction of **5** (R = alkyl) with **4** might be a simpler and more economical way to synthesise **3** (Scheme 2), because **5** (R = alkyl) is a good electron-rich substrate for the Friedel–Crafts reaction. The Friedel–Crafts reaction was achieved by Min *et al.* recently.[13] However, the low values of *E/Z* isomeric ratio of **3** (R = Me) were not desirable (*E/Z* = 10/1). Based on the potential of its industrial application, we sought the optimal process for synthesising Q10. According to Scheme 1 and the literature,[15,16] in which Q0 was prepared quantitatively by oxidation of 2-hydroxy-3,4,5-trimethoxytoluene in air, we deduced that **2** (R = H), easily obtained starting from **3** (R = Bn) *via* intermediate **2** (R = Bn), might produce Q10 in similar way to Q0 in good yield (Scheme 1). The search for a more effective method for preparation of **3** (R = Bn) is necessary.

Recently, it is found that a metal triflate, as an all-purpose Lewis acid, was generally useful as an effective catalyst in organic synthesis,[17] such as in Aldol reaction,[18,19] Mannich-type reaction,[20–24] Diels–Alder reaction[25–27] and Friedel–Crafts reaction.[28–30] To the best of our knowledge, however, metal triflate catalysed Friedel–Crafts allylation of **5** has not been reported. We now report our investigation using metal triflate as a catalyst (Scheme 2, R = Bn) with improved value of *E/Z* ratio. Compound **5** (R = Bn) and compound **5** (R = Me), both of which were derived from 2-hydroxy-3,4,5-trimethoxytoluene, are useful starting materials for synthesising Q10. The former is better compared to the latter, because at the final step in synthesising Q10, **2** (R = Bn) is more readily transformed into **2** (R = H) which leads to **1** quantitatively.

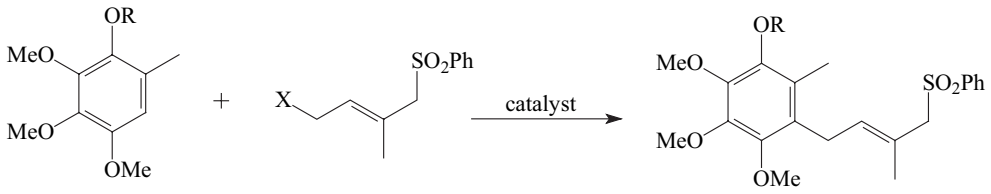
Results and discussion

As a Lewis acid, metal triflate can catalyse the Friedel–Crafts allylation of **5** (R = Bn) with **4** (X =Cl, Br) (Scheme 2). The results are summarised in Table 1.



Scheme 1 The synthetic route of Coenzyme Q10 (**1**) from the compound **3**.

* Correspondent. E-mail: lijh571@163.com



5 **4** **3**

4a, X = Cl **4b**, X = Br

Scheme 2 Preparation of the compound **3** (R = Me, Bn) catalysed by metal triflate.

Table 1 Allylation of **5** (R = Bn) in the presence of metal triflates

Entry	Allylation reagent	Catalyst (equiv)	Condition	Yield% of *E*-3 (R = Bn)
1	**4a**	AgOTf (0.5)	A[a]	ND[c]
2	**4a**	$Cu(OTf)_2$ (0.5)	A[a]	32
3	**4a**	$Y(OTf)_3$(0.5)	A[a]	51
4	**4a**	$Gd(OTf)_3$(0.5)	A[a]	54
5	**4a**	$Ce(OTf)_3$(0.5)	A[a]	62
6	**4a**	$La(OTf)_3$(0.5)	A[a]	66
7	**4a**	$Yb(OTf)_3$(0.1)	B[b]	40
8	**4a**	$Yb(OTf)_3$(0.2)	B[b]	52
9	**4a**	$Yb(OTf)_3$(0.5)	A[a]	78
10	**4a**	$Sc(OTf)_3$(0.5)	A[a]	81
11	**4b**	$Yb(OTf)_3$(0.5)	A[a]	80
12	**4b**	$Sc(OTf)_3$(0.5)	A[a]	83

[a]A: THF at reflux temperature for 12 h. [b]B: THF at reflux temperature for 18 h. [c]Not detected.

The condition of the Friedel–Crafts allylation with 0.5 equiv of metal triflate in THF at reflux temperature for 12 h (condition A in Table 1) was established according to our preliminary study. The reaction also proceeded with a less than stoichiometric amount of metal triflate (condition B in Table 1), however, it required a longer reaction time and produced a lower yield of *E*-3 (R = Bn).

From Table 1, a different effect of each metal triflate on the yield of the coupling product *E*-3 (R = Bn) was noticed. AgOTf was not a good catalyst for this coupling reaction. There was no product *E*-3 (R = Bn) detected in the case of AgOTf. $Cu(OTf)_2$, $Y(OTf)_3$, and $Gd(OTf)_3$ *etc*. generally produced low yields of the product *E*-3 (R = Bn). A good yield of the *E*-isomer of the compound **3** (R = Bn) was obtained in the case of $Yb(OTf)_3$ and $Sc(OTf)_3$. Note that $Sc(OTf)_3$ consistently produced high yields of *E*-3 (R = Bn), where the *E/Z* ratio of 15:1 was maintained. The best result (83%; *E/Z* = 15 : 1, determined by external standard method of HPLC: column VP-ODS 150 L × 4.6, flow rate 0.8 ml/min, eluent 75% methanol–water solution, λ = 254 nm) was observed when **4** (X = Br) and **5** (R = Bn) were coupled using $Sc(OTf)_3$ as catalyst under condition A, and a pure product *E*-3 (R = Bn) can be readily obtained by recrystallisation from methyl *tert*-butyl ether. It was easy to separate the *E*-isomer of **3** (R = Bn) from its *Z*-isomer, which is important and useful for industrial application.

In addition, the recovery and recycling of metal triflate were also investigated, and the results show that the reaction proceeded smoothly with recovered $Yb(OTf)_3$ With the key compound **3** (R = Bn) to hand, we attempted the total synthesis of coenzyme Q10 (**1**) (Scheme 3). Q10 (**1**) was easily prepared by similar methods to those described in the literatures:[3,15] (a) condensing **3b** with solanesyl bromide, (b) treating the resultant product **6b** with $LiHBEt_3/Pd(dppp)Cl_2$ followed by debenzylation with K/EtOH and oxidation with air.

Conclusion

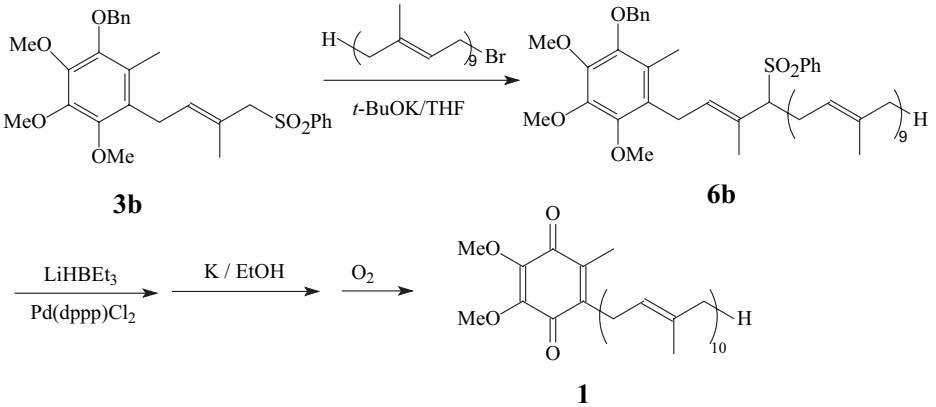
In conclusion, an efficient and convenient procedure for Friedel–Crafts allylation was carried out using a metal triflate as a catalyst under mild conditions with a simple methodology. It offered an important method for Friedel–Crafts allylation of **4** (R = Bn) in order to synthesise compound **3b**, a key intermediate for preparing coenzyme Q10 and an economical method for preparation of Q10 from **3b** was achieved (Scheme 3).

Experimental

Melting points are uncorrected. ^{1}H NMR spectra were determined on a Varian Plus 400 instrument using TMS as an internal standard and $CDCl_3$ as a solvent. IR spectra were recorded on a Perkin-Elmer 683 instrument. Mass spectra were obtained on an AEI MS-902 instrument and ESI-MS was obtained with a Finnigan TSQ 700 instrument.

Procedure for synthesis of **3b**

A solution of 2-(benzyloxy)-3,4,5-trimethoxytoluene **5** (R = Bn) (1.0 mmol) and (*E*)-4-chloro-2-methyl-1-phenylsulfonyl-2-butene **4a** (1.0 mmol) and $Sc(OTf)_3$ (0.50 mmol) in dry THF (10 ml) was refluxed for 12 h. The solution was concentrated under reduced



3b **6b**

1

Scheme 3 Preparation of the Q10 (1) from the compound **3b** (3, R = Bn); dppp: 1,3-bi(diphenylphosphino)propane

pressure and the residue was extracted twice with 1,2-dichloroethane (10 ml) and filtered. The filtrate was evaporated under reduced pressure to give a solid. The solid residue was further purified by recrystallisation from methyl *tert*-butyl ether to give **3b** (*E*) in 81% isolated yield.

3b: M.p. 76–78°C; IR (KBr, cm^{-1}): 2962, 2934, 2899, 1464, 1305, 1132, 734; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94 (3H, s), 1.97 (3H, s), 3.24 (2H, d, J = 6.4 Hz), 3.75 (3H, s), 3.75 (2H, s), 3.90 (3H, s), 3.92 (3H, s), 4.91 (2H, s), 4.91 (1H, br), 7.20–7.28 (10H, m); EI-MS *m/z* (rel. intensity%): 496 (M^+, 11), 405 (100), 263 (74), 231 (48), 91 (34); Anal. calcd. for $C_{28}H_{32}O_6S$, C 67.72%, H 6.49%, Found C 67.66%, H 6.51%.

Procedure for synthesis of **6b**

To a stirred mixture of **3b** (2.0 g, 4.0 mmol), solanesyl bromide (95%, 2.9 g, 4.0 mmol) and THF (28 ml) was added *t*-BuOK (0.5 g, 4.4 mmol) at -20°C. The mixture was stirred at the same temperature for 1 h to complete the reaction, and then acidified with 5% H_3PO_4 to pH = 2-3. The whole mixture was added to water (20 ml) and methyl tert-butyl ether (20 ml) and separated into two layers. The organic layer was washed with water to pH = 7, dried over $MgSO_4$ and concentrated under reduced pressure to give an oily product. The oily residue was further purified by column chromatography on silica gel with petroleum ether/ethyl acetate (10 : 1 v/v) as an eluent to give 4.0 g of pure **6b** (yield 90%).

6b: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.58 (3H, s), 1.60 (3H, s), 1.62 (21H, s), 1.70 (3H, s), 1.85 (3H, s), 1.95 (3H, s), 2.01–2.11 (32H, s), 2.59-2.58 (1H, m), 2.63–2.88 (1H, m), 3.17 (1H, m), 3.28 (1H, m), 3.50 (1H, m), 3.70 (3H, s), 3.92 (3H, s), 3.94 (3H, s), 4.92 (2H, s), 4.90–5.16 (10H, m), 7.34–7.80 (10H, m); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 12.0, 14.0, 15.9, 16.0, 16.3, 17.6, 24.0, 25.7, 26.0, 26.5, 26.6, 26.6, 26.7, 26.7, 39.7, 61.0, 61.0, 61.1, 61.2, 123.7, 124.1, 124.2, 124.2, 124.4, 125.5, 126.5, 127.4, 127.9, 128.1, 128.4, 128.6, 128.7, 131.2, 133.1, 134.2, 134.8, 134.9, 134.9, 134.9, 134.9, 135.0, 135.3, 137.7, 137.8, 138.5, 144.7, 145.3, 146.7, 147.6; ESI-MS *m/z* (%) 1131.7 (M + Na^+, 88), 1126.7 (M + NH_4^+, 100); Anal. calcd. for $C_{73}H_{104}O_6S$, C 79.01%, H 9.45%, Found C 78.90%, H 9.42%.

Preparation of Q10 (**1**)

To a mixture of 808 mg **6b** and $Pd(dppp)Cl_2$ (20 mg) in THF (8 ml) was added dropwise $LiHBEt_3$ in THF (1.94 ml 1 mol/l) at –30°C. After stirring for 6 h, the whole reaction mixture was quenched with 0.8 ml water and concentrated under reduced pressure to 30% of its original volume. The concentrated residue was treated with water (8 ml), extracted with petroleum ether (2 × 2.5 ml), washed with water (2 ml), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a sticky residue (700 mg). The residue was mixed with ethanol (2 ml) and dry THF (25 ml) and K (450 mg) at –40 ~ –20°C, and stirred at the same temperature for 4 h. Then the reaction mixture was stirred with $FeCl_3$•$6H_2O$ in air for 0.5 h. The resulting mixture was partitioned with 1 mol/l HCl and isopropyl ether. The organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to give an orange solid. The solid residue was further purified by column chromatography on silica gel with hexane/isopropyl ether (3:1 v/v) as an eluent, and recrystallised from acetone to give 408 mg of an orange crystalline powder **1** (yield 65%).

Q10 (**1**) m.p. 48–49°C (lit.[32] 47°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (36H, s), 1.97–2.06 (36H, m), 3.19 (2H, d, J = 6.0 Hz), 3.99, 6H,s 5.11 (10H, m); ESI-MS *m/z* (%) 885.6 (M + Na^+, 85), 880.6 (M + NH_4^+, 100).

Received 17 November 2007; accepted 13 December 2007
Paper 07/4946 doi: 10.3184/030823407X270338

References

1 F.L Crane, Y. Hatefi, R.L. Lester and C. Widmer, *Biochim. Biophys. Acta*, 1957, **25**, 220.
2 R.H. Thomson, *Naturally Occurring Quinones*; Academic Press: New York, 1971.
3 P. Mitchell and J. Moyle, *Coenzyme Q*; G. Lenaz, ed.; Wiley: Chichester, UK, 1985.
4 (a) B.H. Lipshutz, S.K. Kim, P. Mollard and K.L. Stevens, *Tetrahedron,* 1998, 1241; (b) B.H. Lipshutz, G. Bulow, F. Fernandez-Lazaro, S.-K. Kim, R. Lowe, P. Mollard and K.L. Stevens, *J. Am. Chem. Soc.,* 1999, **121**, 11664; (c) B.H. Lipshutz, P. Mollard, S.S. Pfeiffer and W. Chrisman, *J. Am. Chem. Soc.,* 2002, **124,** 14282; (d) B.H. Lipshutz, A. Lower, V. Berl, K. Schein and F. Wetterich, *Org. Lett.,* 2005, **7**, 4095; (e) B.H. Lipshutz, V. Berl and A. Lower, *J. Am. Chem. Soc.,* 2006, **128**, 15396.
5 (a) H.F. Dai, F.E. Chen and X.J. Yu, *Helv. Chim. Acta,* 2006, **89**, 1317; (b) X.J. Yu, F.E. Chen, H.F. Dai, X.X. Chen, Y.Y. Kuang and B. Xie, *Helv. Chim. Acta,* 2005, **88,** 2575.
6 (a) P. Gurumurthy, S.M.B. Chennamsettyl, V. Visweswaran, M. Roy and H. Sivaramakrishnan, *WO* 2007004092, 2007; (b) A. Upare, N.Y. Pawar, G. Wagh, A. Chavan, M. Roy and H. Sivaramakrishnan, *WO* 2007004091, 2007; (c) H. Yamane, *JP* 2007008886; (d) S. Zhao, *CN* 1927799; (e) G. Wang, X. Shen, X. Zhu and T. Fu, *CN* 1931818.
7 W.B.S. Van Liemt, W.F. Steggerda, R. Esmeijer and J. Lugtenburg, *Recl. Trav. Chim. Pays-Bas,* 1994, **113,** 153.
8 S. Inoue, R. Yamaguchi, K. Saito and K. Sato, *Bull. Chem. Soc. Jpn.,* 1974, **47**, 3098.
9 X. García, P. Ballester, M. Capó and J.M. Saá, *J. Org. Chem.,* 1994, **59**, 5093.
10 K. Sato, S. Inoue, K. Saito, *J. Chem. Soc., Perkin Trans. 1* 1973, 2289.
11 C.D. Snyder and H. Rapoport, *J. Am. Chem. Soc.,* 1974, **96,** 8046.
12 Y. Naruta, *J. Org. Chem.,* 1980, **45**, 4097.
13 J.H. Min, J.S. Lee, J.D. Yang and S. Koo *J. Org. Chem.,* 2003, **68**, 7925.
14 Y. Fujita, M. Ishiguro, T. Onishi and T. Nishida, *Synthesis,* 1981, 469.
15 S. Terao, K. Kato, M. Shiraishi and H. Morimoto, *J. Org. Chem.,* 1979, **44**, 868.
16 N. Minami and S. Kijima, *Chem. Pharm. Bull.,* 1980, **28**, 1648.
17 S. Kobayashi, M. Sugiura, H. Kitagawa and W.W.L. Lam *Chem. Rev.,* 2002**, 102**, 2227.
18 T. Mukaiyama, K. Narasaka and T. Banno, *Chem Lett.,* 1973, 1011.
19 T. Mukaiyama, K. Banno and K. Narasaka, *J. Am. Chem. Soc*., 1974, **96**, 7503.
20 K. Ikeda, K. Achiwa and M. Sekiya, *Tetrahedron Lett.,* 1983, **24**, 4707.
21 J.E. Dubois and G. Axiotis, *Tetrahedron Lett.,* 1984, **25**, 2143.
22 E.W. Colvin and D.G. McGarry, *J. Chem. Soc., Chem. Commun.,* 1985, 539.
23 S. Shimada, K. Saigo, M. Abe, A. Sudo and M. Hasegawa, *Chem. Lett.,* 1992, 1445.
24 K. Hattori and H. Yamamoto, *Tetrahedron,* 1994, **50**, 2785.
25 W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon: Elmsford, NY, 1990.
26 D. Yates and P. Eaton, *J. Am. Chem. Soc.,* 1960, **82,** 4436.
27 T.K. Hollis, N.P. Robinson and B. Bosnich, *J. Am. Chem. Soc.,* 1992, **114,** 5464.
28 F. Effenberger, E. Sohn and G. Epple, *Chem. Ber.,* 1983, **116**, 1195.
29 S. Répichet, C. LeRoux, J. Dubac and J.R. Desmurs, *Eur. J. Org. Chem.,* 1998, **2743,** 3.
30 J. Matsuo, K. Odashima and S. Kobayashi, *Synlett,* 2000, 403.
31 M. Mohri, H. Kinoshita, K. Inomata, H. Kotake, H. Takagaki and K. Yamazaki, *Chem. Lett.,* 1986, 1177.
32 D. Eren and E. Keinan, *J. Am. Chem. Soc.,* 1988, **110**, 4356.

Synthesis of pyrido[2',3':4,5]thieno[2,3-*d*]pyrimidines through Friedländer reactions

Shawkat A. Abdel-Mohsen* and Ahmed A. Geies

Chemistry Department, Faculty of Science, Assiut University, Assiut 71516, Egypt

A variety of tri-, tetra- and penta–cyclic pyrido[2',3':4,5]thieno[2,3-*d*]pyrimidines have been synthesised from 5-amino-6-formyl-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine by Friedländer condensation with aliphatic, alicyclic, and heterocyclic ketones and other active methylene compounds.

Keywords: fused thiophenes, pyridines, pyrimidines, amino-aldehydes, Friedländer reactions

Annelation reactions involving suitable aromatic hydrocarbon compounds carrying the aminoaldehyde moiety provide a synthetic entry into heterocyclic systems,[1] and the formation of ring structures from substituted heterocyclic aminoaldehydes is often the method of choice for preparation of polycondensed heterocycles.[2-5]

Thienopyrimidines have been the subject of chemical and biological studies due to their interesting pharmacology,[6] including analgesic,[7] antipyretic,[8] herpes virus inhibitory[9] and anti-inflammatory[10,11] properties. In view of the above activities and in continuation of our work in the synthesis and reactions of various fused thiophenes,[12,13] we report here the preparation of some new fused pyrido-thieno-pyrimidines.

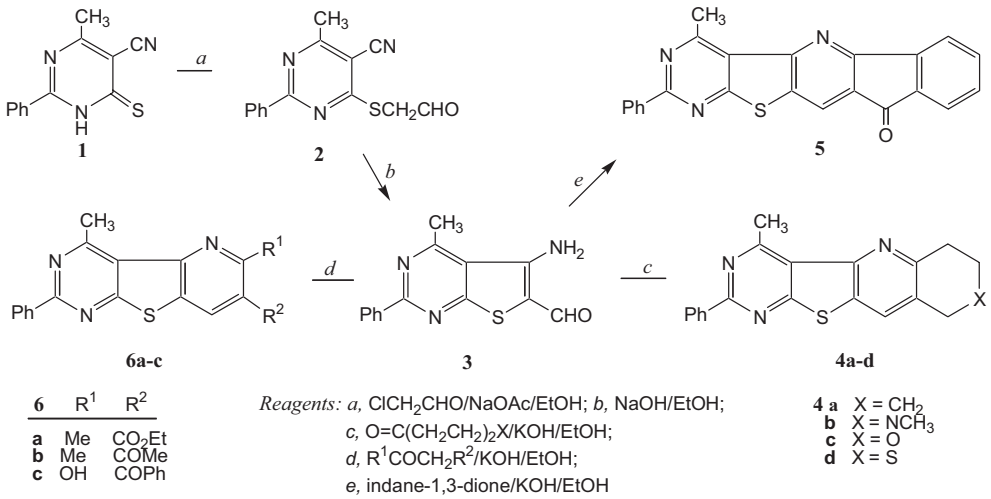
Results and discussion

The synthesis of the desired compounds started with 5-amino-6-formyl-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine (**3**), which was prepared by the reaction of 6-methyl-4-phenyl-2-thioxo-1,2-dihydropyimidine-5-carbonitrile (**1**) with α-chloroacetaldehyde in ethanol containing sodium acetate to give the intermediate 6-(formylmethylthio) derivative **2**. Upon treatment with ethanolic sodium ethoxide, compound **2** underwent cyclisation to afford the starting compound **3**. The heterocyclic aminoaldehyde **3** opens a direct route to the synthesis of condensed heterocycles of the pyridine series. Thus, Friedländer condensation[14] of **3** with aliphatic cyclic and/or heterocyclic ketones in the presence of ethanolic potassium hydroxide solution leads to the formation of fused tetrahydropyrimidothienoquinoline, pyrimidothienonaphthyridine, pyranopyridothienopyrimidine and thiopyranopyridothienopyrimidine compounds **4a–d**, respectively. The ^{1}H NMR spectra of the isolated compounds **4a–d** showed a characteristic singlets at 7.80–8.20 ppm for the H-10 hydrogen. Furthermore, the IR spectra revealed the absence of the characteristic absorption bands at 3450–3300 cm^{-1} for the amino group which indicated the condensation products to be **4a–d**.

Similarly, the aminoaldehyde **3** was allowed to react with indane-1,3-dione under Friedländer condensation conditions to give the indenopyridothienopyrimidine **5.** The IR spectrum of **5** showed a strong absorption band at 1700 cm^{-1} due to C=O. Also the ^{1}H NMR spectrum showed a characteristic singlet at 7.95 ppm for the H-11 hydrogen. (Scheme 1).

Annelation reactions of β-diketones with **3** are greatly facilitated by the presence of a doubly activated α-methylene group, and gave different 6,7-disubstituted pyrido-thienopyrimidines according to the direction of ring closure. Thus, treatment of **3** with ethyl acetoacetate and acetylacetone in ethanolic KOH furnished ethyl 3,6-dimethyl-2-phenylpyrido [2',3':4,5]thieno[2,3-*d*]pyrimidine-7-carboxylate (**6a**) and 7-acetyl-3,6-dimethyl-2-phenylpyrido[2',3':4,5]thieno[2,3-*d*] pyrimidine (**6b**). With ethyl benzoylacetate, compound **3** underwent another route for ring closure, giving 7-benzoyl-4-methyl-2-phenylpyrido[2',3':4,5]thieno[2,3-*d*]pyrimidine-6(5*H*)-one (**6c**). The structure of compound **6c** was confirmed by IR which gave characteristic absorption bands at 1700, 1650 cm^{-1} for 2 CO groups and the ^{1}H NMR revealed the absence of absorptions for the ester group.

In the case of bifunctional compounds (X-CH$_2$-Y; X, Y = cyano, alkoxycarbonyl, carbamoyl and thiocarbamoyl groups), the amino group in **3** attacked the more electrophilic group to form functionalised pyridothienopyrimidines. Thus,



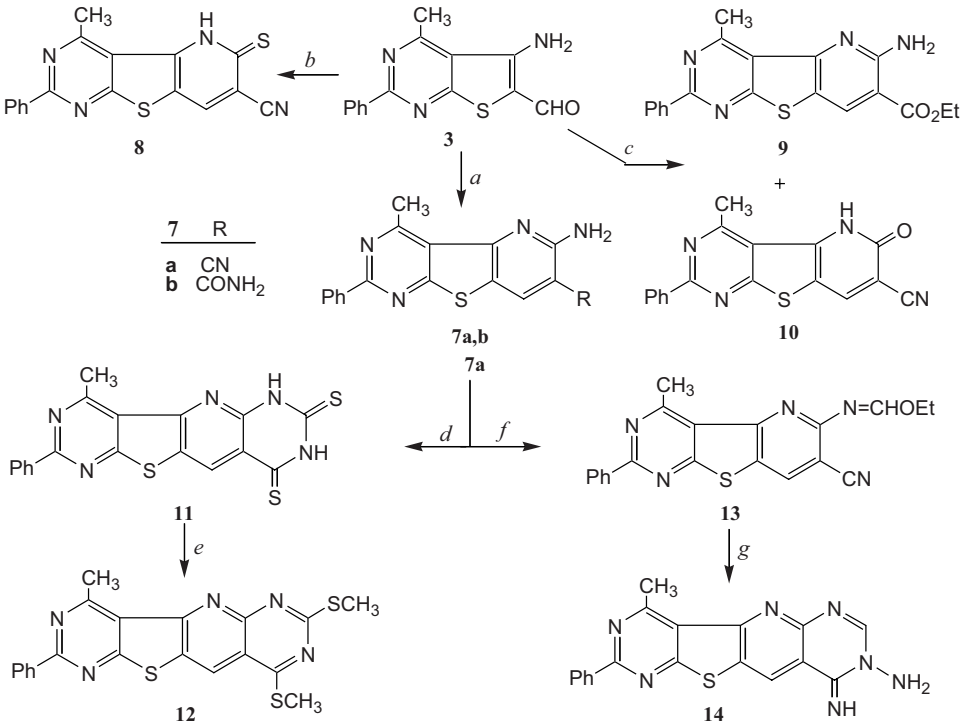
6	R^1	R^2
a	Me	CO_2Et
b	Me	COMe
c	OH	COPh

Reagents: a, $ClCH_2CHO$/NaOAc/EtOH; *b,* NaOH/EtOH; *c,* $O=C(CH_2CH_2)_2X$/KOH/EtOH; *d,* $R^1COCH_2R^2$/KOH/EtOH; *e,* indane-1,3-dione/KOH/EtOH

4 a X = CH_2
b X = NCH_3
c X = O
d X = S

Scheme 1

* Correspondent. E-mail: shawk662001@yahoo.com



Reagents: a, $NCCH_2$-CN/$CONH_2$/piperidine/EtOH; *b*, $NCCH_2$-$CSNH_2$/piperidine/EtOH; *c*, $NCCH_2$-CO_2Et/piperidine/EtOH; *d*, CS_2/pyridine; *e*, CH_3I/acetone/K_2CO_3; *f,* $HC(OEt)_3$/Ac_2O; *g*, N_2H_4/EtOH

Scheme 2

the reaction of **3** with malononitrile and cyanoacetamide in ethanol containing a few drops of piperidine took place via intramolecular addition of the amino group in compound **3** to the cyano function to form the cyclised products 6,7-substituted pyridothienopyrimidines **7a,b**. Unexpectedly, with cyanothioacetamide **3** afforded 7-cyano-4-methyl-2-phenylpyrido[2',3':4,5]thieno[2,3-d]pyrimidine-6(5*H*)-thione (**8**), formed by the loss of an ammonia molecule. (Scheme 2)

The structures of compounds **7a,b** and **8** were consistent with their elemental analyses and spectral data. Thus the IR spectrum of **7a** (R_1 = NH_2, R_2 = CN) reveals characteristic absorption bands at 3450, 3350 cm^{-1} for the NH_2 and at 2230 cm^{-1} for the cyano group. Its ^1H NMR spectrum presents a characteristic singlet at 6.8 for NH_2 and at 8.30 ppm corresponding to H-8 hydrogen. The structure of **8** was confirmed by IR spectrum which revealed the absence of characteristic absorption bands for the NH_2 and showed a band at 2230 cm^{-1} due to CN. The reaction of **3** with ethyl cyanoacetate under the same conditions afforded a mixture of ethyl 6-amino-4-methyl-2-phenylpyrido[2',3':4,5]thieno[2,3-*d*]pyrimidine-7-carboxylate (**9**) and 7-cyano-6-hydroxy-4-methyl-2-phenylpyrido[2',3':4,5]thieno[2,3-*d*]pyrimidine (**10**) which could be separated through fractional crystallisation using acetic acid as a solvent.

The pyridothienopyrimidine derivative **7a** was used as precursor for the synthesis of new pyrimidopyridothieno-pyrimidines **11, 12** and **14** based on the high reactivity of the β-enaminonitrile moiety. Thus, condensation of **7a** with carbon disulfide in pyridine afforded the corresponding 4-methyl-2-phenylpyrimido[5",4":5',6']pyrido[2',3':4,5]thieno [2,3-*d*]pyrimidine-6,8(7*H*,9*H*)-dithione (**11**), which was easily S-methylated by methyl iodide to give the corresponding 7,9-bismethylthio derivative **12**. Furthermore, treatment of **7a** with triethylorthoformate in refluxing acetic anhydride afforded the intermediate ethoxymethyleneamino derivative **13**. Hydrazinolysis of **13** in ethanol yielded the 8-amino-9-iminopyrimidopyridothienopyrimidine derivative **14** in good yield**.** (Scheme 2). The structure of **14** was established on the basis of IR, which showed the absence of CN absorption at 2220 cm^{-1}, while its ^1H NMR spectrum showed signals due to the pyrimidine CH at 8.65 ppm.

Experimental

All melting points were determined on a Gallenkamp apparatus. IR spectra were recorded on a Pye-Unicam spectrophotometer using the KBr wafer technique. ^1H NMR spectra were obtained on a Bruker 250 MHz NMR spectrometer. It should be noted that, to enhance the solubility of a number of samples to a level sufficient to provide an adequate spectrum, several drops of TFA-d_1 were added to the $CDCl_3$ or DMSO-d_6 indicated as the solvent. This probably gave rise to the anomalous deshielding of some of the methyl signals which are reported here. MS were registered on a Jeol JMS-600 mass spectrometer. Elemental analyses were determined using a Perkin-Elmer 240C microanalyser**.**

6-Methyl-4-phenyl-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile (**1**)**:** This compound was synthesised according to a literature procedure; m.p. 228–230°C (lit.[15] m.p. 228–232°C).

5-Cyano-6-(formylmethylthio)-4-methyl-2-phenylpyrimidine (**2**): A mixture of the nitrile **1** (2.27 g, 0.01 mol), fused sodium acetate (2 g) and α-chloroacetaldehyde (0.86 g, 0.01 mol) in ethanol (30 ml) was heated under reflux for 30 min, cool and then poured into water. The solid product obtained was filtered off and crystallised from ethanol to give white crystals (2.30 g, 84%) of **2,** m.p. 155–156°C. IR: ν_{max} 2220 (CN), 1710 cm^{-1} (C=O). NMR ($CDCl_3$): δ_H 2.80 (s, 3H, CH_3), 4.30 (s, 2H, CH_2), 7.40–7.80 (m, 5H, ArH), 9.60(s, 1H, CHO). Anal. calcd. for $C_{14}H_{11}N_3OS$ (269.32): C, 62.44; H, 4.12; N, 15.6; S, 11.9. Found: C, 62.55; H, 4.08; N, 15.71; S, 11.77%.

5-Amino-4-methyl-2-phenylthieno[2,3-d]pyrimidine-6-carbaldehyde (**3**): To compound **2** (2.7 g, 0.001 mol) in absolute ethanol (30 ml) was added a few drops of sodium ethoxide solution, and the mixture was stirred at room temperature for 30 min. The solid product was collected and recrystallised from ethanol to give yellow crystals of **3** (1.90 g 71%), m.p. 200–201°C. IR: ν_{max} 3450, 3300 (NH_2), 1630 cm^{-1} (C=O). NMR (DMSO-d_6): δ_H 2.90 (s, 3H, CH_3), 7.20 (s, 2H, NH_2), 7.40–7.80 (m, 5H, ArH), 10.20 (s, 1H, CHO). MS: *m/z* (%) 269 (100) [M^+]. Anal. calcd. for $C_{14}H_{11}N_3OS$ (269.32):

C, 62.44; H, 4.12; N, 15.60; S, 11.90. Found: C, 62.61; H, 4.18; N, 15.78; S, 12.02%.

Reaction of aminoaldehyde **3** *with cyclic and heterocyclic ketones; formation of* **4a–d**, **5** *and* **6a–c.** *General procedure*

A mixture of **3** (1.35 g, 0.005 mol), the appropriate ketone (0.0055 mol) and a few drops of ethanolic KOH (10%) in ethanol (30 ml) was refluxed for 3–6 h. The solid which separated from the hot mixture was filtered off and recrystallised from the indicated solvent**.**

4-Methyl-2-phenyl-6,7,8,9-tetrahydropyrimido[4',5':5,4]thieno [3,2-b]quinoline (**4a**): Orange crystals (1.30 g, 79%) from dioxan, m.p. 222–223°C. IR: ν_{max} 2900 (CH aliphatic), 1540 cm^{-1} (C=N). NMR (DMSOd_6): δ_H 1.80 (m, 4H, 2 CH_2), 2.60 (m, 2H, CH_2), 2.72(m, 2H, CH_2), 2.95 (s, 3H, CH_3), 7.20–7.50 (m, 5H, ArH), 7.80 (s, 1H, H-10). Anal. calcd. for $C_{20}H_{17}N_3S$ (331.44): C, 72.48; H, 5.17; N, 12.68; S, 9.67. Found: C, 72.37; H, 5.26; N, 12.80; S, 9.75%.

4,8-Dimethyl-2-phenyl-6,7,8,9-tetrahydropyrimido[4',5':5,4] thieno[3,2-b][1,6]naphthyridine (**4b**): Red crystals (1.14 g, 66%) from dioxan, m.p.190–191°C. IR: ν_{max} 2900 (CH aliphatic), 1550 cm^{-1} (C=N). NMR (CF_3COOD): δ_H 2.80 (s, 3H, CH_3), 2.80 (t, 2H, J = 5.2 Hz, CH_2), 3.20 (t, 2H, J = 4.8 Hz, CH_2), 3.45 (s, 3H, CH_3), 4.20 (s, 2H, CH_2-N), 7.20–7.60 (m, 5H, ArH), 8.20 (s, 1H, H-10). Anal. calcd. for $C_{20}H_{18}N_4S$ (346.45): C, 69.34; H, 5.24; N, 16.17; S, 9.25. Found: C, 69.49; H, 5.17; N, 16.31; S, 9.36%.

4-Methyl-2-phenyl-6,7,8,9-tetrahydropyrano[3'',4'':5',6']pyrido [2',3':4,5]thieno[2,3-d]pyrimidine (**4c**): Red crystals (1.08 g, 65%) from acetic acid, m.p. 235–236°C. IR: ν_{max} 2950 (CH aliphatic), 1530 cm^{-1} (C=N). NMR (CF_3COOD): δ_H 2.75 (t, 2H, J = 5.6 Hz, CH_2), 2.95 (s, 3H, CH_3), 3.30 (t, 2H, J = 4.8 Hz, CH_2), 4.80 (s, 2H, CH_2-O), 7.10–7.40 (m, 5H, ArH), 7.65 (s, 1H, H-10). Anal. calcd. for $C_{19}H_{15}N_3OS$ (333.41): C, 68.45; H, 4.53; N, 12.60; S, 9.62. Found: C, 68.61; H, 4.48; N, 12.71; S, 9.53%.

4-Methyl-2-phenyl-6,7,8,9-tetrahydrothiopyrano[3'',4'':5',6']pyrido [2',3':4,5]thieno[2,3-d]pyrimidine (**4d**): Red crystals (1.23 g, 71%) from dioxan, m.p. 227–228°C. IR(KBr) ν = 2950 (CH aliphatic),1540 (C=N) cm^{-1}. NMR (CF_3COOD): δ_H 2.55 (t, 2H, J = 4.6 Hz, CH_2), 2.80 (t, 2H, J = 5.2 Hz, CH_2), 2.90 (s, 3H, CH_3), 3.80 (s, 2H, CH_2-S), 7.10–7.45 (m, 5H, ArH), 7.61(s, 1H, H-10). Anal. calcd. for $C_{19}H_{15}N_3S_2$ (349.47): C, 65.30; H, 4.33; N, 12.02; S, 18.35. Found: C, 65.43; H, 4.29; N, 12.20; S, 18.48%.

4-Methyl-2-phenyl-10H-indeno[2'',3'':5',6']pyrido[2',3':4,5]thieno [2,3-d]pyrimidin-10-one (**5**): Yellow crystals (1.28 g, 68%) from acetic acid, m.p. 301–302°C. IR: ν_{max} 2950 (CH aliphatic), 1720 cm^{-1} (C=O). NMR (DMSO-d_6): δ_H 2.85 (s, 3H, CH_3), 6.90–7.70 (m, 9H, ArH), 7.95 (s, 1H, H-11). Anal. calcd. for $C_{23}H_{13}N_3OS$ (379.44): C, 72.81; H, 3.45; N, 11.07; S, 8.45. Found: C, 73.01; H, 3.47; N, 10.92; S, 8.36%.

Ethyl-3,6-dimethyl-2-phenylpyrido[2',3':4,5]thieno[2,3-d]pyrimidine-7-carboxylate (**6a**): Orange crystals (1.47 g, 81%) from dioxan, m.p. 180–181°C. IR: ν_{max} 2950 (CH aliphatic), 1720 cm^{-1} (C=O). NMR (DMSO-d_6): δ_H 1.50 (t, 3H, J = 7.2 Hz, CH_3), 3.20 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 4.60 (q, 2H, J = 6.8 Hz, CH_2), 7.50–7.90 (m, 5H, ArH), 9.20 (s, 1H, H-8). Anal. calcd. for $C_{20}H_{17}N_3O_2S$ (363.43): C, 66.10; H, 4.71; N, 11.56; S, 8.80. Found: C, 66.26; H, 4.63; N, 11.65; S, 8.68%.

7-Acetyl-3,6-dimethyl-2-phenylpyrido[2',3':4,5]thieno[2,3-d] pyrimidine (**6b**): Orange crystals (1.20 g, 72%) from ethanol, m.p. 212–213°C. IR: ν_{max} 2900 (CH aliphatic), 1720 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): δ_H 2.45 (s, 3H, $COCH_3$), 2.90 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 7.40–7.60 (m, 5H, ArH), 8.20 (s, 1H, H-8). Anal. calcd. for $C_{19}H_{15}N_3OS$ (333.41): C, 68.45; H, 4.53; N, 12.60; S, 9.62. Found: C, 68.58; H, 4.47; N, 12.71; S, 9.56%.

7-Benzoyl-4-methyl-2-phenylpyrido[2',3':4,5]thieno[2,3-d] pyrimidine-6(5H)-one (**6c**): Orange crystals (1.63 g, 77%) from acetic acid, m.p. 205–206°C. IR: ν_{max} 3320 (NH), 2950 (CH aliphatic), 1700 (C=O), 1650 cm^{-1} (C=O). ^{1}H NMR (CF_3COOD): δ_H 3.25 (s, 3H, CH_3), 7.40–8.50 (m, 10H, ArH), 9.60 (s, 1H, H-8). MS: *m/z* (%) 397 (100) [M$^+$]. Anal. calcd. for $C_{23}H_{15}N_3O_2S$ (397.45): C, 69.51; H, 3.80; N, 10.57; S, 8.07. Found: C, 69.42; H, 3.73; N, 10.63; S, 7.89%.

Reaction of **3** *with activated nitriles; preparation of compounds* **7a–d***: General procedure*

A solution containing **3** (1.35 g, 0.005 mol), the appropriate carbonitrile (0.065 mol) and a few drops of piperidine in ethanol (20 ml) was refluxed for 3 h. A solid which separated from the hot mixture was filtered off, washed with ethanol and recrystallised**.**

6-Amino-7-cyano-4-methyl-2-phenylpyrido[2',3':4,5]thieno[2,3-d] pyrimidine (**7a**): From malononitrile, yellow crystals (0.99 g, 62%) from dioxan, m.p. 285–286°C. IR: ν_{max} 3450, 3350 (NH_2), 2220 cm^{-1} (CN). NMR (DMSO-d_6): δ_H 3.40 (s, 3H, CH_3), 6.8 (s, 2H, NH_2), 7.30–7.70 (m, 5H, ArH), 8.30 (s, 1H, H-8). Anal. calcd. for $C_{17}H_{11}N_5S$ (317.37): C, 64.34; H, 3.49; N, 22.07; S, 10.10. Found: C, 64.41; H, 3.42; N, 22.18; S, 9.97%.

6-Amino-4-methyl-2-phenylpyrido[2',3'-4,5]thieno[2,3-d] pyrimidine-7-carboxamide (**7b**): From cyanoacetamide, orange plates (1.37 g, 82%) from acetic acid, m.p. 243–244°C. IR: ν_{max} 3500, 3450, 3300 (NH_2), 1640 cm^{-1} (CO). NMR (DMSO-d_6): δ_H 3.18 (s, 3H, CH_3), 5.60 (s, 2H, NH_2), 6.80 (s, 2H, NH_2), 7.40–7.50 (m, 5H, ArH), 7.85 (s, 1H, H-8). Anal. calcd. for $C_{17}H_{13}N_5OS$ (335.38): C, 60.88; H, 3.91; N, 20.88; S, 9.56. Found: C, 60.69; H, 3.88; N, 20.97; S, 9.64%.

7-Cyano-4-methyl-2-phenylpyrido[2',3'-4,5]thieno[2,3-d] pyrimidine-6(5H)-thione (**8**): From cyanothioacetamide, red crystals (1.15 g, 60%) from acetic acid, m.p. 175–176°C. IR: ν_{max} 3200 (NH), 2230 cm^{-1} (CN). NMR (DMSO-d_6): δ_H 2.95 (s, 3H, CH_3), 7.30–7.60 (m, 5H, ArH), 8.20 (s, 1H, H-8), 9.25 (s, 1H, NH). Anal. calcd. for $C_{17}H_{10}N_4S_2$ (334.41): C, 61.06; H, 3.01; N, 16.75; S, 19.17. Found: C, 61.15; H, 2.97; N, 16.65; S, 19.12%.

Reaction of **3** *with ethyl cyanoacetate. Preparation and separation of compounds* **9** *and* **10**

A mixture of **3** (1.16 g, 4 mmol), ethyl cyanoacetate (4 mmol) and a few drops of piperidine in ethanol (20 ml) was refluxed for 3 h. A precipitate was collected by filtration. First examination (IR spectra and TLC) showed the product to contain two compounds. This mixture was heated in acetic acid and filtered while hot. The solid compound was collected, washed with ethanol and rerystallised from DMF which was shown to be compound **10**. After cooling, the filtrate gave further solid material which was assigned as compound **9**.

Ethyl 6-amino-4-methyl-2-phenylpyrido[2',3':4,5]thieno[2,3-d] pyrimidine-7-carboxylate (**9**): Orange crystals 0.65 g (45%) from acetic acid, m.p. 260–261°C. IR: ν_{max} 3450, 3300 (NH_2), 1700 cm^{-1} (CO). NMR (DMSO-d_6): δ_H 1.30 (t, 3H, J = 7.0 Hz, CH_3), 2.85 (s, 3H, CH_3), 4.30 (q, 2H, J = 6.8 Hz, CH_2), 6.75 (s, 2H, NH_2), 7.40–7.50 (m, 5H, ArH), 8.00 (s, 1H, H-8). Anal. calcd. for $C_{19}H_{16}N_4O_2S$ (364.42): C, 62.62; H, 4.43; N, 15.37; S, 8.80. Found: C, 62.71; H, 4.40; N, 15.41; S, 8.74%.

7-Cyano-4-methyl-2-phenylpyrido[2',3':4,5]thieno[2,3-d] pyrimidine-6(5H)-one (**10**): Yellow crystals (0.27 g 22%) from DMF, m.p. 280–281°C. IR: ν_{max} 3250 (NH), 2220 (CN), 1650 cm^{-1} (C=O). NMR (CF_3COOD): δ_H 3.30 (s, 3H, CH_3), 7.25–7.55 (m, 5H, ArH), 8.30 (s, 1H, H-8). MS: *m/z* (%) 318 (100) [M$^+$]. Anal. calcd. for $C_{17}H_{10}N_4OS$ (318.35): C, 64.14; H, 3.17; N, 17.60; S, 10.07. Found: C, 64.23; H, 3.09; N, 17.71; S, 10.16%.

4-Methyl-2-phenylpyrimido[5'',4'':5',6']pyrido[2',3':4,5]thieno[2,3-d] pyrimidine-7,9(6H,8H)-dithione (**11**): To a solution of **7a** (0.32 g, 0.001 mol) in pyridine (20 ml), carbon disulfide (5 ml) was added. The mixture was refluxed for 24 h. The solid product formed was filtered off, washed several times with ethanol and crystallised from DMF to afford orange crystals (0.35 g (88%), m.p. >300°C. IR: ν_{max} 3340, 3300 cm^{-1} (2NH). NMR (DMSO-d_6): δ_H 2.95 (s, 3H, CH_3), 7.30–7.60 (m, 5H, ArH), 7.70 (s, 1H, H-10), 9.30 (s, 1H, NH), 10.25 (s, 1H, NH). MS: *m/z* (%) 393 (100) [M$^+$]. Anal. calcd. for $C_{18}H_{11}N_5S_3$ (393.50): C, 54.94; H, 2.82; N, 17.80; S, 24.44. Found: C, 55.09; H, 2.79; N, 17.73; S, 24.35%.

4-Methyl-7,9-bis(methylthio)-2-phenylpyrimido[5'',4'':5',6']pyrido [2',3':4,5]thieno[2,3-d]pyrimidine (**12**)**:** A mixture of compound **11** (0.39 g, 0.003 mol), methyl iodide (1.40 g, 0.01 mol) and anhydrous potassium carbonate (0.5 g) in acetone (30 ml) was refluxed 3 h, then allowed to cool, and poured into cold water. The solid product was collected, washed thoroughly with water, dried and recrystallised from ethanol to give yellow crystals, m.p. 270–271°C, yield 0.88 g (70%). IR: ν_{max} 2980 cm^{-1} (CH-aliphatic). NMR (DMSO-d_6): δ_H 2.78 (s, 6H, 2CH_3), 3.10 (s, 3H, CH_3), 7.30–7.60 (m, 5H, ArH), 7.90 (s, 1H, H-10). Anal. calcd. for $C_{20}H_{15}N_5S_3$ (421.55): C, 56.98; H, 3.59; N, 16.61; S, 22.82. Found: C, 56.89; H, 3.62; N, 16.49; S, 22.89%.

7-Cyano-6-(ethoxymethyleneamino)-4-methyl-2-phenylpyrido [2',3'-4,5]thieno[2,3-d]pyrimidine (**13**): A mixture of *o*-aminonitrile **7a** (0.95 g, 0.003 mol), triethylorthoformate (5 ml) and acetic anhydride (5 ml) was refluxed for 6 h. The solvent was removed under reduced pressure and the resulting solid was recrystallised from dioxan to give white plates (0.89 g, 79%), m.p. 195–196°C. IR: ν_{max} 2980 (CH-aliphatic), 2220 cm^{-1} (CN). NMR (DMSO-d_6): δ_H 1.25 (t, 3H J = 6.8 Hz, CH_3), 3.55 (s, 3H, CH_3), 4.20 (q, 2H, J = 7.2 Hz, CH_2), 7.30–7.60 (m, 5H, ArH), 8.25 (s, 1H, H-8), 8.75 (s, 1H, N=CH). Anal. calcd. for $C_{20}H_{15}N_5OS$ (373.43): C, 64.33; H, 4.05; N, 18.75;

S, 8.59. Found: C, 64.40; H, 3.98; N, 18.67; S, 8.61%.

8-Amino-9-imino-4-methyl-2-phenylpyrimido[5'',4'':5',6']pyrido [2',3':4,5]thieno[2,3-d]pyrimidine (**14**): To a well stirred cold solution of **12** (0.75 g, 0.002 mol) in ethanol (10 ml), 99% hydrazine hydrate (3 ml) was added over 2 h, then the mixture was stirred at room temperature for 6 h and left overnight. The solid that precipitated was filtered off and recrystallised from acetic acid to give yellow crystals (0.55 g, 77%), m.p. 305–306°C. IR: ν_{max} 3350, 3200 (NH, NH_2), 2980 cm^{-1} (CH-aliphatic). NMR (DMSO-d_6): δ_H 3.10 (s, 3H, CH_3), 7.45–7.70 (m, 5H, ArH), 8.00 (s, 1H, H-7 pyrimidine), 8.78 (s, 1H, H-10), 9.35 (m, 3H, $NHNH_2$). MS: *m/z* (%) 359 (74) [M^+]. Anal. calcd. for $C_{18}H_{13}N_7S$ (359.41): C, 60.15; H, 3.65; N, 27.28; S, 8.92. Found: C, 60.22; H, 3.70; N, 27.34; S, 8.90%.

Received 8 October 2007; accepted 14 December 2007
Paper 07/4874 doi: 10.3184/030823407X269961

References

1 P. Caluwe, *Tetrahedron*, 1980, **36**, 2359.
2 D.E. Thurston, D.R. Murty, D.R. Langlely and G.B. Jones, *Synthesis*, 1990, 81.
3 D. Tomasik, P. Tomasik and R.A. Abramovitch, *J. Heterocycl. Chem*., 1980, **20**, 1539.
4 B.Y. Riad, S.E. Negm and H.A. Daboun, *Heterocycles*, 1987, **26**, 205.
5 C.T. Alabaster, A.S. Bell, S.F. Campbell, P. Ellis, C.G. Henderson, D.S. Morris, D.A. Roberts, K.S. Ruddock, G.M.R. Samuels and M.H. Stefaniak, *J. Med.Chem*., 1989, **32**, 575.
6 B. Ralf, P. Runland, L. Dieter, L. Gunter and P. Brigitte, Ger. (East) DD, 234, 268; *Chem. Abstr*., 1986**, 105**, 226 631e.
7 C.G. Dave, P.R. Shah, K.C. Dave and V.J. Patel, *J. Indian Chem. Soc*., 1989**, 66**, 48.
8 E. Bousquet, G. Romero, F. Guerrera, A. Caruso and M.A. Roxas, *Farmaco., Ed. Sci.*, 1985**, 40**, 869.
9 N.N. Kaplina, V.L. Shedov, A.N. Fomina, I.S. Nikolaeva, T.V. Pushkina and L.N. Filitis, *U.S.S.R*. 1993, SUI, 389, 23; *Chem. Abstr.,* 1993, **123**, 27 5971w.
10 S. Leistner, G. Wagner, M. Guetscharo and E. Glusa, *Pharmazie*, 1986**, 41**, 54.
11 M. Modica, M. Santagati, A. Santagati, V. Cutuli, N. Mangano and A. Caruso, *Pharmazie*, 2000, **55**, 500.
12 Z.H. Khalil, A.S. Yanni, A.M. Gaber and S.A. Abdel-Mohsen, *Phosphorus, Sulfur Silicon*, 2000, **166**, 57.
13 A.M. Kamal El-Dean, A.A. Geies, H.S. El-Kashef, S. Rault, P. D'Allemagne and J.C. Lancelot, *J. Heterocycl. Chem.,* 2000**, 37***,* 1520.
14 P. Friedländer, *Org. Reactions*, 1982**, 28**, 37.
15 A.M. Kamal El-Dean, *Monash. Chem.,* 1998**, 129**, 523.

MWI-promoted preparation of 4*H*-thiopyran derivatives through one-pot multi-component reactions

Xuesen Fan*, Xia Wang, Xinying Zhang, Xiaoyan Li and Guirong Qu

School of Chemical and Environmental Sciences, Henan Key Laboratory for Environmental Pollution Control, Henan Normal University, Xinxiang, Henan 453007, P.R. China

One-pot reaction of aromatic aldehydes, cyanothioacetamide and malononitrile under microwave irradiation proved to be an efficient way for the synthesis of 2,6-diamino-4-aryl-4*H*-thiopyran-3,5-dicarbonitriles without any added catalyst.

Keywords: microwave heating, thioamides, malononitrile, 4*H*-thiopyrans, multi-component reactions

Recently thiopyran derivatives have gained increasing attention due to their importance as key units in medicinal chemistry and as versatile building blocks in organic synthesis,[1] for example, thiopyrans have been used in the construction of analogues of natural products, such as tetrahydrodicranenone B,[2] serricornin,[3] thromoboxanes,[4] and cyclopentanoids.[5] In view of these points, a great deal of effort has been devoted to developing new and efficient synthetic routes to thiopyrans.[6] However, many of these reported procedures are not fully satisfactory with regard to the cost of the reagents, using of strong basic catalyst, low isolated yield, or long reaction times. Therefore, development of novel methods for the preparation of the above mentioned compounds continues to be an interesting field of research in both synthetic and medicinal chemistry.

Multi-component reactions (MCRs) have recently emerged as valuable tools in the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds.[7] In line with the increasing interest in the preparation of large heterocyclic compound libraries, the development of new and synthetically valuable multi-component reactions remains a challenge for both academic and industrial research teams.[8] Furthermore, the utility of microwave energy in synthetic organic chemistry has been increasingly recognised in recent years since microwave irradiation (MWI) promoted reactions possess advantages such as an environmentally friendly nature, improved selectivity, enhanced reaction rate and cleaner products. Therefore, MWI-mediated multi-component reactions have constituted an especially attractive synthetic strategy for rapid and efficient library generation.[9] In the past few years we have been involved in a program aimed at developing efficient and green synthetic methods for the preparation of several classes of important heterocyclic compounds from inexpensive starting materials. During this phase of our research, we recently reported an efficient preparative procedure for benzopyran derivatives from chalcones and 1,3-cyclohexanedione in the presence of $InCl_3.4H_2O$ under MWI.[10] We have also reported a multi-component reaction of aldehydes, malononitrile and 1,3-diones to give pyran derivatives in ionic liquid medium without any added catalysts.[11] In continuation of our research interests in this field, we report here results of our investigation that enable the preparation of thiopyrans (**4**) from aromatic aldehyde (**1**), malononitrile (**2**) and cyanothioacetamide (**3**) under MWI without any added catalyst (Scheme 1).

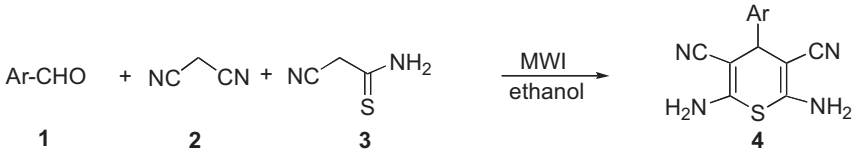
Results and discussion

Initially, the reaction of benzaldehyde (**1a**), malononitrile (**2**) and cyanothioacetamide (**3**) was examined.

A mixture of **1a** (0.5 mmol), **2** (0.5 mmol) and **3** (0.5 mmol) in 5 ml ethanol was put into a commercially available single-mode microwave synthesis apparatus equipped with a high sensitivity IR sensor for temperature control and measurement and irradiated at 250 W (internal temperature 80°C). TLC analysis showed that the reaction thus mediated under MWI came to a conclusion in 15 min. The solid formed was collected by suction. Spectra data of IR, ^{1}H NMR and ^{13}C NMR together with MS results indicated that the product was **4a** in a yield of 85%.

With the above result in hand, we then began the search for the scope of the aldehyde substrate (Scheme 1). The results shown in Table 1 indicated that aromatic aldehydes bearing either electron-donating or electron-withdrawing functional groups such as nitro, chloro, fluoro, bromo, hydroxyl or methoxy groups were able to take part in the reactions forming compounds **4**. At the same time, the electronic property and the position of the substituents on the aromatic ring of the aldehydes have obvious effects on the outcome of the condensation process. In general, shorter reaction times were needed and higher yields were obtained with substrates bearing electron-withdrawing groups on the *para*- or *meta*-position of the aromatic rings (Table 1, entries 2, 4, 7 and 9). On the other hand, while substrates bearing electron-donating groups or groups on the *ortho*-position can afford the corresponding products with good yields, a longer reaction period was necessary to complete the reaction (Table 1, entries 3, 6, 8 and 10) and the yields are somewhat lower. Aliphatic aldehydes including valeraldehyde and hexanal were also tried as substrates. However, the reactions were complicated and gave unidentified mixtures of products.

Although there are several reports of the preparation of this kind of compound, they are usually *via* the reaction of arylidenemalononitrile with 2-cyanothioacetamide in the presence of *N*-methylmorpholine or other basic promoters



1 2 3 4

Scheme 1

* Correspondent. E-mail: xuesen.fan@yahoo.com

Table 1 Preparation of thiopyrans under MWI

Entry	Ar	Reaction time/min)	Product	Yield/%[a]	M.p./°C
1	C_6H_5	15	**4a**	85	185–186 (181–183)[12]
2	*p*-$NO_2C_6H_4$	5	**4b**	91	198–200 (202–204)[13]
3	*o*-$NO_2C_6H_4$	10	**4c**	82	164–165
4	*m*-$NO_2C_6H_4$	8	**4d**	90	210–211
5	*p*-ClC_6H_4	12	**4e**	82	188–189 (189–190)[12]
6	*o*-ClC_6H_4	16	**4f**	75	168–170
7	*p*-BrC_6H_4	10	**4g**	85	187–188 (183) [12]
8	*o*-BrC_6H_4	16	**4h**	76	174–174.5
9	*p*-FC_6H_4	12	**4i**	88	172–172.5 (166–167)[12]
10	*o*-FC_6H_4	15	**4j**	78	181–183 (163–165)[14]
11	4-OH-3-$CH_3OC_6H_3$	18	**4k**	70	170–171

[a]Isolated yields based on aldehyde.

with reaction times of several hours. It is to say that not only are tedious preparative procedures unavoidable in that arylidenemalononitriles need to be prepared in advance from aldehydes and malononitrile, but also undesired products may be formed since the strongly basic conditions employed may be incompatible with functionalities embedded in the substrates. In contrast, with our method, thiopyrans were prepared from commercially available materials and the preparative procedure is usually complete in 5–18 minutes without any added catalysts.

In conclusion, we have developed an efficient MWI-promoted one-pot preparation of thiopyrans from aromatic aldehydes, malononitrile and cyanothioacetamide. The method has the advantages of high efficiency and preparative simplicity. Further efforts to find more applications of MWI-mediated multicomponent reactions are currently in progress in our laboratory.

Experimental

Melting points were measured by a Kofler micro-melting point apparatus. Infrared spectra were recorded on a Bruker Vector 22 spectrometer in KBr discs. ^{1}H NMR spectra were determined on a Bruker AC 400 spectrometer as DMSO-d_6 or CD_3OD solutions. Chemical shifts are reported in ppm downfield from the internal standard tetramethylsilane. Mass spectra were obtained in ESI mode using a Bruker Esquire 3000 mass spectrometer. Elemental analyses were performed on an EA-1110 instrument.

The microwave irradiations were performed in a commercially available single-mode microwave synthesis apparatus equipped with a high sensitivity infrared sensor for temperature control and measurement (MAS-I, Sineo Microwave Chemical Technology Co. Ltd., Shanghai, P.R. China).

Preparation of thiopyran derivatives **4**: *general procedure*
The aromatic aldehyde (**1**, 1 mmol), malononitrile (**2**, 0.066 g, 1 mmol) cyanothioacetamide (**3**, 0.10 g, 1 mmol) and ethanol (5 ml) were mixed in a flask and irradiated at 250 W (internal temperature 80°C) for a sufficient time as required to complete the reaction (monitored by TLC). Upon completion, the reaction mixture was allowed to cool to room temperature and the solid product was collected by filtration and washed with 95% ethanol to give the desired products **4** (Table 1). All the new products were fully characterised by IR, ^{1}H and ^{13}C NMR, MS and elemental analysis.

2,6-Diamino-4-phenyl-4H-thiopyran-3,5-dicarbonitrile (**4a**): IR: ν_{max} 3450, 3320, 2210 cm^{-1}. NMR (DMSO-d_6): δ_H 4.22 (s, 1H, CH), 6.89 (br s, 4H, 2 NH_2), 7.19–7.24 (m, 3H, ArH), 7.30–7.33 (m, 2H, ArH); δ_C 151.3, 143.55, 128.8, 127.2, 126.7, 118.9, 72.1, 43.4. MS (ESI): *m/z* 277 $[M + Na]^+$.

2,6-Diamino-4-(4-nitrophenyl)-4H-thiopyran-3,5-dicarbonitrile (**4b**): IR: ν_{max} 3410, 3315, 2220 cm^{-1}. NMR (CD_3OD): δ_H 4.47 (s, 1H, CH), 7.53 (d, 2H, *J* = 8.0 Hz, ArH), 8.20 (d, 2H, *J* = 8.0 Hz, ArH); δ_C 152.1, 149.5, 146.8, 127.3, 123.2, 117.5, 71.65, 43.2. MS (ESI): *m/z* 322 $[M + Na]^+$.

2,6-Diamino-4-(2-nitrophenyl)-4H-thiopyran-3,5-dicarbonitrile (**4c**): IR: ν_{max} 3400, 3320, 2210 cm^{-1}. NMR (DMSO-d_6): δ_H 4.97 (s, 1H, CH), 7.04 (br s, 4H, 2 NH_2), 7.48–7.55 (m, 2H, ArH), 7.69–7.73 (t, 1H, ArH, *J* = 7.6 Hz), 7.84–7.86 (d, 1H, ArH, *J* = 8.0 Hz); δ_C 151.7, 148.3, 137.6, 133.85, 130.0, 128.8, 124.4, 118.1, 70.7, 37.9. MS (ESI): *m/z* 322 $[M + Na]^+$. Anal. Calcd for $C_{13}H_9N_5O_2S$: C 52.17, H 3.03, N 23.40; found: C 52.20, H 3.18, N 23.29%.

2,6-Diamino-4-(3-nitrophenyl)-4H-thiopyran-3,5-dicarbonitrile (**4d**): IR: ν_{max} 3440, 3325, 2200 cm^{-1}. NMR (DMSO-d_6): δ_H 4.55 (s,1H,CH), 7.06 (br s, 4H, 2 NH_2), 7.65–7.70 (m, 2H, ArH), 8.04 (s, 1H, ArH), 8.10–8.13 (m, 2H, ArH); δ_C 152.05, 148.1, 145.8, 133.6, 130.5, 122.3, 121.1, 118.6, 71.05, 42.5. MS (ESI): *m/z* 322 $[M + Na]^+$. Anal. Calcd for $C_{13}H_9N_5O_2S$: C 52.17, H 3.03, N 23.40; found: C 52.20, H 3.22, N 23.50%.

2,6-Diamino-4-(4-chlorophenyl)-4H-thiopyran-3,5-dicarbonitrile (**4e**): IR: ν_{max} 3460, 3320, 2200 cm^{-1}. NMR (DMSO-d_6): δ_H 4.28 (s, 1H, CH), 6.93 (br s, 4H, 2 NH_2), 7.21 (d, 2H, *J* = 8.4 Hz, ArH), 7.38 (d, 2H, *J* = 8.4 Hz, ArH); δ_C 151.4, 142.5, 131.8, 128.75, 128.6, 118.7, 71.7, 42.7. MS (ESI): *m/z* 311 $[M + Na]^+$.

2,6-Diamino-4-(2-chlorophenyl)-4H-thiopyran-3,5-dicarbonitrile (**4f**): IR: ν_{max} 3480, 3320, 2200 cm^{-1}. NMR (DMSO-d_6): δ_H 4.76 (s, 1H, CH), 6.95 (br s, 4H, 2 NH_2), 7.23–7.41 (m, 4H, ArH); δ_C 151.4, 140.9, 131.65, 129.8, 129.7, 129.1, 128.0, 118.3, 71.0, 42.65. MS (ESI): *m/z* 311 $[M + Na]^+$. Anal. Calcd for $C_{13}H_9ClN_4S$: C 54.07, H 3.14, N 19.40; found: C 54.15, H 3.25, N 19.48%.

2,6-Diamino-4-(4-bromophenyl)-4H-thiopyran-3,5-dicarbonitrile (**4g**): IR: ν_{max} 3460, 3330, 2210 cm^{-1}. NMR (DMSO-d_6) δ: 4.26 (s, 1H, CH), 6.49 (br s, 4H, 2 NH_2), 7.15 (d, 2H, *J* = 8.0 Hz, ArH), 7.52 (d, 2H, *J* = 8.0 Hz, ArH), ^{13}C NMR (DMSO-d_6) δ 151.4, 142.9, 131.7, 129.0, 120.3, 118.7, 71.6, 42.7. MS (ESI): m/z 355, 357 $[M + Na]^+$.

2,6-Diamino-4-(2-bromophenyl)-4H-thiopyran-3,5-dicarbonitrile (**4h**): IR: ν_{max} 3450, 3330, 2220 cm^{-1}. NMR (DMSO-d_6): δ_H 4.78 (s, 1H, CH), 6.94 (br s, 4H, 2 NH_2), 7.15–7.19 (m, 1H, ArH), 7.34–7.37 (m, 2H, ArH), 7.55–7.59 (m,1H, ArH); δ_C 151.0, 142.9, 132.8, 129.95, 129.4, 128.7, 118.2, 71.2, 42.4. MS (ESI): *m/z* 355, 357 $[M + Na]^+$. Anal. Calcd for $C_{13}H_9BrN_4S$: C 46.86, H 2.72, N 16.81; found: C 46.98, H 2.65, N 16.88%.

2,6-Diamino-4-(4-fluorophenyl)-4H-thiopyran-3,5-dicarbonitrile (**4i**): IR: ν_{max} 3450, 3325, 2200 cm^{-1}. NMR (DMSO-d_6): δ_H 4.27 (s, 1H, CH), 6.91 (br s, 4H, 2 NH_2), 7.12–7.24 (m, 4H, ArH); δ_C 151.3, 139.55, 128.7, 128.6, 118.75,115.6, 115.4, 72.0, 42.4. MS (ESI): *m/z* 295 $[M + Na]^+$.

2,6-Diamino-4-(2-fluorophenyl)-4H-thiopyran-3,5-dicarbonitrile (**4j**): IR: ν_{max} 3440, 3325, 2200 cm^{-1}. NMR (DMSO-d_6): δ_H 4.52 (s, 1H, CH), 6.95 (br s, 4H, 2 NH_2), 7.14–7.32 (m, 4H, ArH); δ_C 160.8, 158.4, 152.0, 129.7, 129.6, 129.4, 129.3, 129.0, 129.0, 124.8, 118.45, 115.85, 115.6, 70.7, 37.3. MS (ESI): *m/z* 295 $[M + Na]^+$.

2,6-Diamino-4-(4-hydroxy-3-methoxyphenyl)-4H-thiopyran-3,5-dicarbonitrile (**4k**): IR: ν_{max} 3450, 3310, 2200 cm^{-1}. NMR (DMSO-d_6): δ_H 3.70 (s, 3H, OCH_3), 4.10 (s, 1H, CH), 6.58 (d, 1H, *J* = 8.0 Hz, ArH), 6.68–6.74 (m, 2H, ArH), 6.80 (br s, 4H, 2 NH_2), 8.91 (s, 1H, OH); δ_C 150.8, 147.6, 145.9, 134.5, 119.1, 118.9, 115.6, 111.2, 72.8, 55.7, 43.1. MS (ESI): *m/z* 323 $[M + Na]^+$. Anal. Calcd for $C_{14}H_{12}N_4O_2S$: C 55.99, H 4.03, N 18.65; found: C 56.10, H 4.05, N 18.78%.

We are grateful to the National Natural Science Foundation of China (Project No. 20 772 025).

Received 17 September 2007; accepted 17 December 2007
Paper 07/4839 doi: 10.3184/030823407X270428

References

1 (a) A.H. Ingall, in *Comprehensive Heterocyclic Chemistry* II; A.R. Katritzky, C.W. Rees and E.F.V. Scriven, Eds., Pergamon, Oxford, 1996, **5**, 501; (b) E. Vedejs and G. A. Krafft, *Tetrahedron*, 1982, **38**, 2857.

2 (a) G. Casy and R.J.K. Taylor, *Tetrahedron*, 1989, **45**, 455; (b) G. Casy and R.J.K. Taylor, *J. Chem. Soc., Chem. Commun*., 1988, 454.
3 D.E. Ward, V. Jheengut and G.E. Beye, *J. Org. Chem*., 2006, **71**, 8989.
4 (a) B.P. McDonald, R.W. Steele and J.K. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1988, 675; (b) K.R. Lawson, B.P. McDonald and O.S. Mills, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1397.
5 (a) G.D. McAllister and R.J.K. Taylor, *Tetrahedron Lett*., 2001, **42**, 1197; (b) R.J.K. Taylor, *Chem. Commun*., 1999, 217; (c) H. Matsuyama, S. Fujii, N. Kamigatta, *Heterocycles*, 1991, **32**, 1875.
6 (a) Y.A. Sharanin, V.K. Promonenkov, A.M. Shestopalov, V.N. Nesterov, S.N. Malenchuk, V.E. Shklover and Y.T. Struchkov, *Zh. Org. Khim*., 1989, **25**, 622; (b) V.D. Dyachenko, S.G. Krivokolysko and V.P. Litvinov, *Chem. Heterocycl. Compd*., 1996, **32**, 947; (c) M.G. Barthakur, A. Chetia and R.C. Boruah, *Tetrahedron Lett*., 2006, **47**, 4925; (d) V.D. Dyachenko, *Russ. J. Gen. Chem*., 2005, **75**, 1537. (e) X.H. Bi, D.W. Du and Y. Li, *J. Org. Chem*., 2005, **70**, 10 886; (f) T. Saito, K. Takekawa and T. Takahashi, *Chem. Commun*. 1999, 1001.
7 (a) L.F. Tietze and A. Modi, *Med. Res. Rev*. 2000, **20**, 304; (b) I. Ugi, A. Domling and B. Werner, *J. Heterocycl. Chem*., 2000, **37**, 647; (c) R.V.A. Orru and M. Greef, *Synthesis*, 2003, 1471; (d) A. Domling and I. Ugi, *Angew. Chem. Int. Ed*., 2000, **39**, 3168.
8 (a) L. Weber, K. Illgen and M. Almstetter, *Synlett*, 1999, 366; (b) H. Bienayme, C. Hulme, G. Oddon and P. Schmitt, *Chem. Eur. J*., 2000, **6**, 3321.
9 (a) A. Loupy, *Microwaves in Organic Synthesis*; Wiley-VCH, Weinheim, 2002, p. 147; (b) R.S. Varma, *Green Chem*., 1999, **1**, 43; (c) C.O. Kappe, *Angew. Chem. Int. Ed*., 2004, **43**, 6250; (d) P. Lidstrom, J. Tierney and B. Wathey, *Tetrahedron*, 2001, **57**, 9225.
10 X.Y. Hu, X.S. Fan, X.Y. Zhang and G.R. Qu, *Can. J. Chem.*, 2006, **84**, 1054.
11 X.S. Fan, X.Y. Hu, X.Y. Zhang and J.J. Wang, *Aust. J. Chem.,* 2004, **57**, 1067.
12 Yu.A. Sharanin, A.M. Shestopalov, V.N. Nesterov, S.N. Melenchuk, V.K. Promonenkov, V.E. Shklover, Yu.T. Struchkov and V.P. Litvinov, *Zh. Org. Khim*., 1989, **25**, 1323.
13 J.M. Quintela, M.J. Moreira and C. Peinador, *Heterocycles*, 2000, **52**, 333.
14 V.D. Dyachenko, S.G. Krivokolysko, Yu.A. Sharanin and V.P. Litvinov, *Russ. J. Org. Chem*., 1997, **33**, 1014.

Phosphotungstic acid catalysed synthesis of β-enamino compounds under solvent-free conditions

Geng-Chen Li*

School of Material Science and Engineering, Shijiazhuang Railway Institute, Shijiazhuang 050043, China

A convenient eco-friendly procedure has been developed for the synthesis of β-enaminones and β-enamino esters by reacting 1,3-dicarbonyl compounds with amines in the presence of catalytic amounts of phosphotungstic acid ($H_3PW_{12}O_{40}$, 1 mol%). The reaction proceeds smoothly at room temperature under solvent-free conditions and gives the corresponding β-enamino compounds in high to excellent yields.

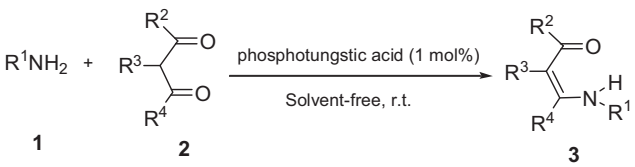
Keyword: 1,3-dicarbonyl compounds, amines, enaminones, enamino esters, phosphotungstic acid, solvent-free conditions

Recently, the use of solid acids as heterogeneous catalysts has attracted much attention and has become an area of active studyin chemistry.[1,2] As part of these studies, the use of heteropoly acids (HPAs) which are strong acids, harmless to the environment and highly stable toward humidity and have flexibility in modifying the acid strength has found attention.[3-7] HPAs are green and are efficient bifunctional catalysts. Their acidity is significantly higher than that of traditional mineral acids and inorganic acids. Furthermore, HPAs are capable of protonating and activating some substrate.[8] In particular, the Keggin-type HPAs such as $H_3PW_{12}O_{40}$ (PW), $H_3PMo_{12}O_{40}$ (PMo) or $H_4SiW_{12}O_{40}$ (SiW) are the most efficient catalysts for a variety of catalytic processes for industrial application.[9] PW is considered to be the strongest heteropoly acid in the Keggin series. It has been reported to be an efficient catalyst for many important organic transformations, including the intramolecular rearrangement of benzyl phenyl ether to 2-benzyl phenol,[9] the Beckmann rearrangement,[10] the Fries rearrangement,[11] the synthesis of 1,1-diacetates,[12] β-acetamido ketones,[13] diaryl sulfoxides,[14] diisobornyl ether,[15] 1,3-dioxolane derivatives,[16] 5-alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2-ones,[17] quinaldines and lepidines,[18] the diacetal of pentaerythritol,[19] 3,4-dihydropyrimidin-2(1H)-ones[20] and α-amino phosphonates.[21] It also catalyses the *N*-*t*-butoxycarbonylation of amines,[22] the chemoselective oxathioacetalisation of carbonyl compounds,[23] trimethylcyanosilylation reactions of aldehydes and ketones,[24] and the Michael addition reaction of thiols to α,β-unsaturated ketones.[25]

β-Enamino compounds have been extensively used as intermediates in organic synthesis.[26-29] In particular, they have been utilised as synthons for the synthesis of various biologically active heterocyclic compounds having anti-inflammatory, antitumor, antibacterial, and anticonvulsant activities[30-31] and as intermediates for the preparation of β-enaminoacids, γ-enaminoaclohols, and β-enamino esters.[32] Due to its wide range of utility in the pharmaceutical industry, the enamination of β-dicarbonyl compounds with various amines has become an important transformation and consequently several methods have been developed for the synthesis of these compounds. Among them, the most simple and straightforward conventional method is the azeotropic removal of water by refluxing an amine and 1,3-dicarbonyl compounds in an aromatic solvent.[33] Several improved procedures have been subsequently reported using catalyst systems, including the use of protic acids,[34] Lewis acids such as $Zn(ClO_4)_2·6H_2O$,[35] $CeCl_3·7H_2O$,[36] $NaAuCl_4$,[37] $Bi(OTf)_3$,[38] $InBr_3$,[32] $CoCl_2·6H_2O$,[39] CAN,[40-41] $Yb(OTf)_3$,[42,43] $SnCl_4·5H_2O$,[44] $ZrCl_4$,[45] $ZrOCl_2·8H_2O$,[46] $Zn(Ac)_2·2H_2O$[47] and $Sc(OTf)_3$,[48] I_2,[49] and solid acids such as montmorillonite K10,[50] silica chloride,[51] silica gel,[52] natural clays,[53] and sulfated zirconia.[54] Recently, $[EtNH_3]NO_3$,[55] and $HClO_4·SiO_2$[56] have also been used to promote this transformation. However, some of these methodologies have not been entirely satisfactory, with disadvantages such as low yields, prolonged reaction time, harsh reaction conditions, use of harmful organic solvents, and a requirement of an excess of the catalysts and of special apparatus. Thus, the development an efficient, practical and environmentally benign synthetic method to overcome the limitations is still an important experimental challenge. Herein, we wish to report a novel and high yielding solvent-free method for the preparation of β-enamino compounds using a catalytic amount of phosphotungstic acid (Scheme 1).

We initially studied the reaction of aniline and ethyl acetoacetate as a benchmark reaction in the presence of 1 mol% of PW at room temperature under solvent-free conditions. To our delight, the reaction occurred to afford ethyl 3-(phenylamino)but-2-enoate (**3f**) in 95% yield when the reaction mixture was allowed to stir for 45 min (Table 1, entry **f**). Further studies established that 1 mol% of catalyst was necessary to promote this reaction. In the absence of catalyst, the model reaction was run and only 30% of the product could be obtained even with stirring for 24 h (Table 1, entry **g**). An increase in the amount of PW to more than 1 mol% showed no substantial improvement in the yield, whereas the yield was reduced by decreasing the amount of PW to 0.1 mol%. Reactions in solvents such as acetonitrile, tetrahydrofuran, ethanol, dichloromethane, ethyl acetoacetate and dimethylformamide gave lower yields of the desired product even at prolonged reaction times. So, we choose the reaction to be proceeded under solvent-free conditions.

Having established the optimised experimental conditions, the scope of the reaction was then explored and several representative results are summarised in Table 1. As shown in Table 1, the present methodology worked efficiently with a wide variety of substrates. In general, primary and benzylic amines reacted with a broad range of structurally diverse 1,3-dicarbonyl compounds to afford the corresponding β-enaminones or β-enamino esters in high yields in short times. However, anilines with an electron-withdrawing group (**1l** and **1y**) retarded the progress of reaction and afforded low yields of the products. It was also found that the substituted groups (**1h** and **1w**) on the *ortho* position in the aniline influenced the reaction rates. Moreover, the optically active (*R*)-(+)-α-methyl benzyl amine (**1d**) was converted into the



Scheme 1

* Correspondent. E-mail: gengchenli@sina.com.cn

Table 1 Synthesis of β-enaminones and β-enamino esters catalysed by phosphotungstic acid

Entry	R^1	R^2	R^3	R^4	Time/min	Yield/%[a]	Ref.
a	$CH_3(CH_2)_3$	OMe	H	Me	15	93	39
b	C_6H_{11}	OEt	H	Me	15	92	39
c	$H_2C{=}CHCH_2$	OMe	H	Me	15	91	39
d	(*R*)-PhCH(CH_3)	OMe	H	Me	15	90	39
e	$PhCH_2$	OEt	H	Me	18	92	19
f	Ph	OEt	H	Me	45	95	39
g	Ph	OEt	H	Me	24 h	30[b]	39
h	2-Me–C_6H_4	OMe	H	Me	60	94	54
i	4-Me–C_6H_4	OEt	H	Me	40	93	40
j	4-OEt–C_6H_4	OEt	H	Me	40	93	39
k	4-^{i}Pr–C_6H_4	OEt	H	Me	40	91	
l	4-Br–C_6H_4	OEt	H	Me	360	72	45
m	$PhCH_2$	OCH_2CH_2	Me	30	90	54	
n	Ph	OCH_2CH_2	Me	75	91	54	
o	4-OMe–C_6H_4	OCH_2CH_2	Me	60	92	39	
p	Ph	OEt	$(CH_2)_3$	90	93	39	
q	4-OMe–C_6H_4	OEt	$(CH_2)_3$	90	92	54	
r	$CH_3(CH_2)_3$	Me	H	Me	15	94	54
s	$H_2C{=}CHCH_2$	Me	H	Me	15	93	39
t	$H_2NCH_2CH_2CH_2$	Me	H	Me	15	95[c]	39
u	$PhCH_2CH_2$	Me	H	Me	15	92	39
v	Ph	Me	H	Me	15	95	54
w	2-Me–C_6H_4	Me	H	Me	20	92	54
x	4-Me–C_6H_4	Me	H	Me	12	95	54
y	2-Br–C_6H_4	Me	H	Me	480	80	54
z	Ph	Ph	H	Me	120	78	54
aa	4-OEt–C_6H_4	Ph	H	Me	120	82	

[a]Yield refer to isolated products, products were characterised by IR, ^{1}H NMR and elemental analysis.
[b]No catalyst.
[c]Two equivalents of acetylacetone were used.

corresponding β-enaminoester (**3d**) without any racemisation or inversion confirmed by measuring **3d**'s optical rotation. When 1,3-diaminopropane (**1t**) was used, two equivalents of acetylacetone were used and the product was formed with two enaminone groups (**3t**). It should be pointed out that when 1,3-diketones with two different substituents, such as 1-benzoylacetone, reacted with amines the regioselective amination of the aliphatic carbonyl group (**2z** and **2aa**) was observed. From linear 1,3-diketones and 1,3-ketoesters we always obtained the corresponding β-enaminones and β-enamino esters having a (*Z*)-configuration of the carbon-carbon double bond due to the formation of intramolecular hydrogen bonding between oxygen atom of carbonyl and NH reside, as determined by ^{1}H NMR analysis ($\delta_H > 8.2$ for NH) and comparison with the chemical shifts of vinylic protons of similar *Z*-enaminones.[32]

Recycling of the catalyst was also investigated. After completion of the benchmark reaction, the catalyst was filtered off, washed with diethyl ether and activated at 100°C for 2 h and reused in another reaction with the same substrates. There was no significant change in the activity after two cycles (95, 93 and 90% of product after three runs).

In order to show the merit of phosphotungstic acid in comparison with other recently reported catalysts for the synthesis of **3f** as a model reaction, we have tabulated some of results in Table 2. It is clear from Table 2, that phosphotungstic acid is an equally efficient but a much cheaper and reusable catalyst.

In summary, an environmentally friendly procedure for the synthesis of β-enaminones and β-enamino esters through phosphotungstic acid–catalysed condensation of 1,3-dicarbonyl compounds and amines has been developed. This method has several unique merits, such as simple experimental procedure, solvent-free conditions, short reaction times, high yields of products and chemo- and stereoselectivities. In addition, the catalyst can be easily recovered and reused, providing thereby eco-friendly and economic advantages over previously reported protocols and rendering this methodology highly suitable for industrial applications.

Experimental

IR spectra were obtained as KBr pellets for samples solid and as thin films for liquid samples with a Thermo Nicolet FT-IR200 spectrometer. NMR spectra were recorded on a Bruker AV 300 spectrometer in $CDCl_3$ using TMS as an internal standard. The melting points are uncorrected and were recorded on a WRR melting point instrument. Elemental analyses were performed on a PE 2400 CHNS/O Analyser.

General procedure for the synthesis of β-*enaminones or* β-*enamino esters*: A mixture of ethyl acetoacetate (1.30 g, 10 mmol) with aniline (0.93 g, 10 mmol), and $H_3PW_{12}O_{40}$ (0.29 g, 0.1 mol) was stirred at room temperature. The progress of reaction was followed by TLC. After completion of reaction, as indicated by TLC, the reaction mixture was extracted with diethyl ether (3 × 10 ml) and the catalyst was filtered off. The combined ether extract was treated with saturated sodium bicarbonate and dried over anhydrous Na_2SO_4, concentrated under reduced pressure and the resulting product was purified by silica gel column chromatography (20% ethyl acetate in *n*-hexane as eluent) to afford pure ethyl 3-phenylamino-but-2-enoate (1.95 g, 95%). The filtered catalyst was repeatedly washed with diethyl ether and reused.

Selective spectroscopic and analytical data for AA'XX' systems in ^{1}H NMR $J^* = J_{23} + J_{25}$.

Methyl (R)-3-(1-phenyl-ethylamino)but-2-enoate (**3d**):[39] A colourless liquid, $[\alpha]_D^{20}$: –540 (*c* 1.15, EtOH); IR (neat): 3280, 2973, 2929, 1653, 1608, 1494, 1446, 1378, 1266, 1054, 764, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.52 (d, J = 6.6 Hz, 3H), 1.78 (s, 3H), 3.67 (s, 3H), 4.49 (s, 1H), 4.65 (q, J = 6.6 Hz, 1H), 7.20–7.38 (m, 5H), 9.00 (br s, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 19.7, 25.0, 50.0, 52.9, 82.9, 125.5, 127.2, 128.8, 150.0, 161.6, 180.0. Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.5; H, 7.8; N, 6.5.

Ethyl 3-(4-isopropylphenylamino)but-2-enoate (**3k**): A yellow oil; IR (neat): 3262, 2962, 2932, 1655, 1620, 1519, 1362, 1332, 1278, 1162, 1058, 758, 668 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.28 (t, J = 7.2 Hz, 3H), 1.39 (d, J = 7.2 Hz, 6H), 1.98 (s, 3H), 2.94 (m, 1H) 4.22 (q, J = 7.2 Hz, 2H), 5.12 (s, 1H), 7.02 (m, J^* = 8.4 Hz, 2H), 7.18 (m, J^* = 8.4 Hz, 2H), 10.28 (brs, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 14.5, 20.0, 23.8, 33.5, 58.5, 85.5, 124.4, 126.8, 137.0, 145.6, 159.0, 170.0. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.7; H, 8.45; N, 5.75.

Table 2 Synthesis of ethyl 3-(phenylamino)but-2-enoate (**3f**) in the presence of different catalysts

Catalyst/solvent	Catalyst load	Time	Yield/%	Ref.
$InBr_3$/solvent-free	1 mol%	10 min	94	32
$Zn(ClO_4)_2{\cdot}6H_2O/CH_2Cl_2$	5 mol%	4 h	95	35
$CeCl_3{\cdot}7H_2O$/solvent-free	10 mol%	35 min	76	36
$Bi(OTf)_3/H_2O$	5 mol%	1 h	64	38
$CoCl_2{\cdot}6H_2O$/solvent-free	5 mol%	15 min	95	39
CAN/solvent-free	1 mol%	60 min	92	40
$Yb(OTf)_3$/solvent-free	2 mol%	60 min	95	43
$ZrCl_4$/solvent-free	1 mol%	40	95	45
$ZrOCl_2{\cdot}8H_2O$/solvent-free	2 mol%	50 min	93	46
$Zn(OAc)_2{\cdot}2H_2O/CH_2Cl_2$	5 mol%	2 days	86	47
$Sc(OTf)_3$/solvent-free	5 mol%	60 min	95	48
I_2/solvent-free	20 mol%	3 min	79	49
Silica gel/solvent-free	10 mg	35 h	95	52
Phosphotungstic acid/solvent-free	1 mol%	45 min	95	This work

Ethyl 3-(4-bromophenylamino)-but-2-enoate (**3l**):[45] A pale yellow solid; m.p. 52–53°C. IR (KBr) 3276, 2978, 1648, 1610, 1580, 1480, 1385, 1261, 1169, 854, 790 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.28 (t, J = 7.2 Hz, 3H), 2.00 (s, 3H), 4.16 (q, J = 7.2 Hz, 2H), 4.72 (s, 1H), 6.96 (m, J^* = 8.4 Hz, 2H), 7.45 (m, J^* = 8.4 Hz, 2H), 10.40 (br s, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 14.6, 20.3, 59.0, 118.0, 125.8, 132.3, 138.6, 162.4, 170.5. Anal. Calcd for $C_{12}H_{14}BrNO_2$: C, 50.72; H, 4.97; N, 4.93; Found: C, 50.85; H, 4.8; N, 5.1.

3-(4-Ethoxyphenylamino)-1-phenylbut-2-en-1-one (**3aa**): A yellow solid, m.p. 85–86°C; IR (KBr) 3415, 2980, 1600, 1505, 1475, 1433, 1372, 1322, 820, 745 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ ppm: 1.44 (t, J = 6.9 Hz, 3H), 2.08 (s, 3H), 4.05 (q, J = 6.9 Hz, 2H), 5.88 (s, 1H), 6.80 (m, J^* = 8.7 Hz, 2H), 7.10 (m, J^* = 8.7 Hz, 2H), 7.43–7.93 (m, 5H), 13.00 (br s, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 14.9, 20.3, 63.8, 93.5, 114.9, 126.6, 127.2, 128.2, 130.8, 131.5, 140.0, 157.2, 163.2, 188.5. Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.95; H, 6.8; N, 4.8.

This research was financially supported in part by the Science and Technology Research and Development Programme from Hebei Province (06213507D-2).

Received 26 October 2007; accepted 18 December 2007
Paper 07/4912 doi: 10.3184/030823407X273488

References

1 G. Sartori and R. Maggi, *Chem. Rev*., 2006, **106**, 1077.
2 J.H. Clark, *Acc. Chem. Res*., 2002, **35**, 791.
3 I.V. Kozhevnikov, *Chem. Rev*., 1998, **98**, 171.
4 M. Misono, I. Ono, G. Koyano and A. Aoshima, *Pure Appl. Chem*., 2000, **72**, 1305.
5 M. Misono, *Chem. Commun*., 2001, 1141.
6 I.V. Kozhevnikov, *Catal. Rev*., 1995, **37**, 311.
7 M.N. Timofeeva, *Appl. Catal A: Gen*., 2003, **256**, 19.
8 K. Lan, S. Fen and Z.X. Shan, *Aust. J. Chem*., 2007, **60**, 80.
9 M.H. Bhure, C.V. Rode, R.C. Chikate, N. Patwardhan and S. Patil, *Catal. Commun*., 2007, **8**, 139.
10 R. Maheswari, K. Shanthi, T. Sivakumar and S. Narayanan, *Appl. Catal A: Gen*., **248**, 291 (2003).
11 E.F. Kozhevnikova, J. Quartararo and I.V. Kozhevnikov, *Appl. Catal A: Gen*., 2003, **245**, 69.
12 M.M. Heravi, F. Derikvand and F.F. Bamoharram, *Synth. Commun*., 2006, **36**, 3109.
13 E. Rafiee, F. Torka and M. Joshaghani, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1221.
14 S.V. Bhilare, A.R. Deorukhkar, N.B. Darvatkar, M.S. Rasalkar and M.M. Salunkhe, *J. Mol. Catal. A: Chem*., 2007, **270**, 123.
15 E.J.L. Lana, K.A. da Silva Rocha, I.V. Kozhevnikov and E.V. Gusevskaya, *J. Mol. Catal. A: Chem*., 2006, **243**, 258.
16 J.-Y. He, F.-X. Gao and R.-M. Hua, *Chin. J. Chem*., 2005, **23**, 1275.
17 T.-S. Jin, J.-C. Xiao, Y.-X. Chen and T.-S. Li, *J. Chem. Res. (S)*, 2004, 190.
18 G. Sivaprasad, R. Rajesh and P.T. Perumal, *Tetrahedron Lett*., 2006, **47**, 1783.
19 B.R. Jermy and A. Pandurangan, *Catal. Commun*., 2006, **7**, 921.
20 B.G. Mishra, D. Kumar and V.S. Rao, *Catal. Commun*., 2006, **7**, 457.
21 A. Heydari, H. Hamadi and M. Pourayoubi, *Catal. Commun*., 2007, **8**, 1224.
22 A. Heydari, R.K. Shiroodi, H. Hamadi, M. Esfandyari and M. Pourayoubi, *Tetrahedron Lett*., 2007, **48**, 5865.
23 H. Firouzabadi, N. Iranpoor, A.A. Jafari and M.R. Jafari, *J. Mol. Catal. A: Chem*., **247**, 14 (2006).
24 H. Firouzabadi, N. Iranpoor and A.A. Jafari, *J. Organomet. Chem*., 2005, **690**, 1556.
25 H. Firouzabadi, N. Iranpoor and A.A. Jafari, *Synlett*, 2005, 299.
26 M. Li, W.-S. Guo, L.-R. Wen and H.-Z. Yang, *Chin. J. Org. Chem*., 2006, **26**, 1192.
27 H.M.C. Ferraz and E.R.S. Goncalo, *Quimica Nova*, 2007, **30**, 957.
28 K.M. Al-Zaydi and L.M. Nhari, *Oriental J. Chem*., 2006, **22**, 1.
29 M.A. Al-Shiekh, *Org. Prep. Proced. Int*., 2005, **37**, 223.
30 G. Palmieri and C. Cimarelli, *Arkivoc*, 2006, (**vi**) 104.
31 G. Dannhardt, A. Bauer and U. Nowe, *J. Prakt. Chem*., 1998, **340**, 256.
32 Z.-H. Zhang, L. Yin and Y.-M. Wang, *Adv. Synth. Catal*., 2006, **348**, 184.
33 P.G. Baraldi, D. Simoni and S. Manfredini, *Synthesis*, 1993, 902.
34 D.F. Martin, G.A. Janusonis and B.B. Martin, *J. Am. Chem. Soc*., 1961, **83**, 73.
35 G. Bartoli, M. Bosco, M. Locatelli, E. Marcantoni, P. Melchiorre and L. Sambri, *Synlett*, 2004, 239.
36 M.M. Khodaei, A.R. Khosropour and M. Kookhazadeh, *Synlett*, 2004, 1980.
37 A. Arcadi, G. Bianchi, S. Di Giuseppe and F. Marinelli, *Green Chem*., 2003, **5**, 64.
38 A.R. Khosropour, M.M. Khodaei and M. Kookhazadeh, *Tetrahedron Lett*, **45**, 2004, 1725.
39 Z.-H. Zhang and J.-Y. Hu, *J. Braz. Chem. Soc*., 2006, **17**, 1447.
40 L.-P. Mo, S.-F. Liu and W.-Z. Li, *J. Chin. Chem. Soc*., 2007, **54**, 879.
41 V. Sridharan, C. Avendaño and J.C. Menéndez, *Synlett*, 2007, 881.
42 F. Epifano, S. Genovese and M. Curini, *Tetrahedron Lett.*, 2007, **48**, 2717.
43 R. Varala, S. Nuvula and S.R. Adapa, *Aust. J. Chem*., 2006, **59**, 921.
44 Z.-H. Zhang, Z.-C. Ma and L.-P. Mo, *Indian J. Chem*., 2007, **46B**, 535.
45 J. Lin and L.-F. Zhang, *Monatsh. Chem*., 2007, **138**, 77.
46 Z.-H. Zhang, T.-S. Li and J.-J. Li, *Catal. Commun*., 2007, **8**, 1615.
47 R.K. Vohra, J.-L. Renaud and C. Bruneau, *Collect. Czech. Chem. Commun*., 2005, **70**, 1943.
48 J.S. Yadav, V.N. Kumar, R.S. Rao, A.D. Priyadarshini, P.P. Rao, B.V.S. Reddy and K. Nagaiah, *J. Mol. Catal. A: Chem*., 2006, **256**, 234.
49 S. Gogoi, R. Bhuyan and N.C. Barua, *Synth. Commun*., 2005, **35**, 2811.
50 M.E.F. Braibante, H.T.S. Braibante, A.F. Morel, C.C. Costa and M.G. Lima, *J. Braz. Chem. Soc*., 2006, **17**, 184.
51 A.R. Gholap, N.S. Chakor, T. Daniel, R.J. Lahoti and K.V. Srinivasan, *J. Mol. Catal. A: Chem*., 2006, **245**, 37.
52 Y.-H. Gao, Q.-H. Zhang and J.-X. Xu, *Synth. Commun*., 2004, **34**, 909.
53 F.C. Silva, M.C.B.V. De Souza, V.F. Ferreira, S.J. Sabino and O.A.C. Antunes, *Catal. Commun*., 2004, **5**, 151.
54 Z.-H. Zhang and L.-M. Song, *J. Chem. Res*., 2006, 817.
55 R.S. Bhosale, P.A. Suryawanshi, S.A. Ingle, M.N. Lokhande, S.P. More, S.B. Mane, S.V. Bhosale and R.P. Pawar, *Synlett*, 2006, 933.
56 B. Das, K. Venkateswarlu, A. Majhi, M.R. Reddy, K.N. Reddy, Y.K. Rao, K. Ravikumar and B. Sridhar, *J. Mol. Catal. A: Chem*., 2006, **246**, 276.

2-Acetyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one in the synthesis of heteroannulated carbazoles

Arputharaj Ebenezer Martin and Karnam Jayarampillai Rajendra Prasad*

Department of Chemistry, Bharathiar University, Coimbatore 641 046, Tamil Nadu, India

The reaction of 2,3,4,9-tetrahydro-1*H*-carbazol-1-ones with ethyl acetate yielded 2-acetyl-1-hydroxycarbazole and 2-acetyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one. These were used to prepare isoxazolo- and pyrazolo-fused carbazoles. Mechanisms for the formation of the end products are proposed.

Keywords: fused carbazoles, isoxazoles, pyrazoles, indazoles

Carbazoles are structural subunits found in numerous naturally occurring compounds as well as synthetic materials, and many of them display high pharmacological activity.[1] For example, ellipticine and its analogs in particular have been found to possess promising antitumor[2-8] and anti-HIV[9] activities, which prompted numerous studies into the structure-activity relationships of heteroannulated carbazoles. Efforts have also been invested in developing efficient synthetic avenues to heteroannulated carbazoles and their structurally modified derivatives, and these are well documented.[3,10] As synthetic materials, many carbazoles exhibit photo-reactive, photoconductive and light emitting properties.[11,12] Carbazole has also been recognised as a useful scaffold in anion binding studies.[13] Consequently the syntheses of carbazoles and their characterisation have been a vigorously active area of study.

In our present work, we planned to prepare functionalised carbazoles from 2,3,4,9-tetrahydro-1*H*-carbazol-1-ones and to elucidate the structures of the newly prepared fused systems.

Results and discussion

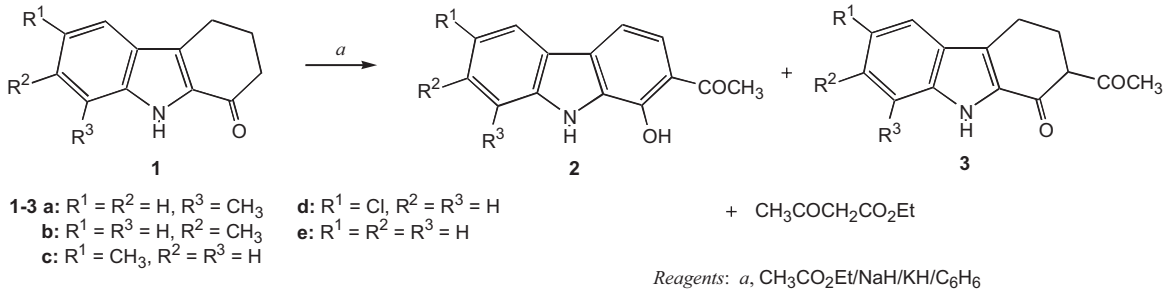
When 8-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**1a**) reacted with ethyl acetate in the presence of sodium hydride and a catalytic amount of potassium hydride as co-reactant, a brown semisolid mass was formed which on separation by column chromatography on silica gel using petroleum ether/ethyl acetate as eluant afforded three products. The first, obtained from the petroleum ether fraction, was simply ethyl acetoacetate. The second fraction, a yellow powder (yield 10%), eluted by petroleum ether/ethyl acetate (98 : 2), melted at 180–182°C, and proved to be the known 2-acetyl-1-hydroxy-8-methylcarbazole (**2a**) (mixed m.p., superimposable IR spectra).[14]

The third product, which was the major component (yield 75%), was obtained from the petroleum ether/ethyl acetate (95 : 5) fraction as a yellow powder, m.p. 129–131°C. Its IR spectrum showed NH stretching at 3308 cm^{-1} and carbonyl bands appeared at 1710 and 1637 cm^{-1}. The ^1H NMR spectrum exhibited a singlet at δ 15.48 for the enolic OH at C1, a one proton broad singlet at δ 8.78 for N9-H, a three proton multiplet between δ 7.29 and 7.04 for C5, C6 and C7 aromatic protons. The aliphatic protons appeared as one proton multiplet between δ 3.74 and 3.67 for C2, two multiplets each for two protons centred at δ 3.00 and 2.65 for C4-H_2 and C3-H_2 respectively, two three-proton singlets at δ 2.49 and 2.35 were assigned to C8-CH_3 and C2-$COCH_3$ respectively. The mass spectrum exhibited the molecular ion peak at *m/z* 241 (43%). The elemental analysis agreed well with the proposed molecular formula $C_{15}H_{15}NO_2$. All the spectral and analytical results were consistent with the product being 2-acetyl-8-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3a**), with the 1-OH enol form a minor tautomeric component. The reaction was performed with other carbazole derivatives **1b–e** in order to realise the respective 2-acetyl-1-hydroxycarbazoles **2b–e** and 2-acetyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-ones **3b–e** (Scheme 1).

It should be noted that the use of potassium hydride as co-reactant proved necessary for the formation of the products. The same reaction without the addition of potassium hydride or using other bases like NaOMe, NaOEt, alc.KOH, pyridine-KOH did not yield the desired products **2** and **3**. The 2-acetyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3**) enolised and this on further aerial oxidation produced the fully aromatised 2-acetyl-1-hydroxy carbazole (**2**). To avoid the concurrent formation of ethyl acetoacetate, we first carried out the reaction of 2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**1**) with ethyl acetate in equimolar ratio. However, the reaction was incomplete and ethyl acetoacetate was still obtained. Therefore we employed an excess of ethyl acetate in the reaction.

In order to achieve the synthesis of heteroannulated carbazoles, we treated the 2-acetyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-ones (**3**) with hydroxylamine hydrochloride, hydrazine hydrate and semicarbazide hydrochloride.

The reaction of 2-acetyl-8-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3a**) with hydroxylamine hydrochloride in glacial acetic acid yielded colourless needles which melted at 198–200°C. Its IR spectrum showed NH stretching at 3372

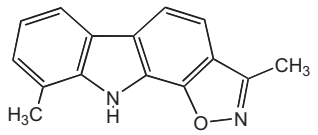


Scheme 1

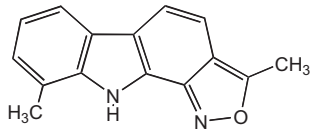
* Correspondent. E-mail: prasad_125@yahoo.com

cm^{-1}. The ^1H NMR spectrum in $CDCl_3$ exhibited a one proton broad singlet at δ 8.63 due to N10-H, a two proton multiplet between δ 8.03 and 7.89 was due to C5- and C6- protons, a one proton doublet (J = 8.20 Hz) at δ 7.45–7.41 was due to C4-H, a two proton multiplet at δ 7.34–7.20 for C7- and C8-H. Two three-proron singlets at δ 2.68 and δ 2.66 were due to C3-and C9-CH_3 respectively. The absence of aliphatic protons for C3- and C4-H_2 indicated that the resulted product was fully aromatised. The ^{13}C NMR spectrum also showed the presence of 15 nonequivalent carbons, and the elemental analysis was in agreement with the molecular formula $C_{15}H_{12}N_2O$. The mass spectrum showed the molecular ion peak at *m/z* 236.

Since the starting material **3a** contained two keto groups and the reaction had taken place at these sites, the spectral and analytical results suggested the structure of the product to be either 3,9-dimethyl-10*H*-isoxazolo[5,4-*a*]carbazole (**4a**) or 3,9-dimethyl-10*H*-isoxazolo[3,4-*a*]carbazole (**4a'**).



4a



4a'

A distinction between these structures was achieved as follows:

(i) Support for structure **4a** was obtained from MM2 energy calculations. The steric energy was calculated for both structures, and that for **4a** was found to be 24.9145 kcal/mol whereas for **4a'** it was found to be 25.1349 kcal/mol. The lower energy structure **4a** was preferred over the higher energy structure **4a'**.

(ii) X-ray crystallographic studies[15] confirmed the structure to be **4a**. The bond lengths of C3a–C10b (1.364 Å) and C3–C3a (1.420 Å) suggested that an aromatic double bond was at C3a–C10b (for a pure double bond 1.34 Å is expected) and this strongly supported the structure of the product as 3,9-dimethyl-10*H*-isoxazolo[5,4-*a*]carbazole (**4a**). The X-ray crystal structure is shown in Fig. 1.

From all the above facts, we assigned the structure of the product as 3,9-dimethyl-10*H*-isoxazolo[5,4-*a*]carbazole (**4a**). This reaction was generalised for other carbazole derivatives (**1b–e**) to form the respective 3-methyl-10*H*-isoxazolo[5,4-*a*] carbazoles (**4b–e**) (Scheme 2).

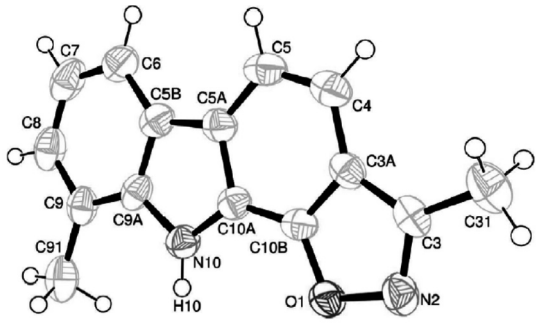


Fig. 1 Crystal structure of 3,9-dimethyl-10*H*-isoxazolo[5,4-*a*] carbazole (**4a**).

The reaction of 2-acetyl-8-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3a**) with hydrazine hydrate in glacial acetic acid yielded a mixture of two products. The products were separated by column chromatography over silica gel using petroleum ether/ethyl acetate as eluant. The major product (yield 75%) obtained from the petroleum ether/ethyl acetate (98 : 2) fraction melted at 142–144°C; Its IR spectrum exhibited NH stretching at 3275 cm^{-1}. The C=N stretching appeared at 1630 cm^{-1}. Its ^1H NMR spectrum in $CDCl_3$ exhibited two broad singlets at δ 12.00 and 11.12 for N1-H and N10-H; four doublets in the aromatic region for C6, C5, C4 and C8-H respectively and a further one-proton multiplet at δ 7.07–7.01 for C7–H, and two singlets at δ 2.55 and 2.49 for C9–CH_3 and C3–CH_3 respectively. The molecular ion peak appeared at *m/z* 235.

Similar to the previous case, this product was also a fully aromatised compound. Conclusive evidence for structure **5a** was obtained from an X-ray crystallographic study (Fig. 2).[16] The product was thus identified as 1,10-dihydro-3,9-dimethyl pyrazolo[3,4-*a*]carbazole (**5a**).

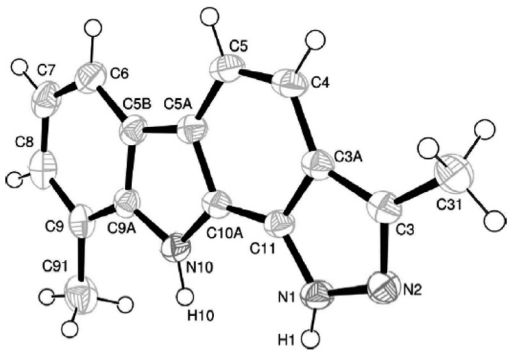
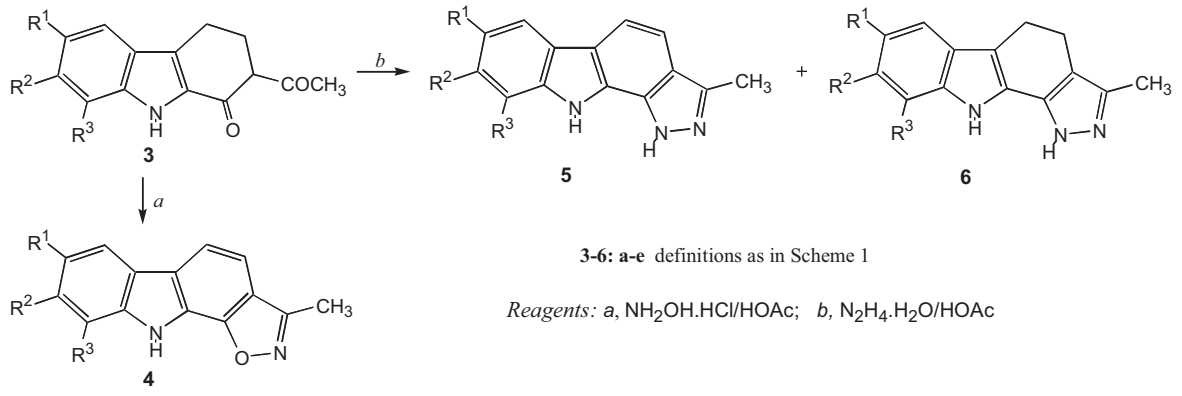


Fig. 2 Crystal structure of 1,10-dihydro-3,9-dimethylpyrazolo [3,4-*a*]carbazole (**5a**).



3-6: a-e definitions as in Scheme 1

Reagents: a, $NH_2OH.HCl/HOAc$; *b*, $N_2H_4.H_2O/HOAc$

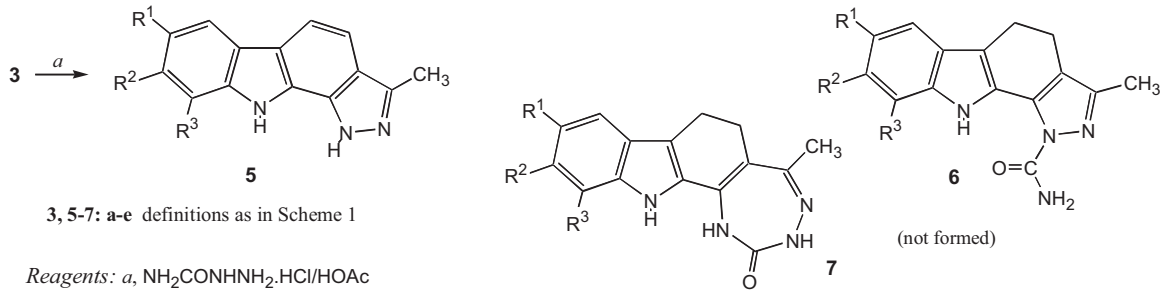
Scheme 2

The minor product (yield 15%) obtained from the petroleum ether/ethyl acetate (95.5) fraction melted at 168–170°C. Its IR spectrum showed the absence of a free carbonyl group, clearly indicating a cyclised product. The ^{1}H NMR spectrum in $CDCl_3$ showed two broad singlets each for one proton at δ 12.05 and 11.13 for N1- and N10-protons respectively, a one proton doublet at δ 7.90–7.82 for C6-H and a multiplet at δ 7.19–7.01 for two protons corresponding to C7 and C8–H in the aromatic region. Two more multiplets at δ 3.00–2.89 and 2.82–2.70 each for two protons were assigned to methylene protons at C5 and C4 respectively, and two three-proton singlets at δ 2.57 and 2.23 corresponding to C9–CH_3 and C3–CH_3 groups respectively. The elemental analysis showed the molecular formula as $C_{15}H_{15}N_3$. The mass spectrum showed the molecular ion peak at *m/z* 237. All the spectral and analytical results thus supported the structure as 1,4,5,10-tetrahydro-3,9-dimethylpyrazolo[3,4-*a*]carbazole (**6a**) (Scheme 2).

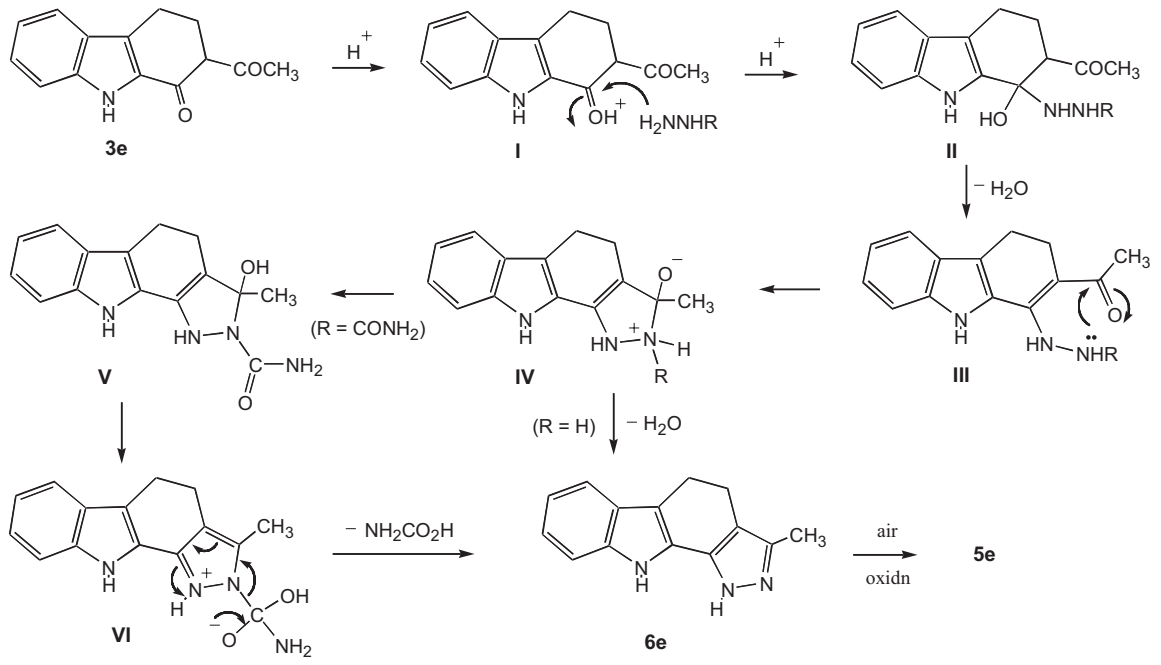
It should be noted that, on keeping this tetrahydro compound for a week in the open air, it was slowly oxidised to **5a**. The generality was tested with other carbazole derivatives, **1b–e**. (Scheme 2)

Our earlier work on methyl 2-(1-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)oxoacetate[19] with semicarbazide hydrochloride prompted us to apply similar reaction conditions to 2-acetyl-8-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3a**). This reaction resulted in the exclusive formation of 1,10-dihydro-3,9-dimethylpyrazolo[3,4-*a*]carbazole (**5a**) as product, which was one of the products of the reaction of **3a** with hydrazine hydrate. The tetrahydro product, **6a**, was not realised in this case. Also we did not observe other possible products such as 4,6,7,12-tetrahydro-5,9-dimethyl[1,2,4]triazepino[5,6-*a*]carbazol-2(1*H*)-one(**7**)and/or4,5-dihydro-3,7-dimethylpyrazolo[3,4-*a*]carbazole-1(10*H*)-carboxamide (**8**). The product **5a** was confirmed by mixed m..p., superimposable IR, ^{1}H NMR and mass spectra. The generality was tested with the other 2-acetyltetrahydrocarbazolone derivatives **3b–e** (Scheme 3).

A mechanistic rationalisation for the formation of **5** from the reaction of **3** with hydrazine hydrate as well as with semicarbazide hydrochloride is given in Scheme 4 (for simplicity, exemplified in the **e** series). The initial event is formation of the protonated intermediate **I** in presence of an acid catalyst.The nucleophile, NH_2NHR (R = H, $CONH_2$), can then add to the carbon of the hydroxycarbenium (oxonium) ion **I** to give the tetrahedral intermediate **II**, which loses a water molecule and a proton to give the intermediate **III**. This intermediate thus formed can, in principle, cyclise by the intramolecular nucleophilic attack of the amino group of the hydrazine part to give a five-membered 1,3-pyrazoline zwitterion derivative **IV**. If R = H, then the 1,3-pyrazoline derivative formed on prototropic shift and water elimination to give the dihydro product (**6**). Otherwise, if R = $CONH_2$ then the zwitterion **IV** on losing the elements of CO_2 and NH_3 gives the dihydro product, **6**. Finally **6** on aerial oxidation produced the fully aromatised product **5** as shown in Scheme 4.



Scheme 3



Scheme 4

Our results show that an important precursor, 2-acetyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one, for the construction of some heteroannulated carbazoles can conveniently be prepared. It was successfully utilised for the syntheses of heteroannulated carbazoles like 1,10-dihydro-3-methyl-pyrazolo[3,4-*a*]carbazoles and 3-methyl-10*H*-isoxazolo[5,4-*a*]carbazoles.

Experimental

Melting points were determined using a Mettler FP 51 apparatus (Mettler Instruments, Switzerland). IR spectra were recorded in KBr on a Shimadzu FTIR-8201PC spectrophotometer (Shimadzu, Japan). ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian AMX 400 FT-NMR (Varian, Australia) using TMS as internal standard. Mass spectra were recorded on a Jeol JMS-D-300 mass spectrometer (70 eV) (Jeol, Japan). Micro analyses were done on a Vario EL III Model CHNS analyser (Vario, Germany). The purity of the products was tested by TLC using glass plates coated with silica gel G (Hi Media Laboratories, India) and petroleum ether: ethyl acetate (90: 10) as the developing solvents. Ethyl acetate and sodium hydride (60% suspension in mineral oil) were obtained from LOBA Chemie Pvt. Ltd., India, and potassium hydride (30% suspension in mineral oil) from Aldrich.

Reaction of 2,3,4,9-tetrahydro-1H-carbazol-1-ones (**1a-e**) *with ethyl acetate: General procedure*

2,3,4,9-Tetrahydro-1*H*-carbazol-1-one **1** (8 mmol) was added to sodium hydride (2.4 g) suspended in benzene (20 ml) in a two necked round-bottomed flask fitted with reflux condenser and calcium chloride guard tube, and heated on a water bath for 5 minutes. Then potassium hydride was added carefully (*Caution*: dry potassium hydride is highly pyrophoric). It was heated to reflux for 2 minutes. To this ethyl acetate was added dropwise from a dropping funnel. After the addition was complete reflux was continued for 2 h. The solution became red. After cooling in an ice bath the solution was cautiously neutralised with acetic acid. Some further acetic acid was added and then the whole was poured into ice water and extracted using ethyl acetate. The extract was washed thoroughly with water and brine, then dried (Na_2SO_4). Filtration and solvent removal *in vacuo* left a crude mass which was purified by column chromatography over silica gel using petroleum ether/ethyl acetate mixtures (100 : 0; 98 : 2 and 95 : 5) as eluant. The petroleum ether fraction yielded ethyl acetoacetate. The petroleum ether/ethyl acetate (98 : 2) fraction yielded 2-acetyl-1-hydroxycarbazole (**2**). The petroleum ether/ethyl acetate (95 : 5) fraction yielded 2-acetyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3**).

2-Acetyl-8-methylcarbazol-1-ol (**2a**): Yellow crystalline powder (10%, EtOH), m.p. 177–178°C.

2-Acetyl-8-methyl-2,3,4,9-tetrahydro-1H-carbazol-1-one (**3a**): Yellow powder (56%); m.p. 129–131°C. IR: ν_{max} 3308, 2926, 1710, 1637, 1542 cm^{-1}. NMR: δ_H 15.48 (s, C1 enolic OH), 8.78 (br s, 1H, N9-H), 7.29–7.04 (m, 3H, C5, C6, C7-H), 3.74–3.67 (m, 1H, C2-H), 3.06–2.93 (m, 2H, C4-H_2), 2.70–2.59 (m, 2H, C3-H_2), 2.49 (s, 3H, C8-CH_3), 2.35 (s, 3H, C2-$COCH_3$); δ_C 200.2 (C2-$\underline{C}OCH_3$), 190.5 (C1), 134.3, 133.6, 129.4, 128.4, 126.4, 119.7, 118.6, 112.3 (eight aromatic C), 56.7 (C2), 28.5 (C2-CO$\underline{C}H_3$), 25.7 (C8-CH_3), 24.8 (C3), 22.6 (C4). MS: *m/z* (%) 241 (43). Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81; Found: C, 74.79; H, 6.18; N, 5.84%.

2-Acetyl-7-methylcarbazol-1-ol (**2b**): Yellow powder (12%, EtOH), m.p. 146–148°C.

2-Acetyl-7-methyl-2,3,4,9-tetrahydro-1H-carbazol-1-one (**3b**): Yellow powder (50%), m.p. 137–139°C. IR: ν_{max} 3270, 2929, 1718, 1650, 1592 cm^{-1}. NMR: δ_H 15.50 (s, C1-enolic OH), 8.70 (br s, 1H, N9-H); 7.30–7.14 (m, 3H, C5, C6, C8-H); 3.71–3.64 (m, 1H, C2-H), 3.30–3.13 (m, 2H, C4-H_2), 3.06–2.94 (m, 2H, C3-H_2), 2.65 (s, 3H, C7-CH_3), 2.34 (s, 3H, C2-$COCH_3$); δ_C 202.3 (C2-$\underline{C}OCH_3$), 194.7 (C1), 138.4, 134.2, 130.1, 128.9, 127.6, 120.1, 118.1, 111.4 (eight aromatic C), 60.1 (C2), 29.3 (C2-CO$\underline{C}H_3$), 27.5 (C7-CH_3), 24.1 (C3), 20.7 (C4). MS: *m/z* (%) 241 (34). Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81; Found: C, 74.37; H, 6.20; N, 5.81%.

2-Acetyl-6-methylcarbazol-1-ol (**2c**): Pale yellow powder (10%, EtOH), m.p. 170–172°C.

2-Acetyl-6-methyl-2,3,4,9-tetrahydro-1H-carbazol-1-one (**3c**): Yellow powder (54%), m.p. 125–127°C. IR: ν_{max}, KBr, 3278, 2926, 1716, 1640, 1582 cm^{-1}. NMR: δ_H 15.48 (s, C1-enolic OH), 8.92 (br s, 1H, N9-H), 7.48–7.15 (m, 3 H, C5, C7, C8-H); 3.73–3.66 (m, 1H, C2-H), 3.08–2.94 (m, 2H, C4-H_2), 2.86–2.78 (m, 2H, C3-H_2), 2.45 (s, 3H, C6-CH_3), 2.15 (s, 3H, C2-$COCH_3$); δ_C 203.0 (C2-$\underline{C}OCH_3$), 189.9 (C1), 138.6, 135.0, 129.7, 128.9, 127.3, 119.8, 117.2, 109.5 (eight aromatic C), 62.3 (C2), 29.3 (C2-CO$\underline{C}H_3$), 28.4 (C6-CH_3), 25.3 (C3), 19.7 (C4). MS: *m/z* (%) 241 (38). Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81; Found: C, 74.29; H, 6.18; N, 5.87%.

2-Acetyl-6-chlorocarbazol-1-ol (**2d**): Yellow powder (15%, EtOH), m.p. 204–206°C. IR: ν_{max} 3403, 3259, 2924, 1693 cm^{-1}. NMR: δ_H 13.08 (s, 1H, C1-OH), 8.43 (br s, 1H, N9-H), 7.96–7.91 (d, 1H, C4-H, *J* = 8.00 Hz), 7.58–7.48 (m, 2H, C7, C8-H), 7.30 (s, 1H, C5-H), 7.12–7.08 (d, 1H, C3-H, *J* = 8.20 Hz), 2.54 (s, 3H, C2-$COCH_3$). MS: *m/z* (%) 259 (16). Anal. Calcd. for $C_{14}H_{10}ClNO_2$: C, 64.75; H, 3.88; N, 5.39; Found: C, 64.50; H, 3.92; N, 5.44%.

2-Acetyl-6-chloro-2,3,4,9-tetrahydro-1H-carbazol-1-one (**3d**): Yellow powder (48%), m.p. 141–143°C. IR: ν_{max} 3308, 2926, 1710, 1637, 1542 cm^{-1}. NMR: δ_H 15.43 (s, C1-enolic OH), 9.16 (br s, 1H, N9-H), 7.40–7.23 (m, 3 H, C5, C6, C7-H), 3.76–3.70 (m, 1H, C2-H), 3.00–2.90 (m, 2H, C4-H_2), 2.84–2.77 (m, 2H, C3-H_2), 2.18 (s, 3H, C2-$COCH_3$). δ_C 199.8 (C2-$\underline{C}OCH_3$), 192.0 (C1), 139.4, 134.6, 129.8, 127.6, 126.4, 120.8, 118.9, 112.3 (eight aromatic C), 64.3 (C2), 29.7 (C2-CO$\underline{C}H_3$), 26.1 (C3), 20.0 (C4). MS: *m/z* (%) 261 (24). Anal. Calcd. for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62; N, 5.35; Found: C, 64.48; H, 4.57; N, 5.30%.

2-Acetylcarbazol-1-ol (**2e**): Pale yellow crystalline powder (20%; EtOH), m.p. 180–182°C.

2-Acetyl-2,3,4,9-tetrahydro-1H-carbazol-1-one (**3e**): Yellow powder (54%), m.p. 125–127°C. IR: ν_{max} 3270, 2920, 1709, 1643, 1578 cm^{-1}. NMR: δ_H 15.49 (s, C1-enolic OH), 8.78 (br s, 1H, N9-H), 7.44–7.11 (m, 4H, C5, C6, C7, C8-H), 3.05–2.94 (m, 2H, C4-H_2), 2.86–2.78 (m, 2H, C3-H_2), 2.36 (s, 3H, C2-$COCH_3$); δ_C 200.1 (C2-$\underline{C}OCH_3$), 191.7 (C1), 140.4, 136.7, 130.2, 124.7, 124.2, 120.6, 118.2, 112.9 (eight aromatic C), 64.4 (C2), 28.9 (C2-CO$\underline{C}H_3$), 24.3 (C3), 22.7 (C4). MS: *m/z* (%) 227 (33). Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16; Found: C, 74.09; H, 5.81; N, 6.14%.

Preparation of 3-methyl-10H-isoxazolo[5,4-a]carbazoles (**4a–e**): *General procedure*

To the appropriate 2-acetyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3**, 1 mmol) in glacial acetic acid (15 ml) was added hydroxylamine hydrochloride (10 mmol) and the solution was refluxed on an oil bath for 4 h. The reaction was monitored by TLC. After the completion of the reaction it was poured onto crushed ice. The precipitate was filtered off, washed with water and dried. It was purified by column chromatography over silica gel using petroleum ether: ethyl acetate (85 : 15) as eluant.

3,9-Dimethyl-10H-isoxazolo[5,4-a]carbazole (**4a**): Colourless needles (60%), m.p. 198–200°C. IR: ν_{max} 3372, 2920, 1657, 1565, 1445, 1386 cm^{-1}. NMR: δ_H 8.63 (br s, 1H, N10-H), 8.03–7.89 (m, 2H, C5, C6-H), 7.45–7.41 (d, 1H, C4-H, *J* = 8.20 Hz), 7.34–7.20 (m, 2H, C7, C8-H), 2.68 (s, 3H, C3-CH_3), 2.66 (s, 3 H, C9-CH_3); δ_C 156.3, 149.3, 134.7, 132.3, 128.3, 126.4, 124.3, 120.1, 118.7, 115.7, 112.3, 108.3, 104.3 (13 aromatic C), 21.4 (C9-CH_3), 19.6 (C3-CH_3) MS: *m/z* (%) 236 (28). Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86; Found: C, 76.20; H, 5.15; N, 11.87%.

3,8-Dimethyl-10H-isoxazolo[5,4-a]carbazole (**4b**): White amorphous powder (52%), m.p. 210–212°C. IR: ν_{max}, KBr, 3384, 2919, 1651, 1570, 1453 cm^{-1}. NMR: δ_H 8.60 (br s, 1H, N10-H), 8.03–7.90 (m, 2H, C5, C9-H), 7.45–7.35 (m, 3H, C4, C6, C7-H), 2.68 (s, 3H, C3-CH_3), 2.57 (s, 3 H, C8-CH_3); δ_C 157.6, 117.1, 135.6, 133.4, 127.9, 127.1, 125.1, 119.6, 116.8, 116.1, 115.2, 110.3, 109.1 (13 aromatic C), 20.7 (C8-CH_3), 20.1 (C3-CH_3). MS: *m/z* (%) 236 (22). Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86; Found: C, 75.98; H, 5.07; N, 11.89%.

3,7-Dimethyl-10H-isoxazolo[5,4-a]carbazole (**4c**): Colourless needles (65%), m.p. 225–227°C. IR: ν_{max} 3409, 2921, 1649, 1580, 1455 cm^{-1}. NMR: δ_H 8.61 (br s, 1H, N10-H), 7.98 (s, 1H, C6-H), 7.97–7.92 (d, 1H, C5-H, *J* = 8.00 Hz), 7.50–7.46 (d, 1H, C9-H, *J* = 8.26 Hz), 7.41–7.37 (d, 1H, C8-H, *J* = 8.26 Hz), 7.35–7.31 (d, 1H, C4-H, *J* = 8.00 Hz), 2.67 (s, 3H, C3-CH_3), 2.56 (s, 3 H, C7-CH_3); δ_C 152.4, 146.7, 135.3, 133.8, 129.1, 124.1, 122.1, 121.0, 114.8, 111.7, 110.3, 107.9, 108.7 (13 aromatic C), 24.0 (C6-CH_3), 22.5 (C3-CH_3). MS: *m/z* (%) 236 (30). Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86; Found: C, 76.67; H, 5.10; N, 11.81%.

7-Chloro-3-methyl-10H-isoxazolo[5,4-a]carbazole (**4d**): White powder (58%), m.p. 187–189°C. IR: ν_{max} 3427, 2925, 1652, 1580, 1460, 1435 cm^{-1}. NMR: δ_H 8.73 (br s, 1H, N10-H), 8.10 (s,1H, C6-H), 7.97–7.93 (d, 1H, C5-H, *J* = 8.00 Hz), 7.55–7.42 (m, 3H, C4, C7, C8-H), (s, 3H, C3-CH_3); δ_C 154.9, 146.1, 132.8, 130.3, 129.0, 127.4, 126.9, 122.6, 114.7, 111.7, 110.0, 108.7, 107.1 (13 aromatic C), 21.7 (C3-CH_3). MS: *m/z* (%) 256 (28). Anal. Calcd. for $C_{14}H_9N_2ClO$:

C, 65.51; H, 3.53; N, 10.91; Found: C, 65.60; H, 3.47; N, 10.85%.

3-Methyl-10H-isoxazolo[5,4-a]carbazole (**4e**): White amorphous powder (65%), m.p. 198–200°C. IR: ν_{max} 3376, 2923, 1642, 1575, 1440 cm^{-1}. NMR: δ_H 8.70 (br s, 1H, N10-H), 8.18–8.13 (d, 1H, C6-H, J = 7.84 Hz), 8.04–7.99 (d, 1H, C5-H, J = 8.24 Hz), 7.62–7.58 (d, 1H, C9-H, J = 8.08 Hz), 7.54–7.49 (m,1H, C8-H), 7.44–7.41 (d, 1H, C4-H, J = 8.24 Hz), 7.36–7.32 (m,1H, C7-H), 2.68 (s, 3H, C3-CH_3); δ_C 157.2, 145.1, 135.0, 134.6, 130.3, 127.4, 121.6, 120.4, 117.9, 110.6, 108.3, 106.0, 105.1 (13 aromatic C), 21.4 (C3-CH_3). MS: *m/z* (%) 222 (18). Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60; Found: C, 75.76; H, 4.49; N, 12.64%.

Reaction of 2-acetyl-2,3,4,9-tetrahydro-1H-carbazol-1-ones (**3a-e**) *with hydrazine hydrate: General procedure*

To the appropriate 2-acetyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3**, 1 mmol) in glacial acetic acid (15 ml) was added hydrazine hydrate (2 mmol) and the whole was refluxed on an oil bath for 1 h. The reaction was monitored by TLC. After completion of the reaction the mixture was poured onto crushed ice. The precipitate was collected, washed with water, and dried. It was purified by column chromatography over silica gel using petroleum ether/ethyl acetate (successively 98 : 2 and 85 : 15) as eluant. The former fraction yielded the respective 1,10-dihydro-3-methylpyrazolo[3,4-*a*]carbazole (**5**), the latter the respective 3-methyl-1,4,5,10-tetrahydropyrazolo[3,4-*a*]carbazole (**6**).

1,10-Dihydro-3,9-dimethylpyrazolo[3,4-a]carbazole (**5a**): White powder (75%), m.p. 142–144°C. IR: ν_{max} 3275, 2934, 1630, 1574, 1458 cm^{-1}. NMR: δ_H 12.00 (br s, H, N1-H), 11.12 (br s, 1H, N10-H), 7.89–7.83 (d, 1H, C6-H, J = 8.84 Hz), 7.73–7.66 (d, 1H, C5-H, J = 8.48 Hz), 7.36–7.29 (d, 1H, C4-H, J = 8.48 Hz), 7.14–7.08 (d, 1H, C8-H, J = 7.00 Hz), 7.07–7.01 (m, 1H, C7-H), 2.55 (s, 3H, C9-CH_3), 2.49 (s, 3H, C3-CH_3); δ_C 142.1, 139.4, 132.3, 129.9, 128.7, 127.6, 122.3, 120.1, 118.9, 117.8, 116.3, 111.3, 107.5 (13 aromatic C), 20.7 (C9-CH_3), 18.6 (C3-CH_3). MS: *m/z* (%) 235 (42). Anal. Calcd. for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86; Found: C, 76.60; H, 5.51; N, 17.82%.

3,9-Dimethyl-1,4,5,10-tetrahydropyrazolo[3,4-a]carbazole (**6a**): White powder (15%), m.p. 168–170°C. IR: ν_{max} 3253, 2923, 1624, 1576, 1446 cm^{-1}. NMR: δ_H 12.05 (br s, 1H, N1-H),11.13 (br s, 1H, N10-H), 7.90–7.82 (d, 1H, C6-H, J = 8.00 Hz), 7.19–7.01 (m, 2H, C7, C8-H), 3.00–2.89 (m, 2H, C5-H_2), 2.82–2.70 (m, 2H, C4-H_2), 2.57 (s, 3H, C9-CH_3), 2.23 (s, 3H, C3-CH_3); δ_C 142.8, 138.1, 130.7, 128.9, 124.1, 120.1, 119.0, 118.1, 114.3, 111.9, 108.4 (11 aromatic C), 28.7 (C9-CH_3), 24.4 (C5), 21.8 (C4), 20.7 (C3-CH_3). MS: *m/z* (%) 237 (40). Anal. Calcd. for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71; Found: C, 76.03; H, 6.32; N,17.76%.

1,10-Dihydro-3,8-dimethylpyrazolo[3,4-a]carbazole (**5b**): Pale yellow powder (80%), m.p. 164–166°C. IR: ν_{max} 3274, 2923, 1628, 1574, 1440 cm^{-1}. NMR: δ_H 12.43 (br s, 1H, N1-H), 11.17 (br s, 1H, N10-H), 8.01–7.96 (d, 1H, C5-H, J = 7.92 Hz), 7.77–7.72 (d, 1H, C6-H, J = 8.46 Hz), 7.45 (s, 1H, C9-H), 7.40–7.35 (d, 1H, C7-H, J = 8.46 Hz), 7.05–7.00 (d, 1H, C4-H, J = 7.92 Hz), 2.37 (s, 3H, C8-CH_3), 2.20 (s, 3H, C3-CH_3); δ_C 144.3, 138.5, 136.1, 130.9, 129.0, 128.1, 124.4, 122.1, 120.9, 114.3, 112.3, 108.4, 107.0 (13 aromatic C), 24.7 (C8-CH_3), 22.6 (C3-CH_3). MS: *m/z* (%) 235 (32). Anal. Calcd. for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86; Found: C, 76.67; H, 5.63; N, 17.71%.

3,8-Dimethyl-1,4,5,10-tetrahydropyrazolo[3,4-a]carbazole (**6b**): Pale yellow powder (10%), m.p. 150–152°C. IR: ν_{max} 3250, 2919, 1630, 1576, 1440 cm^{-1}. NMR: δ_H 12.43 (br s, 1H, N1-H), 11.29 (br s, 1H, N10-H), 7.40 (s, 1H, C9-H), 7.04–6.95 (m, 2H, C6, C7-H), 2.61–2.51 (m, 4H, C4-H_2, C5-H_2), 2.40 (s, 3H, C8-CH_3), 2.20 (s, 3H, C3-CH_3); δ_C 146.4, 140.7, 135.1, 129.9, 122.8, 120.4, 118.0, 116.1, 113.3, 112.5, 106.9 (11 aromatic C), 28.0 (C8-CH_3), 25.7 (C5), 22.6 (C4), 19.7 (C3-CH_3). MS: *m/z* (%) 237 (28). Anal. Calcd. for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71; Found: C, 75.99; H, 6.31; N, 17.65%.

1,10-Dihydro-3,7-dimethylpyrazolo[3,4-a]carbazole (**5c**): Needles (65%), m.p. 157–159°C. IR: ν_{max} 3354, 2947, 1630, 1564, 1449 cm^{-1}. NMR: δ_H 12.47 (br s, 1H, N1-H), 11.04 (br s, 1H, N10-H), 7.91 (s, 1H, C6-H), 7.81–7.71 (d, 1H, C5-H, J = 8.24 Hz), 7.61–7.51 (d, 1H, C4-H, J = 8.24 Hz), 7.43–7.34 (d, 1H, C9-H, J = 8.00 Hz), 7.24–7.15 (d, 1H, C8-H, J = 8.00 Hz), 2.57 (s, 3H, C7-CH_3), 2.49 (s, 3H, C3-CH_3); δ_C 145.1, 138.6, 136.8, 131.5, 130.4, 127.6, 123.9, 120.4, 118.9, 116.9, 110.3, 108.4, 105.6 (thirteen aromatic C), 26.7 (C7-CH_3), 21.6 (C3-CH_3). MS: *m/z* (%) 235 (52). Anal. Calcd. for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86; Found: C, 76.59; H, 5.60; N, 17.9%.

3,7-Dimethyl-1,4,5,10-tetrahydropyrazolo[3,4-a]carbazole (**6c**): White powder (15%), m.p. 187–189°C. IR: ν_{max} 3253, 2923, 1628, 1574, 1445 cm^{-1}. NMR: δ_H 12.49 (br s, 1H, N1-H),11.07 (br s, 1H, N10-H), 7.92 (s, 1H, C6-H), 7.50–7.38 (d, 1 H, C9-H, J = 8.48 Hz), 7.50–7.38 (d, 1H, C8-H, J = 8.48 Hz), 2.79–2.61 (m, 2H, C5-H_2), 2.60–2.51 (m, 2H, C4-H_2), 2.45 (s, 3H, C7-CH_3), 2.05 (s, 3H, C3-CH_3); δ_C 148.1, 144.0, 135.1, 132.6, 123.1, 122.8, 118.6, 118.1, 112.5, 109.4, 105.7 (11 aromatic C), 26.7 (C7-CH_3), 22.4 (C5), 20.9 (C4), 19.4 (C3-CH_3). MS: *m/z* (%) 237 (28). Anal. Calcd. for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71; Found: C, 75.67; H, 6.29; N, 17.68%.

7-Chloro-1,10-dihydro-3-methylpyrazolo[3,4-a]carbazole (**5d**): White powder (70%), m.p. 167–169°C. IR: ν_{max} 3234, 2920, 1618, 1572, 1440 cm^{-1}. NMR: δ_H, 12.34 (br s, 1H, N1-H), 11.56 (br s, 1H, N10-H), 7.84–7.80 (d, 1H, C5-H, J = 8.54 Hz), 7.68–7.64 (d, 1H, C4-H, J = 8.54 Hz), 7.49–7.48 (d, 1H, C6-H, J_{meta} = 1.90 Hz), 7.32–7.28 (d, 1H, C9-H, J = 8.52 Hz), 7.03–6.98 (dd, 1H, C8-H, J_{ortho} = 8.52, J_{meta} = 1.90 Hz), 2.20 (s, 3H, C3-CH_3); δ_C 143.9, 140.4, 138.2, 137.1, 128.4, 126.6, 123.7, 120.1, 118.9, 114.4, 112.6, 110.1, 109.1 (13 aromatic C), 23.7 (C3-CH_3). MS: *m/z* (%) 255 (26). Anal. Calcd. for $C_{14}H_{10}ClN_3$: C, 65.76; H, 3.94; N, 16.43; Found: C, 65.89; H, 3.90; N, 16.40%.

7-Chloro-3-methyl-1,4,5,10-tetrahydropyrazolo[3,4-a]carbazole (**6d**): White powder (12%), m.p. 172–174°C. IR: ν_{max} KBr, 3218, 2923, 1627, 1579, 1440 cm^{-1}. NMR: δ_H 12.32 (br s, 1H, N1-H), 11.57 (br s, 1H, N10-H), 7.47 (s, 1H, C6-H), 7.32–7.25 (d, 1H, C9-H, J = 8.48 Hz), 7.03–6.96 (d, 1H, C8-H, J = 8.48 Hz), 2.90–2.83 (m, 2H, C5-H_2), 2.73–2.67 (m, 2H, C4-H_2), 2.19 (s, 3H, C3-CH_3); δ_C, 146.0, 141.9, 134.7, 130.9, 128.1, 120.6, 118.0, 115.1, 114.1, 112.9, 109.4 (11 aromatic C), 26.4 (C5), 22.3 (C4), 21.0 (C3-CH_3). MS: *m/z* (%) 237 (28). Anal. Calcd. for $C_{14}H_{12}ClN_3$: C, 65.25; H, 4.69; N, 16.30; Found: C, 65.05; H, 4.73; N, 16.39%.

1,10-Dihydro-3-methylpyrazolo[3,4-a]carbazole (**5e**): White powder (68%), m.p. 150–152°C. IR: ν_{max} 3216, 2923, 1627, 1580, 1444 cm^{-1}. NMR: δ_H 12.45 (br s, 1H, N1-H), 11.32 (br s, 1H, N10-H), 8.14–8.08 (d, 1H, C5-H, J = 7.92 Hz), 7.81–7.77(d, 1H, C9-H, J = 8.52 Hz), 7.67–7.62 (d, 1H C6-H, J = 7.96 Hz), 7.32–7.28 (d, 1H, C4-H, J = 7.92 Hz), 7.05–6.93 (m, 2H, C7, C8-H), 2.20 (s, 3H, C3-CH_3); δ_C 148.0, 144.2, 132.1, 131.9, 127.4, 127.3, 124.4, 124.1, 120.1, 118.9, 112.3, 110.4, 109.4 (13 aromatic C), 21.8 (C3-CH_3). MS: *m/z* (%) 221 (46). Anal. Calcd. for $C_{14}H_{11}N_3$: C, 76.00; H, 5.01; N, 18.99; Found: C, 75.89; H, 5.01; N, 19.03%.

3-Methyl-1,4,5,10-tetrahydropyrazolo[3,4-a]carbazole (**6e**): White powder (15%), m.p. 190–192°C. IR: ν_{max} 3218, 2923, 1627, 1579, 1440 cm^{-1}. NMR: δ_H 12.23 (br s, 1H, N1-H), 11.33 (br s, 1H, N10-H), 7.45–7.40 (d, 1H, C9-H, J = 7.60 Hz), 7.32–7.26 (d, 1H, C6-H, J = 7.88 Hz), 7.04–6.93 (m, 2H, C7, C8-H), 2.92–2.84 (m, 2H, C5-H_2), 2.73–2.67 (m, 2H, C4-H_2), 2.19 (s, 3H, C3-CH_3); δ_C 148.9, 144.3, 132.4, 129.9, 122.7, 120.1, 119.3, 118.0, 116.1, 111.9, 109.4 (11 aromatic C), 26.4 (C5), 24.3 (C4), 22.0 (C3-CH_3). MS: *m/z* (%) 223 (35). Anal. Calcd. for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82; Found: C, 75.51; H, 5.86; N, 18.88%.

Reaction of 2-acetyl-2,3,4,9-tetrahydro-1H-carbazol-1-ones (**3a-e**) *with semicarbazide hydrochloride: General procedure*

To the appropriate 2-acetyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3**, 1 mmol) in glacial acetic acid (15 ml) was added semicarbazide hydrochloride (2 mmol) and the solution was refluxed on an oil bath for 1 h. The reaction was monitored by TLC. After the completion of the reaction it was poured onto crushed ice. The precipitate was filtered off, washed with water and dried. It was purified by column chromatography over silica gel using petroleum ether/ethyl acetate (98 : 2 to get the respective 1,10-dihydro-3-methylpyrazolo[3,4-*a*] carbazole (**5**).

1,10-Dihydro-3,9-dimethylpyrazolo[3,4-a]carbazole (**5a**): White powder (80%).

1,10-Dihydro-3,8-dimethylpyrazolo[3,4-a]carbazole (**5b**): Pale yellow powder (75%).

1,10-Dihydro-3,7-dimethylpyrazolo[3,4-a]carbazole (**5c**): Needles (78%).

7-Chloro-1,10-dihydro-3-methylpyrazolo[3,4-a]carbazole (**5d**): White powder (65%).

1,10-Dihydro-3-methylpyrazolo[3,4-a]carbazole (**5e**): White powder (75%).

Received 29 September 2007; accepted 23 December 2007
Paper 07/4859 doi: 10.3184/030823407X272976

References

1 D. Mal, B. Senapati and P. Pahari, *Tetrahedron Lett.*, 2006, **47**, 1071.
2 U. Pindur, *Chimia*, 1990, **44**, 406.
3 H.J. Knolker and K.R. Reddy, *Chem. Rev*., 2002, **102**, 4303.
4 M.J.E. Hewlins, A.M.O. Campos and P.V.R. Shannon, *Synthesis*, 1984, 289.
5 G.W. Gribble, *The Alkaloids,* ed. A. Brossi, Academic Press, New York 1990, Vol. 39, 239-241.
6 V.K. Kansal and P. Potier, *Tetrahedron,* 1986, **32**, 2389.
7 N. Haider, R. Jabara, F. Khadami and R. Wanko, *Heterocycles,* 1998, **48**, 1609.
8 V.M. Hedin, T. Tabka, L. Poulin, T. Godard, M. Lachevrel, C. Saturnino, J.C. Lancelot, J.Y. Le Talaer and P. Gauduchon, *Anti Cancer Drug Design,* 2000, **15**, 109.
9 K. Hirata, C. Ito, H. Furukawa, M. Itoigawa, L. Mark Cosentino and K.H. Lee, *Bioorg. Med. Chem. Lett.,* 1999, **9**, 119.
10 M. Ishikura, A. Hino, T. Yaginuma, I. Agata and N. Katagiri, *Tetrahedron,* 2000, **56**, 193.
11 K.R.J. Thomas, J.T. Lin, Y.T. Tao and C.W. Ko, *J. Am. Chem. Soc*., 2001, **123**, 9404.
12 A. Van Dijken, J.A.M. Bastiaansen, N.M.M. Kiggen, B.M.W. Langeveld, C. Rothe, A. Monkman, I. Bach, P. Stoessel and K. Brunner, *J. Am. Chem. Soc.,* 2004, **126**, 7718.
13 M.J. Chmielewski, M. Charon and J. Jurczak, *Org. Lett.,* 2004, **6**, 3501.
14 Vandana and K.J. Rajendra Prasad, *J. Chem. Res*., 2004, 717.
15 A. Thiruvalluvar, A. Thomas Gunaseelan, A. Ebenezer Martin, K.J. Rajendra Prasad and R.J. Butcher, *Acta Cryst*., 2007, **E63**, o3631.
16 A. Ebenezer Martin, A. Thomas Gunaseelan, A. Thiruvalluvar, K.J. Rajendra Prasad and R.J. Butcher, *Acta Cryst*., 2007, **E63**, o3471.
17 I.A. Danish and K.J. Rajendra Prasad, *Collect. Czech. Chem. Commun.*, 2005, **70**, 223.
18 I.A. Danish and K.J. Rajendra Prasad, *J. Chem. Res.*, 2005,107.
19 A. Ebenezer Martin and K.J. Rajendra Prasad, *J. Chem. Res*., 2006, 473.

Synthesis and characterisation of the lithium, sodium and potassium americium(β) complexes of hexaoxoperiodate: $M^I_2[Am(OH)_2H_2IO_6].xH_2O$

Xinhua Qi, Xueqing Jia, Ying Yang*, YaPing Gao and Li-e Niu

College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P.R. China

Novel complexes of trivalent Americium with hexaoxoperiodate have been prepared for the first time from an aqueous caustic solution. Chemical analysis indicated that the composition of the complexes is $M^I_2[Am(OH)_2H_2IO_6].xH_2O$ (M^I = alkali metal: x = 4, M^I = Na, K; X = 11, M^I = Li) and all the complexes have been characterised by X-ray powder diffraction, UV-Visible, IR, and Raman spectroscopic studies, and by thermal analysis.

Keywords: alkali metal, americium, hexaoxoperiodate complexes, synthesis

In alkaline solution, the hexaoxoperiodate ion ($H_nIO_6^{n-5}$) is a potential polydentate ligand with oxygen as donor atoms, and can be used in stabilising rather unusual high oxidation states, such as Ag^{3+} and Ni^{4+}.[1,2] Recent work in this field has revealed that tetravalent lanthanide complexes of hexaoxoperiodate can be synthesised from solution.[3,4] A study has been undertaken to synthesise actinide compounds of hexaoxoperiodate, in which the less common oxidation states of actinides might be generated and stabilised.[5] Up to now, however, hexaoxoperiodate complexes of americium have not been reported.

As a part of our continuing investigation into the preparation of unusual oxidation state lanthanide and actinide compounds in aqueous medium, we report here the preparation of novel Am^{3+} complexes with hexaoxoperiodate for comparative purposes, as well as their characterisation by means of chemical analysis, X-ray powder diffraction, IR and Raman, UV-visible spectra and thermal analysis.

Results and discussion

Chemical analysis of complexes

Am^{3+} contents were determined by EDTA titration with xylenol orange as indicator. The hexaoxoperiodate contents were determined by iodometric titration whereby a known amount of the complex was dissolved in 2 mol/l H_2SO_4 with an excess of solid KI, then the liberated iodine was titrated against a standard sodium thiosulfate solution in 0.2 mol/l acid medium at room temperature, using starch as indicator. It was found that each mole of the americium(III) complex required 8 mol of sodium thiosulfate, which corresponds to the reaction as follows:

$$[Am(OH)_2H_2IO_6]^{2-} + 7\ I^- + 12\ H^+ = Am^{3+} + 4I_2 + 8H_2O$$

The data of chemical analysis are listed in Table 1.

UV—visible spectra

After dissolving a small amount of a fresh sample in 0.5 mol/l KOH, the UV—visible spectra of the complexes were recorded from 200 to 700 nm. The absorption bands for americium complexes of Li^+, Na^+, K^+ are almost the same. There is an absorption band in the visible region at *ca* 503nm (middle) arising from the f →f transfer of Am^{3+};[6,7] and a very strong band in the UV region at 233 nm, due to the $A^1_1 \rightarrow T^1_2$ transfer of the IO_6 octahedron.[8] Compared with free IO_6, the absorption involves a bathochromic shift from 220 to 233nm, which is attributed to the coordination function of IO_6 to Am^{3+}.

Vibrational spectra

As described previously, the americium(III) complexes were prepared from an aqueous caustic solution, which does not provide crystals suitable for X-ray study. Hence, a detailed spectroscopic study by IR and Raman was performed to ascertain structure. Table 2 shows the selected IR bands of the complexes (KBr discs), from which we can see that a strong and broad band observed in the range of 3630–2920 cm^{-1} can be assigned to the OH stretching vibration. Broadening of the band is likely caused by hydrogen bonding of the type …OH…O. The peak at 1655–1633 cm^{-1} is ascribed to the bending vibration of H_2O and a large number of absorptions are observed at 1390–1349 cm^{-1} as a result of I–OH deformation.[9] The peaks due to Am(III)-OH deformation in the complexes are weaker, appearing at 1108–1055 cm^{-1}. In the lower wave number region, the spectra are very complicated. $\nu_{I\text{-}O}$ ranges from 674 to 714 cm^{-1}, and $\nu_{Am\text{-}O}$, appears at 412 cm^{-1}.[10] The alkali metal–oxygen band may also be present in the lower wave number region but it is difficult to assign.

There is a notable feature in IR spectra of the complexes, that is, $\delta_{I\text{-}O\text{-}H}$ (assigned at *ca* 1365 cm^{-1}) has been observed in all of these complexes, and the large number of peaks assigned to δ_{IOH} and δ_{IOI} reveals that the arrangement of the six oxygen

Table 1 The results of chemical analysis

Complexes	Am^{3+}%		IO_6^{5-}%		M%	
	Found	Calc.	Found	Calc.	Found	Calc.
$Li_2[Am(OH)_2H_2IO_6].11H_2O$	33.8	33.9	31.65	31.3	2.0	1.9
$Na_2[Am(OH)_2H_2IO_6].4H_2O$	39.3	39.0	36.2	36.1	8.0	7.4
$K_2[Am(OH)_2H_2IO_6].4H_2O$	37.1	37.1	34.3	34.3	12.1	12.0

Table 2 Selected IR bands in cm^{-1} of the alkali americium(III) complexes with hexaoxidoiodate

Complexes	ν_{H2O}	δ_{H2O}	$\delta_{I\text{-}OH}$	$\nu_{I\text{-}O}$	$\nu_{Am\text{-}O}$
$Li_2[Am(OH)_2H_2IO_6].11H_2O$	3332 s.b	1652 s	1365,vs	674.2vs	412 m
$Na_2[Am(OH)_2H_2IO_6].4H_2O$	3300 s.b	1640 s	1368,vs	706.4vs	412 m
$K_2[Am(OH)_2H_2IO_6].4H_2O$	3300 s.b	1633 s	1366,vs	714.1vs	412 m

* Correspondent. E-mail: yangying@lzu.edu.cn

atoms around iodine may not be symmetrical. This indicates that the hexaoxoperiodate ligand exists in these complexes predominantly in the form of $H_2IO_6^{3-}$.[11] This is consistent with the acid dissociation constant of H_5IO_6: $K_{a1} = 2.1 \times 10^{-4}$, $K_{a2} = 4.9 \times 10^{-9}$, $K_{a3} = 2.5 \times 10^{-12}$, which means that in alkaline solution, only three hydrogens can be dissociated.[12] The expected absorption bands of $\nu_{Am\text{-}OH}$ have been observed also, which indicates that the americium(III) complexes involve hydroxyl groups as ligands in the inner-sphere. This is very common in lanthanide and actinide compounds.[13]

The same conclusion can be obtained from the Raman spectra also. Figure 1 shows the comparative Raman spectra of $K_2[Am(OH)_2H_2IO_6].4H_2O$ and $K_3H_2IO_6$, by which we can see that $\delta_{I\text{-}O\text{-}H}$ appears at 1209–1295 cm^{-1} for the free anion $H_2IO_6^{3-}$, and at 1354–1376 cm^{-1} for the coordinated ion in the americium(III) complex. The shift is due to the coordinated function of IO_6 to Am^{3+}. The very strong band at 1056 cm^{-1} is the Am(III)-OH stretching vibration, which is relatively weaker in the IR spectrum.[10,14]

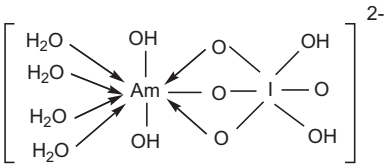
Thermal analysis

The simultaneous TG-DTA curves of americium(III) complexes were carried out using α-Al_2O_3 as reference material. Samples of about 10 mg were placed in a platinum crucible and heated at the rate of 10°C/min from room temperature up to 700°C at ambient pressure. In order to simplify the decomposition procedure, the operation was handled in a high purity nitrogen atmosphere (flow rate 60 ml min^{-1}). The determination indicates that the decomposition patterns of the sodium and potassium compounds are very similar and quite different from that of the lithium compound due to the highly hydrated tendency and the flexibility of the lithium compound at high temperature. Both of the sodium and potassium compounds lose weight at 160–250°C, arising from loss of water, the relatively higher temperature indicates that the H_2O is coordinated to the central americium(III). Chemical analysis of the residual gave the formula $M^I_2[Am(OH)_2H_2IO_6]$. The second step, over 463–533°C, is the decomposition procedure of the hexaoxoperiodate complex of americium(III) to form alkali oxide, iodide, and americium dioxide (the colour of the residual is dark brown, consistent with that of tetravalent americium oxide[15]). The determined weight loss in this step for the lithium, sodium and potassium compounds are 13.0%, 15.0% and 14.1%; and the calculated value are 12.9%, 14.9% and 14.15% respectively. Based on the results, the stepwise thermal decomposition procedure of these complexes could be considered to involve the following steps:

(1) $M_2[Am(OH)_2H_2IO_6].11H_2O \rightarrow M_2[Am(OH)_2H_2IO_6].4H_2O + 7H_2O$(only for lithium)
(2) $M_2[Am(OH)_2H_2IO_6].4H_2O \rightarrow M_2[Am(OH)_2H_2IO_6] + 4H_2O$
(3) $M_2[Am(OH)_2H_2IO_6] \rightarrow MI + 1/2M_2O + AmO_2 + 2H_2O + 7/4O_2$

Table 3 shows the data of thermal analysis for the americium complexes.

According to the results discussed above, we deduce that the hexaoxoperiodate in an americium complex exist as the $H_2IO_6^{3-}$ ion, with two hydroxyl ions coordinated to americium in the inner-sphere. An outline structure for the americium complex anion of hexaoxoperiodate is proposed as follows:



Experimental

$Am(NO_3)_3.6H_2O$ (A.R, Amersham Radiochemical centre product), and KIO_4 (A.R.) were directly used for preparing the hexaoxoperiodate complexes. Other chemicals used were of A.R. grade. Lithium, sodium and potassium were determined with a Hitachi 180-80 polarised Zeeman atomic absorption spectrophotometer, X-ray powder diffraction patterns were taken on a XD-3A diffractometer, electronic spectra were recorded on a Shimadzu UV-240 spectrometer, vibration spectra were recorded on a Nicolet FTIR 170SX spectrophotometer and a SPEX 1403 laser Raman spectrometer respectively, and thermal analysis were carried out on PCT-2 thermal balance.

Preparation of Am(β) hexaoxoperiodate complexing solution

KIO_4 (0.5 g, 0.002 mol) and KOH (0.6 g) were weighed and dissolved in distilled water (20 ml). The mixture was stirred for 5 h at room temperature while Am^{3+} nitrate solution (20 ml, 0.01 mol/l) was added dropwise to it. The complexing solution of Am^{3+} was filtered through a sintered crucible to remove the americium hydroxide and a pink filtrate was obtained, which was confirmed to contain the $[Am(OH)_2H_2IO_6]^{2-}$ complexing anion, because the ratio of IO_6^{5-}/Am^{3+} in the alkaline solution was determined to be nearly 1 : 1.

Preparation of the complexes $M^I_2[Am(OH)_2H_2IO_6].XH_2O$ (M^I = Li, Na, K)

An excess of saturated lithium, sodium or potassium nitrate solution was added to the Am^{3+} complexing solution, respectively. The pale pink precipitate of the hexaoxoperiodate complexes of americium was obtained. The complexes were isolated from the solution by centrifugation, then washed with 0.1 mol/l KOH solution several times to remove the coprecipitated alkali periodates and finally washed with distilled water to remove alkali and other impurities. After that, the complexes were dried in a vacuum desiccator. The freshly prepared complexes can be slightly dissolved in KOH solution, and the solubility of the americium(III) complexes of hexaoxoperiodate was found to be in the order $K^+ > Na^+ > Li^+$. Attempts to grow a crystal of the americium(III) complexes from

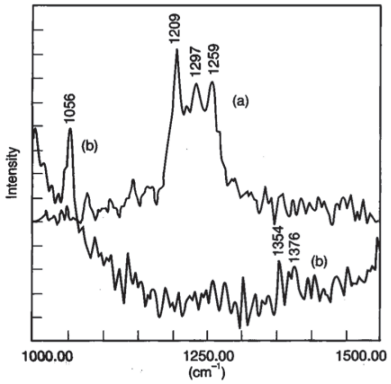


Fig.1 Comparative Raman $K_2[Am(OH)_2H_2IO_6].4H_2O$(b) and $K_3H_2IO_6$(a).

Table 3 Thermal analysis data for the complexes

Complexes	Thermal decomposition range/°C			Peaks temp. of
	(a)	(b)	(c)	Endo in DTA/°C
$Li_2[Am(OH)_2H_2IO_6].11H_2O$	50–108	125–168	422–464	85,139,443
$Na_2[Am(OH)_2H_2IO_6].4H_2O$		156–224	471–524	171,496
$K_2[Am(OH)_2H_2IO_6].4H_2O$		163–228	496–533	187,518

caustic solution were unsuccessful, and the X-ray diffraction pattern showed that all of the americium(III) complexes of hexaoxoperiodate are amorphous.

Received 16 October 2007; accepted 31 December 2007
Paper 07/4895 doi: 10.3184/030823407X273514

References

1 P. Ray, *Inorg. Synth*., 1957, **5**, 201.
2 N.N. Halligudi, S.M. Desai and S.T. Nandibewoor, *J. Chem. Kinet.,* 1999, **31**, 789.
3 L.P. Ma, Y. Yang and R.D. Yang, *J. Chem. Chin. Univ*., 1993, **14**, 233.
4 Y. Yang and R.D. Yang, *Polyhedron,* 1992, **11**, 963.
5 Y. Yang, Y.W. Shen and R.D. Yang, *Radiochimica Acta,* 1998, **80,** 147.
6 W.W. Schulz, *J Less Common Met.,* 1978, **59**, 97.
7 L.J. Nugent, R.D. Baybarz, J.L. Burnett and J.L. Ryan, *J. Inorg. Nucl. Chem*., 1971, **33**, 2509.
8 C.E. Crouthamel, A.M. Hayes and D.S. Martin, *J. Am. Chem. Soc*., 1951, **73**, 82.
9 A.H.J. Lokio and J.R. Kyrki, *Suomen Kemis B*., 1973, **46**, 206.
10 Kazuo Nakanoto, *Infared and Raman Spectra of Inorganic and Coordination Compounds*, 4th edn., John Wiley and Sons, 1986.
11 F. Peter, J. Hradilovo and B. Hajek, *J. Inorg. Nucl. Chem.,* 1970, **32**, 1485.
12 G.J. Buist, W.C.P. Hipperson and J.D. Kwis, *J. Chem. Soc*(*A*)., 1969, 307.
13 T. Kimura and Y. Kato, *J. Alloys Comp*., 1998, **271**, 867.
14 L.C.W. Baker, H.G. Mukherjee and B.K. Chaudhuri, *J. Indian. Chem. Soc.,* 1982, **59**, 930.
15 B.F. Myasoedov, M.S. Milyakova, I.A. Lebedov, M.N. Litvina and V.Y. Frenkel, *J. Inorg. Nucl. Chem.,* 1975, **37**, 1475.

A three-component reaction between trialkyl phosphites or triphenylphosphine, dimethyl acetylenedicarboxylate and *N*-aryl-3-hydroxynaphthalene–2-carboxamide

Mohammad Anary-Abbasinejad*, Alireza Hassanabadi and Manouchehr Mazraeh-Seffid

Department of Chemistry, Islamic Azad University, Yazd Branch, P.O. Box 89195-155, Yazd, Iran

A three-component reaction between dimethyl acetylenedicarboxylate (DMAD) and trialkyl phosphites in the presence of *N*-aryl-3-hydroxynaphthalene-2-carboxamide leads to dialkyl 2-(dimethoxyphosphoryl)-3-[2-hydroxy-3-(arylcarbamyl)naphthalen-1-yl] succinate in excellent yields. A similar reaction with triphenylphosphine, instead of phosphites, produces dimethyl 2-[2-hydroxy-3-(arylcarbamoyl)naphthalen-1-yl]maleates. In the absence of triphenylphosphine or phosphite, DMAD adds to *N*-aryl-3-hydroxynaphthalene-2-carboxamide to produce alkyl 2-(alkoxycarbonylmethyl)-4-oxo-3-aryl-3,4-dihydro-2*H*-naphtho[2,3-*e*][1,3]oxazine-2-carboxylates in good yields.

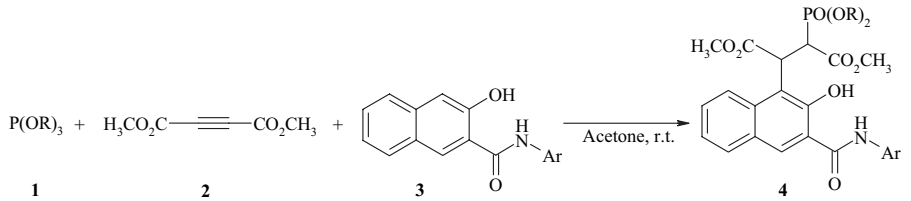
Keywords: dimethyl acetylenedicarboxylate, thialkyl phosphites; *N*-aryl-3-hydroxynaphthalene-2-carboxamide, stereoselective synthesis, triphenylphosphine

The nucleophilic addition of trialkyl phosphites to electron-deficient triple bonds leads to a highly reactive zwitterionic intermediate, which may be trapped by various electrophiles. There have been many studies on the reactions between trivalent phosphorus nucleophiles and unsaturated carbonyl compounds in the presence of a proton source such as an alcohol.[1] The reaction of trimethyl phosphite with dimethyl acetylenedicarboxylate (DMAD) in the presence of alcohols is reported to produce phosphite ylide derivatives which are stable at low temperatures, but converted to phosphonate derivatives by warming or by treatment with water.[2] The reaction of trimethyl phosphite with DMAD in the presence of 2-naphthol has been reported to afford stable dimethyl oxa-2,5-phosphaphenanthrene derivatives in good yields.[3] In continuation of our previous work on three-component reactions between trivalent phosphorus nucleophiles, acetylenic esters and organic acidic compounds,[4-8] we report herein the results of our study on the reaction between acetylenic esters and trialkyl phosphites or triphenylphosphine in the presence of *N*-aryl-3-hydroxynaphthalene-2-carboxamides.

Reaction of DMAD with trimethyl (or triethyl or tributyl) phosphite in the presence of N-phenyl (or 2-methylphenyl) (3-hydroxynaphthalene-2-carboxamide leads to dialkyl 2-(dimethoxyphosphoryl)-3-[2-hydroxy-3-(arylcarbamyl) naphthalen-1-yl] succinates in excellent yields (Scheme 1).

The ^{1}H NMR spectrum of **4a** exhibits two sharp lines at δ = 3.61 and 3.93 ppm for the protons of two methoxy groups. Two methoxy groups of phosphoryl moiety are diastereotopic and appear as two doublets at 3.37 and 3.45 ppm ($^3J_{HP}$ = 11H_Z). The ^{1}H NMR spectrum of **4a** also exhibits signals for vicinal methine protons at δ = 4.23 and 5.49 ppm as two sets of doublet of doublets, with $^2J_{HP}$ = 21 H_Z, $^3J_{HP}$ = 6 H_Z and $^3J_{HH}$ = 11 H_Z. The vicinal proton–proton coupling constants can be obtained from the Karplus equation.[9,10] Typically, J_{gauche} varies between 1.5 and 5 H_Z and J_{anti} between 10 and 14 H_Z. Observation of $^3J_{HH}$ = 11 H_Z for vicinal protons in compound **4a** indicates an anti arrangement for these centres. Since compound **4a** possesses two stereogenic centres, two diastereomers with anti HCCH arrangements are possible (Scheme 2). The three-bond carbon–phosphorus coupling, $^3J_{CP}$, depends on configuration, as expected, transoid couplings being larger than cisoid ones.[11] The observation for $^3J_{CP}$ of 19 H_Z for the ester carbonyl carbon, is in agreement with the (2*R,* 3*S*)-**4a** and its mirror image (2*S,* 3*R*)-**4a** geometries. The NMR spectra of compounds **4b–f** also show only (2*R,* 3*R*) isomer and its enantiomer.

It is reasonable to assume that compounds **4** result from the initial addition of trimethyl phosphite to DMAD and subsequent protonation of the 1:1 adduct by *N*-aryl-3-hydroxynaphthalene–2-carboxamide **3** (Scheme 3). Then,



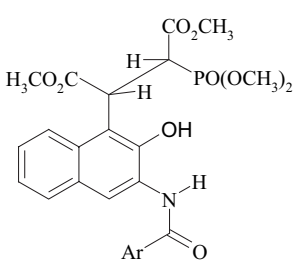
1 **2** **3** **4**

4	Ar	R	Yield*(%)
a	Ph	Me	93
b	Ph	Et	89
c	Ph	Bu	91
d	2-Me-C_6H_4	Me	95
e	2-Me-C_6H_4	Et	93
f	2-Me-C_6H_4	Bu	90

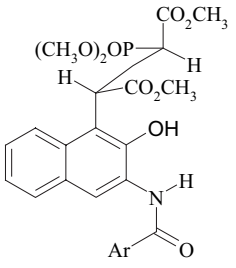
*Isolated yield

Scheme 1

* Correspondent. E-mail: mohammadanary@yahoo.com



(2*S*, 3*R*)-**4a**



(2*R*, 3*S*)-**4a**

Scheme 2

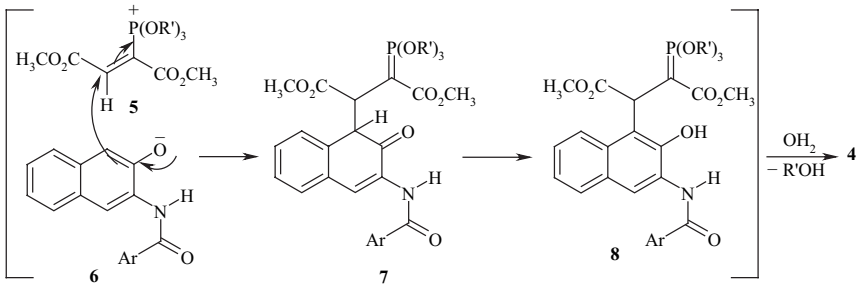
the positively charged ion **5** is attacked by the anion **6** to form ylide **7** that then tautomerises and is hydrolysed to phosphonate **4**.

The reaction of acetylenic ester **9** with triphenylphosphine (**8**) in the presence of *N*-aryl 3-hydroxynaphthalene-2-carboxamide **3** leads to dialkyl 2-[2-hydroxy-3-(arylcarbamoyl)naphthalen-1-yl]but-2-enedioate **10** in excellent yields (Scheme 4).

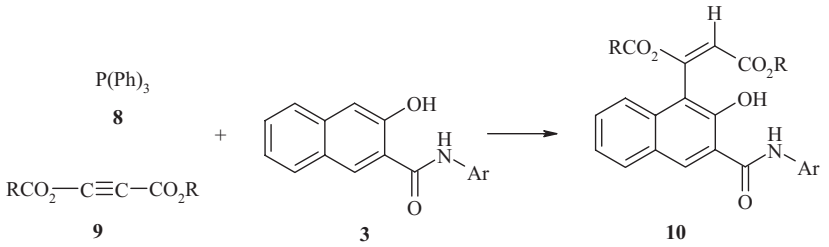
The ^{1}H NMR spectrum of **10a** exhibits three sharp lines at δ = 3.74, 3.83 and 6.44 ppm for the protons of two methoxy groups and olefinic proton, respectively. Two single signals are observed at 10.17 and 12.33 ppm that disappeared after addition of a few drops of D_2O to d_6-DMSO solution of compound **10a**. These signals are related to OH and NH protons. Aromatic protons resonate between 7.21 and 8.75 ppm as multiplets. The chemical shift of 6.44 ppm of the olefinic proton in the ^{1}H NMR spectrum of compound **10a** is consistent with the *E*-geometry of the carbon–carbon double bond.[13] ^{13}C NMR spectra of compound **10a** shows 21 distinct signals, which is consistent with the proposed structure.

It is reasonable to assume that compound **10** results from the initial addition of triphenylphosphine **2** to acetylenic ester **9** and subsequent protonation of the 1:1 adduct by *N*-aryl-3-hydroxynaphthalene–2-carboxamide **3** (Scheme 5). Then, the positively charged ion **11** is attacked by the anion **6** to form ylide **12** that loses triphenylphosphine to produce compound **10**.

When acetylenic ester **9** was treated with *N*-aryl 3-hydroxynaphthalene-2-carboxamide **3** in the absence of triphenylphospline the addition product alkyl 2-(alkoxy-



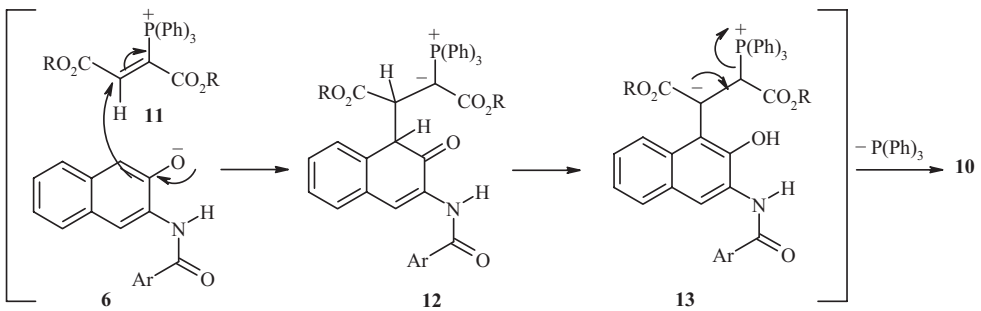
Scheme 3



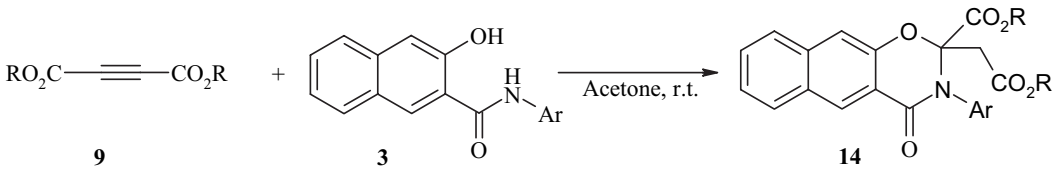
10	Ar	R	Yield*(%)
a	Ph	Me	92
b	Ph	Et	90
c	Me-C_6H_4	Me	90
d	Me-C_6H_4	Et	89

*isolated yields

Scheme 4



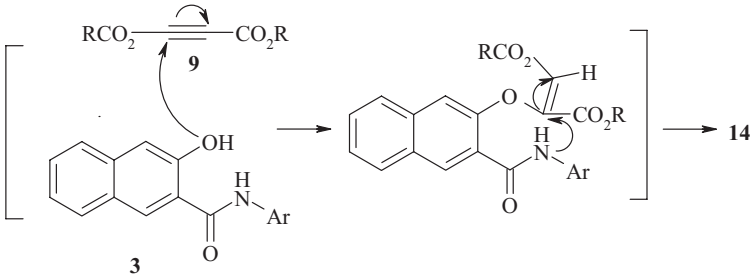
Scheme 5



14	Ar	R	Yield*(%)
a	Ph	Me	92
b	Ph	Et	87
c	2-Me-C_6H_4	Me	93
d	2-Me-C_6H_4	Et	90

*Isolated yield

Scheme 6



Scheme 7

carbonylmethyl)-4-oxo-3-aryl-3,4-dihydro-2*H*-naphtho[2,3-*e*][1,3]oxazine-2-carboxylate **14** was obtained in good yield (Scheme 6).

The ^{1}H NMR spectrum of **14a** exhibits two sharp lines at δ = 3.74 and 3.83 ppm for the protons of two methoxy groups. The methylene protons resonate at 3.28 ppm as an AB-quartet (δ_1 = 3.24, δ_2 = 3.32, $^2J_{HH}$ = 16 Hz). Aromatic protons resonate between 7.21 and 8.75 ppm as multiplets. The IR spectrum of compound **14a** does not show the stretching absorption bonds related to OH or NH bonds.

Compound **14** is probably produced by the addition of *N*-aryl 3-hydroxynaphthalene-2-carboxamide **3** to ecetylenic ester **9** as shown in Scheme 7.

In summary functionalised phosphonates may be prepared by a simple, one-pot, three-component reaction between DMAD, aryl 3-hydroxynaphthalene–2-carboxamides, and trialkyl phosphites. The addition reaction between acetylenic esters and *N*-aryl-3-hydroxynaphthalene-2-carboxamides catalysed by triphenylphosphine produces dialkyl 2-[2-hydroxy-3-(arylcarbamoyl)naphthalen-1-yl]-but-2-enedioates in good yields. In the absence of triphenylphosphine *N*-aryl-3-hydroxynaphthalene-2-carboxamides add to acetylenic esters to produce alkyl 2-(alkoxycarbonylmethyl)-4-oxo-3-aryl-3,4-dihydro-2*H*-naphtho[2,3-*e*][1,3]oxazine-2-carboxylates in excellent yields. The present method carries the advantage that the reaction is performed under neutral conditions and starting materials can be mixed without any activation or modification.

Experimental

Melting points were determined with an electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solutions in d_6-DMSO using TMS as internal standard or 85% H_3PO_4 as external standard. The chemicals used in this work purchased from fluka (Buchs, Switzerland) and were used without further purification.

Dimethyl 2-(dimethoxyphosphoryl)-3-[2-hydroxy-3-(phenylcarbamoyl) naphthalen-1-yl]succinate **(4a)**

General procedure for preparation of compounds **4a–f**

To a magnetically stirred solution of 0.53 g *N*-phenyl-3-hydroxynaphthalene–2-carboxamide **3** (2 mmol) and 0.28 g DMAD (2 mmol) in 10,ml acetone was added a mixture of 0.25 g trimethyl phosphite **1** (2 mmol) in 2 ml acetone at room temperature. The reaction mixture was then allowed to stir for 24 h. The solvent was evaporated at reduced pressure. The residue was precipitated in a solution of diethyl ether–hexane. The solid was filtered and washed with diethyl ether to give the pure product.

White powder, yield 0.96 g (93%), m.p. 177–180°C, IR (KBr) (ν_{max} cm^{-1}): 3245 OH and NH), 1727 (C=O, ester), 1642 (C=O, amide). Analyses: Calcd. for $C_{25}H_{26}NO_9P$: C, 58.25; H, 5.08; N, 2.72%. Found: C, 58.34; H, 4.93; N,2.80. MS (*m/z*,%): 515 (5). ^{1}H NMR (500 MHz, d_6-DMSO): δ 3.37 and 3.45 (6 H, 2d, $^3J_{HP}$ = 11 Hz, 2 $POCH_3$), 3.61 and 3.93 (6 H, 2 s, 2 OCH_3), 4.70 (1 H, dd, $^2J_{HP}$ = 21 Hz, $^3J_{HH}$ = 11 H_Z, CH), 5.33 (1 H, dd, $^3J_{HP}$ = 6 Hz, $^3J_{HH}$ = 11 H_Z, CH), 7.16–8.15 (10 H, m, aromatic),). 9.09 and 12.66 (2 H, 2 s, NH and OH). ^{13}C NMR (125.8 MHz, d_6-DMSO–Me_4Si): δ 41.95 (d, $^2J_{cp}$ = 2 H_Z, P–C–*C*), 43.95 (d, $^1J_{cp}$ = 131 H_Z, P-*C*), 53.17 and 53.28 (2 OCH_3), 66.32 and 66.58 (2 d, $^2J_{cp}$ = 7 H_Z, 2 POCH_3), 116.21, 116.77, 123.04, 123.83, 125.86, 127.40, 129.16, 130.26, 135.76 and 156.55 (naphthol moiety), 121.89, 122.81, 129.30, 137.34 (phenyl moiety), 169.00 (C=O), 170.43 (d, $^2J_{CP}$ = 6 H_Z, C=O), 173.49 (d, $^3J_{CP}$ = 21 H_Z, C=O). ^{31}P NMR (202.5 MHz, d_6-DMSO): δ 19.94.

Dimethyl 2-(diethoxyphosphoryl)-3-[2-hydroxy-3-(phenylcarbamoyl) naphthalen-1-yl]succinate **(4b):** White powder, yield 0.97 g (89%), m.p. 185–188°C, IR (KBr) (ν_{max} cm^{-1}): 3255(OH),1729 (C=O, ester),1643 (C=O, amide). Analyses: Calcd. for $C_{27}H_{30}NO_9P$: C, 59.67; H, 5.56; N, 2.58%. Found: C, 59.72; H, 5.48; N, 2.60. MS (*m/z*,%): 543 (11). ^{1}H NMR (500 MHz, d_6-DMSO): δ 0.87 and 0.93 (6 H, t, 2 CH_3), 3.71–3.76(4 H, m, 2 $POCH_2$), 3.50 and 3.82 (6 H, 2 s, 2 OCH_3), 4.54 (1 H, dd, $^2J_{HP}$ = 21 Hz, $^3J_{HH}$ = 11 H_Z, CH), 5.21 (1 H, dd, $^3J_{HP}$ = 6 Hz, $^3J_{HH}$ = 11 H_Z, CH), 7.13–8.57 (10 H, m, aromatic), 9.91 and 12.43 (2 H, 2 s, NH and OH). ^{13}C NMR (125.8 MHz, d_6-DMSO-Me_4Si): δ 16.08 and 16.22 (2 *C*H_3), 41.93 (d, $^2J_{cp}$

= 2 H_Z, P–C–*C*), 43.78 (d, $^1J_{cp}$ = 131 H_Z, P-*C*), 53.28 and 53.60 (2 O*C*H_3), 61.73 and 62.38 (2 d, $^2J_{cp}$ = 7 H_Z, 2 PO*C*H_2), 116.27, 117.77, 123.33, 123.80, 125.52, 127.46, 129.43, 130.76, 136.06 and 156.09 (naphthol moiety), 121.80, 122.77, 129.54, 137.31 (phenyl moiety), 169.27(C=O), 170.16(d, $^2J_{CP}$ = 6 H_Z, C=O), 173.03 (d, $^3J_{CP}$ = 21 H_Z, C=O). ^{31}P NMR (202.5 MHz, d_6-DMSO): δ 19.80.

Dimethyl 2-(dibutoxyphosphoryl)-3-[2-hydroxy-3-(phenylcarbamoyl) naphthalen-1-yl]succinate **(4c):** White powder, yield 1.12 g (91%), m.p. 190–193°C, IR (KBr) (ν_{max} cm^{-1}): 3250 (OH),1724 (C=O, ester), 1641 (C=O, amide). Analyses: Calcd. for $C_{31}H_{38}NO_9P$: C, 62.10; H, 6.39; N, 2.34%. Found: C, 62.18; H, 6.30; N, 2.42. MS (*m/z*,%): 599 (7). ^{1}H NMR (500 MHz, d_6-DMSO): δ 0.83 (6 H, t, 2 CH_3), 0.93 (4 H, sextet, 2 CH_2), 1.32(4 H, quintet, 2 CH_2), 3.71–3.86 (4 H, m, 2 POCH_2), 3.60 and 3.92 (6 H, 2 s, 2 OCH_3), 4.72 (1 H, dd, $^2J_{HP}$ = 21 Hz, $^3J_{HH}$ = 11 H_Z, CH), 5.34 (1 H, dd, $^3J_{HP}$ = 6 Hz, $^3J_{HH}$ = 11 H_Z, CH), 7.12–8.56 (10 H, m, aromatic), 9.06 and 12.64 (2 H, 2 s, NH and OH). ^{13}C NMR (125.8 MHz, d_6-DMSO-Me_4Si): δ 13.94 and 14.02 (2 *C*H_3), 18.87 and 18.96 (2CH_2), 32.32 and 32.64 (2 d, $^3J_{CP}$ = 7 Hz, 2 CH_2), 42.12 (d, $^2J_{cp}$ = 2 H_Z, P–C–*C*), 44.82 (d, $^1J_{cp}$ = 131 H_Z, P-*C*), 53.11 and 53.38 (2 O*C*H_3), 66.53 and 66.91 (2 d, $^2J_{cp}$ = 7 H_Z, 2 PO*C*H_2), 116.22, 117.01, 123.27, 123.71, 125.78, 127.47, 129.04, 130.17, 135.86 and 156.61 (naphthol moiety), 121.50, 122.82, 129.29 and 137.39 (phenyl moiety), 169.01 (C=O), 170.16(d, $^2J_{CP}$ = 6 H_Z, C=O), 172.92 (d, $^3J_{CP}$ = 21 H_Z, C=O). ^{31}P NMR (202.5 MHz, d_6-DMSO): δ 21.65.

Dimethyl 2-(dimethoxyphosphoryl)-3-[2-hydroxy-3-(2-methylphenyl-carbamoyl)naphthalen-1-yl]succinate **(4d):** White powder, yield 1.03 g (95%), m.p. 194–197°C, IR (KBr) (ν_{max} cm^{-1}): 3200(OH), 1729(C=O, ester), 1641(C=O, amide). Analyses: Calcd. for $C_{26}H_{28}NO_9P$: C, 58.98; H, 5.33; N, 2.65%. Found: C, 59.45; H, 5.22; N, 2.73. MS (*m/z*,%): 529 (6). ^{1}H NMR (500 MHz, d_6-DMSO): δ 2.34 (3 H, s, C*H*$_3$), 3.13 and 3.43 (6 H, 2d, $^3J_{HP}$ = 11 Hz, 2 POCH_3), 3.60 and 3.90 (6 H, 2 s, 2 OCH_3), 4.62 (1 H, dd, $^2J_{HP}$ = 21 Hz, $^3J_{HH}$ = 11 H_Z, CH), 5.32 (1 H, dd, $^3J_{HP}$ = 6 Hz, $^3J_{HH}$ = 11 H_Z, CH), 7.17–8.21 (9 H, m, aromatic), 8.90 and 12.61 (2 H, 2 s, NH and OH). ^{13}C NMR (125.8 MHz, d_6-DMSO–Me_4Si): δ 18.46 (*C*H_3), 41.95 (d, $^2J_{cp}$ = 2 H_Z, P–C–*C*), 43.95 (d, $^1J_{cp}$ = 131 H_Z, P–*C*), 53.17 and 53.28 (2 O*C*H_3), 66.32 and 66.58 (2 d, $^2J_{cp}$ = 7 H_Z, 2 PO*C*H_3), 116.13, 117.14, 123.20, 124.08, 126.49, 127.47, 129.00, 130.36, 135.06 and 156.49 (naphthol moiety), 127.34, 127.43, 129.21, 131.10, 133.31 and 135.89 (phenyl moiety), 169.23 (C=O), 170.30 (d, $^2J_{CP}$ = 6 H_Z, C=O), 173.31 (d, $^3J_{CP}$ = 21 H_Z, C=O). ^{31}P NMR (202.5 MHz, d_6-DMSO): δ 20.71.

Dimethyl2-(diethoxyphosphoryl)-3-[2-hydroxy-3-(2-methylphenyl-carbamoyl)naphthalen-1-yl]succinate **(4e):** White powder, yield 1.05 g (93%), m.p. 175–178°C, IR (KBr) (ν_{max} cm^{-1}): 3195 (OH), 1725 (C=O, ester),1642 (C=O, amide). Analyses: Calcd. for $C_{28}H_{32}NO_9P$: C, 60.32; H, 5.79; N, 2.51%. Found: C, 60.48; H, 5.70; N, 2.55. MS (*m/z*,%): 557 (9). ^{1}H NMR (500 MHz, d_6-DMSO): δ 0.96 and 1.11 (6 H, t, 2 CH_3), 2.36 (3 H, s, C*H*$_3$), 3.72–3.82 (4 H, m, 2 POCH_2), 3.61 and 3.91 (6 H, 2 s, 2 OCH_3), 4.62 (1 H, dd, $^2J_{HP}$ = 21 Hz, $^3J_{HH}$ = 11 H_Z, CH), 5.34 (1 H, dd, $^3J_{HP}$ = 6 Hz, $^3J_{HH}$ = 11 H_Z, CH), 7.15–8.72 (9 H, m, aromatic), 8.95 and 12.50 (2 H, 2 s, NH and OH). ^{13}C NMR (125.8 MHz, d_6-DMSO-Me_4Si): δ 16.34 and 16.48 (2*C*H_3),18.43 (*C*H_3),42.09(d,$^2J_{cp}$=2H_Z,P-C-*C*),44.23(d,$^1J_{cp}$=131H_Z, P-*C*), 53.14 and 53.43 (2 O*C*H_3), 62.66 and 62.88 (2 d, $^2J_{cp}$ = 7 H_Z, 2 PO*C*H_2), 116.29, 117.53, 123.69, 124.12, 126.10, 127.45, 129.70, 130.87, 135.01 and 156.40 (naphthol moiety), 127.17, 127.37, 130.13, 131.15, 133.62 and 136.08 (phenyl moiety), 169.12 (C=O), 170.49(d, $^2J_{CP}$ = 6 H_Z, C=O), 173.17 (d, $^3J_{CP}$ = 21 H_Z, C=O). ^{31}P NMR (202.5 MHz, d_6-DMSO): δ 20.31.

Dimethyl2-(dibutoxyphosphoryl)-3-[2-hydroxy-3-(2-methylphenyl-carbamoyl)naphthalen-1-yl]succinate **(4f):** White powder, yield 1.10 g (90%), m.p. 181–184°C, IR (KBr) (ν_{max} cm^{-1}): 3150 (OH), 1727 (C=O, ester), 1640 (C=O, amide). Analyses: Calcd. for $C_{32}H_{40}NO_9P$: C, 62.63; H, 6.57; N, 2.28%. Found: C, 62.70; H, 6.47; N, 2.30. MS (*m/z*,%): 613 (8). ^{1}H NMR (500 MHz, d_6-DMSO): δ 0.82 (6 H, t, 2 CH_3), 0.91 (4 H, sextet, 2 CH_2), 1.29 (4 H, quintet, 2 CH_2), 2.35 (3 H, s, C*H*$_3$), 3.70–3.78 (4 H, m, 2 POCH_2), 3.60 and 3.89 (6 H, 2 s, 2 OCH_3), 4.63 (1 H, dd, $^2J_{HP}$ = 21 Hz, $^3J_{HH}$ = 11 H_Z, CH), 5.34 (1 H, dd, $^3J_{HP}$ = 6 Hz, $^3J_{HH}$ = 11 H_Z, CH), 7.13–8.76 (9 H, m, aromatic), 8.80 and 12.47 (2 H, 2 s, NH and OH). ^{13}C NMR (125.8 MHz, d_6-DMSO-Me_4Si): δ 13.96 and 14.00 (2 *C*H_3), 18.46 (*C*H_3), 18.85 and 18.93 (2CH_2), 32.66 and 32.58 (2 d, $^3J_{CP}$ = 7 Hz, 2 CH_2), 42.11 (d, $^2J_{cp}$ = 2 H_Z, P–C–*C*), 44.63 (d, $^1J_{cp}$ = 131 H_Z, P–*C*), 53.09 and 53.42 (2 O*C*H_3), 66.32 and 66.57 (2 d, $^2J_{cp}$ = 7 H_Z, 2 PO*C*H_2), 116.24, 117.50, 123.61, 124.08, 126.14, 127.47, 129.66, 130.83, 135.06 and 156.43 (naphthol moiety), 127.15, 127.38, 130.13, 131.13, 134.01 and 136.05 (phenyl moiety), 169.10 (C=O), 170.45(d, $^2J_{CP}$ = 6 H_Z, C=O), 173.46 (d, $^3J_{CP}$ = 21 H_Z, C=O). ^{31}P NMR (202.5 MHz, d_6-DMSO): δ 21.37

General procedure for preparation of compounds **10a–d**

Dimethyl 2-[2-hydroxy-3-(phenylcarbamoyl)naphthalen-1-yl]-but-2-enedioate (**10a**)*:* To a magnetically stirred solution of 0.53 g of phenyl (3-hydroxynaphthalene)–2-carboxamide (2 mmol) and 0.28 g of DMAD (2 mmol) in 10 ml acetone was added a mixture of 0.53 g triphenylphosphine (2 mmol) in 2 ml acetone at room temperature. The reaction mixture was then allowed to stir for 24 h. The solvent was evaporated at reduced pressure. The residue was precipitated in a solution of diethyl ether-hexane. The solid was filtered and washed with diethyl ether to give the pure product.

Yellow powder, yield 92%, m.p. 179–181°C, IR (KBr) (ν_{max} cm^{-1}): 3305 OH), 1722 (C=O, ester), 1692 (C=O, amide). MS (*m/z*,%): 405 (7). ^{1}H NMR (500 MHz, δ, $CDCl_3$): 3.74 and 3.83 (6 H, 2 s, 2 OCH_3), 6.44 (1 H, s, CH), 7.21–8.75 (10 H, m, aromatic),). 10.17 and 12.33 (2 H, 2 s, NH and OH). ^{13}C NMR (125.8 MHz, δ, $CDCl_3$): 51.78 and 52.06 (2 O*C*H_3), 130.17 (C), 139.20 (C), 117.21, 118.01, 124.46, 125.44, 127.24, 129.87, 129.95, 130.46, 135.40 and 155.09 (naphthol moiety), 122.00, 123.91, 129.21, 138.09 (phenyl moiety), 165.77 (C=O), 167.12 (C=O), 169.08 (C=O). Anal. Calcd. for $C_{23}H_{19}NO_6$: C, 68.14; H, 4.72; N, 3.46%. Found: C, 68.5; H, 4.45; N,3.65%.

Diethyl 2-[2-hydroxy-3-(phenylcarbamoyl)naphthalen-1-yl]-but-2-enedioate (**10b**)**:** Yellow powder, yield 90%, m.p. 168–170°C, IR (KBr) (ν_{max} cm^{-1}): 3390(OH), 1704 (C=O, ester), 1683 (C=O, amide). MS (*m/z*,%): 433 (10). ^{1}H NMR (500 MHz,,δ, $CDCl_3$): 1.24 and 1.35 (6 H, 2t, 2 CH_3), 4.18 and 4.31(4 H, 2q, 2 OCH_2), 6.42 (1 H, s, CH), 7.21–8.57 (10 H, m, aromatic), 10.17 and 12.31 (2 H, 2 s, NH and OH). ^{13}C NMR (125.8 MHz, δ, $CDCl_3$): 13.71 and 13.94 (2 *C*H_3), 61.02 and 61.26 (2 O*C*H_2), 130.20 (C), 139.28 (C), 117.24, 118.26, 124.42, 125.42, 127.24, 129.78, 129.93, 130.39, 135.46 and 155.09 (naphthol moiety), 121.98, 124.00, 129.20, 138.12 (phenyl moiety), 165.34(C=O), 166.64(C=O), 169.24 (C=O). Anal. Calcd. for $C_{25}H_{23}NO_6$: C, 69.27; H, 5.35; N, 3.23%. Found: C, 69.40; H, 5.25; N, 3.3%.

Dimethyl 2-[2-hydroxy-3-(2-methylphenylcarbamoyl)naphthalen-1-yl]-but-2-enedioate (**10c**)**:** Yellow powder, yield 90%, m.p. 163–165°C, IR (KBr) (ν_{max} cm^{-1}): 3375 (OH), 1713 (C=O, ester), 1642 (C=O, amide). MS (*m/z*,%): 419 (9). ^{1}H NMR (500 MHz, δ, $CDCl_3$): 2.94 (3 H, s, C*H*$_3$), 3.51 and 3.73 (6 H, 2 s, 2 OCH_3), 6.45 (1 H, s, CH), 7.26–8.87 (9 H, m, aromatic), 10.11 and 12.41 (2 H, 2 s, NH and OH). ^{13}C NMR (125.8 MHz, δ, $CDCl_3$): 17.81(*C*H_3), 51.45 and 52.59 (2 O*C*H_3), 129.90 (C), 138.85 (C), 116.69, 117.26, 123.61, 123.99, 126.66, 127.26, 128.90, 130.94, 135.39 and 154.52 (naphthol moiety), 127.05, 127.17, 129.04, 131.40, 133.03 and 135.40 (phenyl moiety), 164.66 (C=O), 166.73(C=O), 169.52 (C=O). Anal. Calcd. for $C_{24}H_{21}NO_6$: C, 68.73; H, 5.05; N, 3.34%. Found: C, 68.9; H, 4.95; N, 3.4%.

Diethyl 2-[2-hydroxy-3-(2-methylphenylcarbamoyl)naphthalen-1-yl]-but-2-enedioate (**10d**)**:** Yellow powder, yield 89%, m.p. 154–156°C, IR (KBr) (ν_{max} cm^{-1}): 3320(OH), 1719(C=O, ester), 1648(C=O, amide). MS (*m/z*,%): 447 (6). ^{1}H NMR (500 MHz, δ, $CDCl_3$): 0.99 and 1.28 (6 H, 2t, 2 CH_3), 2.50 (3 H, s, C*H*$_3$), 4.38 and 4.50 (4 H, 2q, 2 OCH_2), 6.30 (1 H, s, CH), 7.17–8.52 (9 H, m, aromatic), 9.03 and 11.80 (2 H, 2 s, NH and OH). ^{13}C NMR (125.8 MHz, δ, $CDCl_3$): 14.09 and 14.46 (2 *C*H_3), 18.43 (*C*H_3), 61.13 and 62.80 (2 O*C*H_2), 131.04 (C), 140.42 (C), 117.02, 117.83, 122.86, 124.28, 125.25, 127.30, 129.54, 131.63, 135.60 and 154.00 (naphthol moiety), 126.37, 127.09, 129.69, 132.17, 134.84 and 138.11 (phenyl moiety), 165.13 (C=O), 166.68 (C=O), 168.66 (C=O). Anal. Calcd. for $C_{26}H_{25}NO_6$: C, 69.79; H, 5.63; N, 3.13%. Found: C, 69.9; H, 5.5; N,3.2%.

General procedure for preparation of compounds **14a–d**

Dimethyl 2-(methoxycarbonylmethyl)-4-oxo-3-phenyl-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-2-carboxylate (**14a**): A mixture of 0.53 g of *N*-phenyl-3-hydroxynaphthalene)–2-carboxamide (2 mmol) and 0.28 g of DMAD (2 mmol) in 10 ml acetone was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was purified by silica gel (Merck silica gel 60, 230–400 mesh) column chromatography using hexane-ethyl acetate as eluent. The solvent was removed under reduced pressure to afford the product.

Yellow powder, yield 92%, m.p. 161–163°C, IR (KBr) (ν_{max} cm^{-1}): 3458 (OH), 1744 (C=O, ester), 1673 (C=O, amide). MS (*m/z*,%): 405 (8). ^{1}H NMR (500 MHz,,δ, $CDCl_3$): 3.28 (2 H, AB quartet, $^2J_{HH}$ = 16 H_Z, CH_2), 3.42 and 3.72 (6 H, 2 s, 2 OCH_3), 7.46–8.59 (11 H, m, aromatic). ^{13}C NMR (125.8 MHz, δ, $CDCl_3$): 42.84 (*C*H_2), 52.37 and 53.92 (2 O*C*H_3), 91.57 (C), 112.70, 118.48, 129.24, 129.47, 129.70, 129.98, 130.02, 131.24, 136.84 and 151.31(naphthol moiety), 125.69, 127.40, 130.85, 137.14 (phenyl moiety), 162.44 (C=O), 167.87 (C=O), 168.83 (C=O). Anal. Calcd. for $C_{23}H_{19}NO_6$: C, 68.14; H, 4.72; N, 3.46%. Found: C, 68.3; H, 4.70; N, 3.5%.

Diethyl 2-(methoxycarbonylmethyl)-4-oxo-3-phenyl-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-2-carboxylate (**14b**)**:** Yellow powder, yield 87%, m.p. 126–128°C, IR (KBr) (ν_{max} cm^{-1}): 3465 (OH), 1727 (C=O, ester),1673 (C=O, amide). MS (*m/z*,%): 433 (9). ^{1}H NMR (500 MHz, δ, $CDCl_3$): 1.05 and 1.11 (6 H, 2t, 2 CH_3), 3.27 (2 H, AB quartet, $^2J_{HH}$ = 16 H_Z, CH_2), 3.78–4.18 (4 H, m, 2 OCH_2), 7.47–8.53 (11 H, m, aromatic). ^{13}C NMR (125.8 MHz, δ, $CDCl_3$): 13.62 and 13.67 (2CH_3), 42.38 (*C*H_2), 60.93 and 62.75 (2 O*C*H_2), 91.78 (C), 112.56, 119.21, 129.05, 129.23, 129.78, 129.92, 130.12, 131.43, 137.13 and 151.65(naphthol moiety), 125.71, 127.36, 131.64, 137.42 (phenyl moiety), 161.86 (C=O), 166.97 (C=O), 168.05 (C=O). Anal. Calcd. for $C_{25}H_{23}NO_6$: C, 69.27; H, 5.35; N, 3.23%. Found: C, 69.4; H, 5.24; N, 3.3%.

Dimethyl 2-(methoxycarbonylmethyl)-4-oxo-3-o-tolyl-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-2-carboxylate (**14c**)**:** Yellow powder, yield 93%, m.p. 158–160°C, IR (KBr) (ν_{max} cm^{-1}): 3470 (OH), 1730 (C=O, ester), 1675(C=O, amide). MS (*m/z*,%): 419 (9). ^{1}H NMR (500 MHz, δ, $CDCl_3$): 2.84 (3 H, s, C*H*$_3$), 3.30 (2 H, AB quartet, $^2J_{HH}$ = 16 H_Z, CH_2), 3.36 and 3.71 (6 H, 2 s, 2 OCH_3), 7.46–8.55 (10 H, m, aromatic). ^{13}C NMR (125.8 MHz, δ, $CDCl_3$): 17.90 (*C*H_3), 42.40 (*C*H_2), 60.95 and 62.77 (2 O*C*H_3), 91.80 (C), 112.74, 119.21, 125.72, 126.81, 129.06, 129.95, 130.18, 131.36, 137.13 and 151.65(naphthol moiety), 127.37, 129.25, 131.12, 131.66, 136.41 and 138.21 (phenyl moiety), 161.61 (C=O), 168.06 (C=O), 169.04 (C=O). Anal. Calcd. for $C_{24}H_{21}NO_6$: C, 68.73; H, 5.05; N, 3.34%. Found: C, 68.8; H, 4.9; N, 3.4%.

Diethyl 2-(methoxycarbonylmethyl)-4-oxo-3-o-tolyl-3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-2-carboxylate (**14d**)**:** Yellow powder, yield 90%, m.p. 125–127°C, IR (KBr) (ν_{max} cm^{-1}): 3430 (OH), 1745 (C=O, ester), 1681 (C=O, amide). MS (*m/z*,%): 447 (6). ^{1}H NMR (500 MHz,,δ, $CDCl_3$): 1.14 and 1.16 (6 H, 2t, 2 CH_3), 2.34 (3 H, s, C*H*$_3$), 3.10 (2 H, AB quartet, $^2J_{HH}$ = 16 H_Z, CH_2), 3.76–4.25 (4 H, m, 2 OCH_2), 7.29–8.62 (10 H, m, aromatic). ^{13}C NMR (125.8 MHz, δ, $CDCl_3$): 14.26 and 14.30 (2CH_3), 18.69 (*C*H_3), 42.30 (*C*H_2), 61.60 and 63.21 (2 O*C*H_2), 91.81 (C), 112.76, 118.90, 125.65, 127.41, 129.58, 129.94, 130.02, 131.29, 137.16 and 151.88(naphthol moiety), 127.21, 129.22, 130.83, 131.41, 136.16 and 138.04 (phenyl moiety), 161.92 (C=O), 167.35 (C=O), 168.50 (C=O). *Anal*. Calcd. for $C_{26}H_{25}NO_6$: C, 69.79; H, 5.63; N, 3.13%. Found: C, 69.9; H, 5.6; N, 3.2%.

Received 7 November 2007; accepted 17 December 2007
Paper 07/4899 doi: 10.3184/030823407X272138

References

1 D.E.C. Corbridge, *Phosphorus an Outline of the Chemistry Biochemistry and Uses*, 5th edn, Elsevier, Amsterdam, 1995.
2 A.W. Johnson, W.C. Kaska, A.O. Starzewski and D.A. Dixon, *Ylides and Imines of Phosphorus*, John Wiley & Sons, 1993, pp.386-387.
3 I. Yavari and M. Anary-Abbasinejad, *Org. Biomo.l Chem.,* 2003, **3**, 560.
4 M. Anary-Abbasinejad and N. Ascarrian, *J Chem Res.*, 2007, 11.
5 M. Anary-Abbasinejad, N. Rostami, A. Parhami and A. Hassanabadi*, J. Chem. Res.*, 2007, 257.
6 M. Anary-Abbasinejad, A. Hassanabadi and H. Anaraki-Ardakani, *J. Chem. Res.*, 2007, 455.
7 M. Anary-Abbasinejad and A. Hassanabadi, *J. Chem. Res.*, 2007, 475.
8 M. Anary-Abbasinejad, H. Anaraki-Ardakani, A. Dehghan, A. Hassanabadi and M.R. Seyedmir, *J. Chem. Res., 2007*, in press.
9 M. Karplus, *J. Am. Chem. Soc.*, 1963, **88**, 2870.
10 C.A.G. Haasnot, F.A.A.M. De Leeuww and C. Altona, *Tetrahedron*, 1980, **36**, 2783.
11 E. Breitmaier and W. Voelter, *Carbon-13 NMR Spectroscopy,* 3rd edn, VCH New York, 1990, p. 250.

Synthesis and characterisation of modified germanium (IV) isopropoxide with internally functionalised oximes: soft transformation of some of these to pure nano-sized germania

Sangeeta Agrawal[a], R. Bohra[a]*, Meena Nagar[a] and V.S. Raju[b]

[a]*Department of Chemistry, University of Rajasthan, Jaipur 302004, India*

[b]*National Centre for Composition of Materials, Bhabha Atomic Research Centre, Hyderabad-500062, India*

Reactions of $[Ge(OPr^i)_4]$ with internally functionalised oximes in 1:1 and 1:2 molar ratios in refluxing anhydrous benzene yielded complexes of the type $[Ge(OPr^i)_{4-n}\{ONC(CH_3)C_4H_3O\text{-}2\}_n]$ **(1, 2)**; $[Ge(OPr^i)_{4-n}\{ONC(CH_3)C_4H_3S\text{-}2\}_n]$ **(3, 4)**; $[Ge(OPr^i)_{4-n}\{ONC(CH_3)C_5H_4N\text{-}2\}_n]$ **(5, 6)**; $[Ge(OPr^i)_{4-n}\{ONC(H)C_4H_3O\text{-}2\}_n]$ **(7, 8)**; $[Ge(OPr^i)_{4-n}\{ONC(H)C_4H_3S\text{-}2\}_n]$ **(9, 10)**; $[Ge(OPr^i)_{4-n}\{ONC(H)C_5H_4N\text{-}2\}_n]$ **(11, 12)** (where n = 1 or 2), All the above monomeric complexes are soluble in organic solvents and have been characterised by elemental analyses and spectroscopy. Thermal and hydrolytic studies of complexes **2, 4** and **8** suggest them to be potential molecular precursors for the synthesis of pure GeO_2 at low temperatures by the sol-gel technique. Powder X-ray diffraction, IR spectral studies as well as SEM images of the GeO_2 indicate formation of pure nano-crystalline hexagonal (α-quartz) germania at 550°C.

Keywords: nano-sized germania, germanium(IV) isopropoxide

Interest in the development of a sol-gel method for the preparation of germania-based glasses is growing continuously.[1-3] Germania (GeO_2) is a promising material for optical devices such as optical wave guides[4,5] for integrated optical systems and for nano-connections in future opto-electronic communications.[6-1○]

One of the advantages of the sol-gel process using metal alkoxides is that the required temperature can be kept quite low to allow deposition of oxides on thermo-sensitive substrates such as organic substrates.[11] Recently, a few experimental data on the mechanisms of chemical modifications, hydrolysis and polycondensation of alkoxides have been reported. It has been shown that the low reactivity of $Si(OR)_4$ [or $Ge(OR)_4$] is improved either by basic catalysis exploiting an SN^2 mechanism, or by acidic catalysis facilitating a proton-assisted SN^1 mechanism, as well as by modification with chelating ligands.[12]

The alkoxy and glyoxy derivatives of tetravalent germanium have received less attention as compared to other tetravalent elements (Si, Sn, Ti and Zr).[13-15] Alkoxy derivatives of Ge(IV) generally prefer a tetracoordinated structure even with alkoxy alkanols.[16] Penta- and hexacoordinated-derivatives of Ge(IV) with complex organic moieties have also been cited in the literature.[17-19] The synthesis and characterisation of Ge(IV) diolates of the type $[Ge\ (OPr^i)_{4-2n}\ (O\text{-}G\text{-}O)_n]$ (n = 1,2) and the crystal structure of a unique diolato-bridged compound $[Ge_2(O_2C_2H_4)_4]$, in which the geometry around the germanium atom is distorted trigonal bipyramidal, have been reported.[20]

The preparation and the morphology of germanium oxide[6,21] nanofibres from isopropanol solutions of $Ge(OPr^i)_4$ in presence of a few drops of propionic acid and deionised water have been reported. Low-temperature transformation of some tin(IV) complexes to yield pure SnO_2 microcrystals using a sol-gel technique has also been achieved.[22,23]

In this article, we report the synthesis and characterisation of modified germanium(IV) isopropoxides with weakly acidic organic ligands such as internally functionalised oximes. Results of the hydrolysis-condensation reactions of some of these derivatives are also reported.

Results and discussion

Compounds of the type $[Ge\{ONC(R)Ar\}_n\ (OPr^i)_{4-n}\}]$ have been prepared by the reactions of germanium tetraisopropoxide and internally functionalised oximes in 1 : 1 and 1 : 2 molar ratios in refluxing anhydrous benzene, as shown in equation (1).

$$[Ge(OPr^i)_4] + n\ HONC(R)Ar \rightarrow [Ge\{\ ONC(R)Ar\}_n\ (OPr^i)_{4-n}] + n\ Pr^iOH \quad (1)$$

(where R = Me, H; Ar = 2-C_4H_3O, 2-C_4H_3S or 2-C_5H_4N and n = 1 or 2)

All these reactions are quantitative and the liberated isopropanol was removed as a benzene-isopropanol azeotrope in ~5 h. Completion of these reactions was checked by estimating (oxidimetrically) the liberated isopropanol in the azeotrope. All the complexes are coloured liquids, semi-solids or solids and are soluble in organic solvents. Elemental analyses corresponded to the expected formula (Table 3).

Table 1 IR spectral data (cm^{-1}) of germanium(IV) complexes with internally functionalised oximes

Compound	Isopropoxy moiety ν (C–O)	ν (Ge– + –O)	ν (C=N)
$[Ge(OPr^i)_3\{ONC(Me)C_4H_3O\text{-}2\}]$ **(1)**	1010 m	875 m	1430 m
$[Ge(OPr^i)_2\{ONC(Me)C_4H_3O\text{-}2\}_2]$ **(2)**	1015 m	877 s	1475 m
$[Ge(OPr^i)_3\{ONC(Me)C_4H_3S\text{-}2\}\ ]$ **(3)**	1020 m	865 s	1480 s
$[Ge(OPr^i)_2\{ONC(Me)C_4H_3S\text{-}2\}_2]$ **(4)**	1025 m	872 s	1482 m
$[Ge(OPr^i)_3\{ONC(Me)C_5H_4N\text{-}2\}]$ **(5)**	1018 m	869 s	1483 s
$[Ge(OPr^i)_2\{ONC(Me)C_5H_4N\text{-}2\}_2]$ **(6)**	1015 m	883 m	1477 m
$[Ge(OPr^i)_3\{ONC(H)C_4H_3\text{-}O\text{-}2\}]$ **(7)**	1006 m	878 m	1483 m
$[Ge(OPr^i)_2\{ONC(H)C_4H_3\text{-}O\text{-}2\}_2]$ **(8)**	1009 m	874 m	1472 m
$[Ge(OPr^i)_3\{ONC(H)C_4H_3\text{-}S\text{-}2\}]$ **(9)**	1014 m	888 m	1478 s
$[Ge(OPr^i)_2\{ONC(H)C_4H_3\text{-}S\text{-}2\}_2]$ **(10)**	1028 m	873 m	1480 m
$[Ge(OPr^i)_3\{ONC(H)C_5H_4\text{-}N\text{-}2\}]$ **(11)**	1021 m	869 m	1486 m
$[Ge(OPr^i)_2\{ONC(H)C_5H_4\text{-}N\text{-}2\}_2]$**(12)**	1026 m	870 s	1492 m

* Correspondent. E-mail: rkbohra@satyam.net.in

Molecular weight measurements indicate the monomeric nature of these complexes in refluxing benzene. The FAB mass spectra of two of the compounds, **(8)** and **(12)**, also supports the monomeric nature of these derivatives.

IR spectra

IR spectra of these compounds were interpreted by comparing their spectra with those of the free ligands and related derivatives. A medium intensity band at 3100–3300 cm^{-1} in the free ligands due to ν(OH) is absent in the IR spectra of all these complexes, indicating deprotonation of the internally functionalised oximes and the formation of a metal–ligand bond through the oxygen atom. This is further supported by the appearance of a new broad band due to both $GeOPr^i$ and Ge-oxime bonds[24] in the region 865–888 cm^{-1}. In the case of pure $Ge(OPr^i)_4$, ν (Ge-O) appears at 855 cm^{-1}. The isopropoxy ν (C-O) has been observed in the region 1006–1028 cm^{-1} in all the complexes. Appearance of a medium to strong band in the region 1430–1492 cm^{-1} due to ν(C=N), suggests the monodentate behaviour of the oxime moiety (Table 1).

^1H NMR spectra

In the ^1H NMR spectra of all these compounds, the hydroxyl proton resonances of the free ligands (8.6–10.1 ppm, br.) are absent, indicating deprotonation of the –OH group of the oxime moiety and formation of a Ge–O bond. No appreciable shift was observed in the positions of heterocyclic ring protons in the ligand moiety, which were observed at their expected positions, ruling out the possibility of coordination through the hetero-atom of the oxime moiety. The methyl group of the isopropoxy moiety[25] in all these complexes appears in the range δ 1.11–1.31 ppm as doublets and the CH proton appears in the range δ 3.8–4.6 ppm as multiplets.

$^{13}C\{^1H\}$ NMR spectra

In the ^{13}C NMR and ^1H NMR spectra of all these complexes a slight shift (0.1–1.1 ppm) in the C=N signal was observed as compared to its position in the corresponding free oxime, indicating the formation of the Ge–O bond. The carbon signals due to the heterocyclic ring of the functionalised oximes are observed at their expected positions indicating that the

Table 2 NMR data in $CDCl_3$ for $[Ge(OPr^i)_{4-n}\{ONC(R)Ar\}_n]$ complexes

Compound	^1H NMR δ ppm	$^{13}C\{^1H\}$ NMR δ ppm
$[Ge(OPr^i)_3\{ONC(Me)C_4H_3O\text{-}2\}]$ **(1)**	1.28 (d, 6.0 Hz, isopropoxy-CH_3); 4.49 (m, -OCH); 2.24 (s, oxime-CH_3); 6.43 (m, H-4); 6.68 (d, 15.4 Hz, H-3); 7.47 (d, 5.9 Hz, H-5).	25.4 (isopropoxy-CH_3); 68.2 & 67.8 (-OCH); 11.0 (oxime-CH_3); 109.5 (C-4); 111.2 (C-3); 143.4 (C-5); 147.3 (C-2); 150.1 (C=N).
$[Ge(OPr^i)_2\{ONC(Me)C_4H_3O\text{-}2\}_2]$ **(2)**	1.31(d, 6.0 Hz, isopropoxy-CH_3); 4.55 (m, -OCH); 2.24 (s, oxime-CH_3); 6.42 (m, H-4); 6.69 (d, 3.3 Hz, H-3); 7.45 (br., H-5).	25.6(isopropoxy-CH_3); 68.4 & 69.2 (-OCH); 11.2 (oxime-CH_3); 109.6 (C-4); 111.3(C-3), 143.5 (C-5); 145.7 (C-2); 150.0 (C=N).
$[Ge(OPr^i)_3\{ONC(Me)C_4H_3S\text{-}2\}]$ **(3)**	1.29 (d, 6.0 Hz, isopropoxy-CH_3); 4.43 (m, -OCH); 2.32 (s, oxime-CH_3); 7.01 (m, H-4); 7.25 (m, H-3); 7.27 (m, H-5).	26.5 (isopropoxy-CH_3); 67.3 & 63.1 (-OCH); 12.2 (oxime-CH_3); 126.1 (C-4); 126.8 (C-3); 127.5 (C-5); 140.2 (C-2); 151.4 (C=N).
$[Ge(OPr^i)_2\{ONC(Me)C_4H_3S\text{-}2\}_2]$ **(4)**	1.31(d, 6.0 Hz, isopropoxy-CH_3); 4.59 (m, -OCH); 2.30 (s, oxime-CH_3), 7.0 (m, H-4); 7.27(m, H-3 & H-5).	25.4 (isopropoxy-CH_3); 67.4 & 69.1 (-OCH); 12.0 (oxime-CH_3); 126.1 (C-4); 126.7 (C-3); 127.1 (C-5); 140.0 (C-2); 151.2 (C=N).
$[Ge(OPr^i)_3\{ONC(Me)C_5H_4N\text{-}2\}]$ **(5)**	1.28 (m, isopropoxy-CH_3); 4.32 (m, -OCH); 2.42 (s, oxime-CH_3); 7.27(d, d, 5.7 Hz-d, 4.9 Hz-d, H-4); 7.68 (td, 7.8 Hz-t, 1.8 Hz-d, H-5); 7.93 (d, 8.0 Hz, H-3); 8.61(d, 4.9 Hz, H-6).	25.3 (isopropoxy-CH_3); 68.3 & 67.4 (-OCH); 10.5 (oxime-CH_3); 120.9 (C-5); 123.6 (C-3); 136.2 (C-4); 148.7 (C-6); 154.1 (C-2); 156.1 (C=N).
$[Ge(OPr^i)_2\{ONC(Me)C_5H_4N\text{-}2\}_2]$ **(6)**	1.29 (d, 6.0 Hz, isopropoxy-CH_3); 4.45 (m, -OCH); 2.44(s, oxime-CH_3); 7.27 (m, H-4); 7.67 (m, H-5); 7.94 (d, 8.1 Hz, H-3); 8.60 (d, 4.4 Hz, H-6).	25.7 (isopropoxy-CH_3); 67.4 & 68.3 (-OCH); 10.6 (oxime-CH_3); 120.6 (C-5); 123.0 (C-3); 136.0 (C-4); 148.8 (C-6); 154.2 (C-2); 155.8 (C=N).
$[Ge(OPr^i)_3\{ONC(H)C_4H_3\text{-}O\text{-}2\}]$ **(7)**	1.23 (d, 6.0 Hz, isopropoxy-CH_3); 4.0 (m, -OCH); 6.50(m, H-4); 7.29 (d, 2.7 Hz, H-3); 7.47(m, H-5); 7.62 (s, CH-aldoxime).	26.0 (isopropoxy-CH_3); 67.6 & 62.5(-OCH); 111.7 (C-4); 112.2 (C-3); 143.9 (C-5); (C-2) not obsd; 157.9 (C=N).
$[Ge(OPr^i)_2\{ONC(H)C_4H_3\text{-}O\text{-}2\}_2]$ **(8)**	1.22(d, 6.0 Hz, isopropoxy-CH_3); 4.0 (m, -OCH); 6.54 (m, H-4); 7.30 (m, H-3); 7.45 (m, H-5); 7.90 (s, CH-aldoxime).	24.6 (isopropoxy-CH_3); 62.6 (-OCH); 111.0 (C-4); 112.0 (C-3); 144.2 (C-5); 143.6 (C-2); (C=N) not obsd.
$[Ge(OPr^i)_3\{ONC(H)C_4H_3\text{-}S\text{-}2\}]$ **(9)**	1.20(d, 6.0 Hz, isopropoxy-CH_3); 4.4 (m, -OCH); 7.12 (m, H-4); 7.41(m, H-3); 7.58 (d, 5.13 Hz, H-5); 8.2 (s, CH-aldoxime).	25.2 (isopropoxy-CH_3); 62.5 (-OCH); 125.9 (C-4); 130.4 (C-3); 130.5 (C-5); 139.9 (C-2); 150.1 (C=N).
$[Ge(OPr^i)_2\{ONC(H)C_4H_3\text{-}S\text{-}2\}_2]$ **(10)**	1.11(d, 6.0 Hz, isopropoxy-CH_3); 3.8 (m, -OCH); 7.14 (m, H-4); 7.43(m, H-3); 7.58 (m, H-5); 8.3 (s, CH-aldoxime).	25.2 (isopropoxy-CH_3); 64.2 (-OCH); 126.1 (C-4); 131.3 (C-3); 131.2 (C-5); 138.3(C-2); C=N not obsd.
$[Ge(OPr^i)_3\{ONC(H)C_5H_4\text{-}N\text{-}2\}]$ **(11)**	1.23 (m, isopropoxy-CH_3); 4.03 (m, -OCH); 7.26(m, H-4), 7.69 (m, H-5); 7.80 (m, H-3), 8.6 (m, H-6), 8.30 (s, CH-aldoxime).	25.2 (isopropoxy-CH_3); 67.3 & 68.2 (-OCH); 120.8 (C-5); 123.8 (C-3); 136.1 (C-4); 148.7 (C-6); 151.0 (C-2); 153.0 (C=N).
$[Ge(OPr^i)_2\{ONC(H)C_5H_4\text{-}N\text{-}2\}_2]$ **(12)**	1.30 (d, 6.0 Hz, isopropoxy-CH3); 4.42 (m, -OCH); 7.29 (m, H-4); 7.69 (m, H-5); 7.91 (m, H-3); 8.39 (s, CH-aldoxime); 8.61 (d, 4.8 Hz, H-6).	25.6(isopropoxy-CH_3); 68.4 (-OCH); 120.8 (C-5); 123.5 (C-3); 136.5 (C-4); 149.6 (C-6); 151.1 (C-2); 152.4 (C=N).

Table 3 Synthetic and analytical data of Ge(IV) complexes with internally functionalised oximes

S.No.	Reactants (g)	Molar ratio	Yield/%	Physical state (colour)	M.p. ./b.p.°C/mm	Analysis found% (Cal.)			
	a. $Ge(OPr^i)_4$ b. HONC(R)Ar					Ge	OPr^i	N	Pr^iOH (g.)
1.	a. 2.13 b. R = Me; Ar = C_4H_3O-2 (0.86)	1:1	97.7	Liquid (brown)	Disproportionate	19.1 (19.4)	47.3 (47.4)	3.7 (3.7)	0.41 (0.41)
2.	a. 1.15 b. R = Me; Ar = C_4H_3O-2 (0.93)	1:2	97.8	Viscous	–	16.1 (16.5)	26.5 (26.9)	6.3 (6.4)	0.42 (0.44)
3.	a. (2.15) b. R = Me; Ar = C_4H_3S-2 (0.98)	1:1	98.9	Liquid	–	18.4 (18.6)	45.3 (45.4)	3.5 (3.6)	0.41 (0.41)
4.	a. 1.86 b. R = Me; Ar = C_4H_3S-2 (0.1.70)	1:2	98.5	Viscous (yellow)	–	15.39 (15.4)	24.7 (25.6)	5.7 (5.9)	0.71 (0.72)
5.	a. 2.11 b. R = Me; Ar = C_5H_4N-2 (0.93)	1:1	96	Semi solid (pink)	–	18.5 (18.8)	46.0 (46.0)	7.2 (7.3)	0.41 (0.41)
6.	a. 1.70 b. R = Me; Ar = C_5H_4N-2 (1.50)	1:2	98	Solid (canary yellow)	165	15.5 (15.7)	25.5 (25.6)	12.1 (12.1)	0.65 (0.66)
7.	a. 2.47 b. R = H; Ar = C_4H_3O-2 (0.89)	1:1	97.1	Semi solid (brown)	–	19.9 (20.1)	49.2 (49.2)	3.8 (3.9)	0.48 (0.48)
8.	a. 1.36 b. R = H; Ar = C_4H_3O-2 (0.98)	1:2	96.2	Solid (brown)	210 Dec.	17.2 (17.6)	28.5 (28.7)	6.5 (6.8)	0.53 (0.53)
9.	a. 2.17 b. R = H; Ar = C_4H_3S-2 (0.89)	1:1	99.5	Semi solid	–	19.1 (19.3)	47.0 (47.1)	3.7 (3.7)	0.42 (0.42)
10.	a. 2.32 b. R = H; Ar = C_4H_3S-2 (1.91)	1:2	97.1	Solid	180 Dec.	16.0 (16.3)	26.4 (26.6)	6.2 (6.3)	0.90 (0.90)
11.	a. 1.61 b. R = H; Ar = C_5H_4N-2 (0.63)	1:1	96.9	Semi solid (dirty yellow)	–	19.0 (19.5)	47.4 (47.7)	7.5 (7.5)	0.31 (0.31)
12.	a. 2.23 b. R = H; Ar = C_5H_4N-2 (1.76)	1:2	99.3	Solid (light brown)	130	16.6 (16.7)	26.8 (27.2)	12.8 (12.9)	0.86 (0.86)

heteroatom (O, N or S) of the ring does not take part in bond formation with the central germanium atom. A comparison of the ^{13}C NMR spectra of 1 : 1 complexes with those of 1 : 2 complexes does not indicate any significant change in the chemical shift values.

FAB mass spectra

The FAB mass spectra of two representative compounds, $[Ge(OPr^i)_2\{ONC(H)C_4H_3O\text{-}2\}_2]$ **(8)** and $[Ge(OPr^i)_2\{ONC(H)C_5H_4N\text{-}2\}_2]$ **(12)** have been recorded and the molecular ion patterns are in accord with monomeric complexes.

Thermal studies

A thermogravimetric analysis was also carried out on complex **8** with the heating rate 25–650/10°C. There are two weight loss stages for this sample (one is below 325°C and the other is from 325 to 610°C). The first weight reduction (64.1%) appears to be due to the combustion of the organic part ($C_{16}H_{11}O_2N_2$) followed by another weight reduction (8.5%) and formation of a residue.

Hydrolytic studies

Hydrolysis of three of the representative compounds $[Ge(OPr^i)_2\{ONC(Me)C_4H_3O\text{-}2\}_2]$ **(2),** $[Ge(OPr^i)_2\{ONC(Me)C_4H_3S\text{-}2\}_2]$ **(4)** and $[Ge\{OCH(CH_3)_2\}_2\{ONC(H)C_4H_3O\text{-}2\}_2]$ **(8)** provide pure GeO_2 under mild chemical conditions using a sol-gel technique. The general reaction may be illustrated as shown below:

$$\text{Complex} + Pr^iOH \text{ (used as supplied)} \xrightarrow{\text{Stirring}} \text{sol} \xrightarrow{1\text{ h}} \text{gel} \xrightarrow[110°C]{\text{Dried at}} \text{xerogel} \xrightarrow[(>600°C)]{\text{Sintered}} GeO_2 \text{ Pure nano-crystalline}$$

XRD

Powder X-ray diffraction patterns of xerogel (GeO_2) obtained from the hydrolysis of **8** and annealed at 300°C for two hours, show that crystallisation started at this temperature and is completed at higher sintering temperature (550°C for 3 h). The XRD pattern of GeO_2 obtained from other starting precursors (**2, 4**) and sintered at 550°C also suggest the formation of a hexagonal (α-quartz) phase.[7a,b] The positions of the XRD peaks are in good agreement with those of the hexagonal GeO_2 obtained by conventional method[6a] (675–1050°C) or by the sol-gel method[21](500–1000°C) using $Ge(OPr^i)_4$. The oxime-modified germanium isopropoxide yields pure GeO_2 at low-temperature.

SEM

Scanning electron micrograph images of GeO_2 obtained from the hydrolysis of the above complexes and sintered at different temperatures indicate occurrence of crystallisation and good morphology at 550°C.

IR spectra

IR spectra of xerogel obtained from the hydrolysis of **2, 4** and **8**, and sintered at 550°C show the presence of ν(Ge–O) band in the region 860–950 cm^{-1} and absence of any hydrocarbonated vibrations, confirming the formation of pure GeO_2.[26a,b]

Experimental

All the experimental manipulations were carried out under strictly inert conditions in an anhydrous atmosphere. The solvents and reagents were purified by conventional techniques. *Hazardous benzene was handled with all the necessary precautions*. Germanium tetraisopropoxide[27] and oximes[28] were synthesised and purified according to the literature methods. Germanium[29] and isopropanol[30] were estimated as reported earlier. Microanalyses were carried out on a Perkin Elmer-C, H, N & S II series analyser. The IR spectra were recorded as nujol mulls on a Nicolet magna-550 spectrometer in the range 4000–400 cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a JEOL FX 90 Q spectrometer using TMS as an internal reference in $CDCl_3$ and $CHCl_3$, respectively. FAB mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer/data system using argon/xenon (6KV, 10MA) as the FAB gas, *m*-nitrobenzyl alcohol was used as the matrix. Powder X-ray diffraction patterns were obtained on a Philips-1840 diffractometer (Fe^{57}; at λ 1.937 Å). Thermogravimetric analysis was performed on Mettler Toledo Star SW 701 with the heating rate 25 – 650/10°C. SEM images were taken on a Philips XL30 scanning electron microscope with the powders spread on a conducting carbon tape. The secondary electron imaging and backscattered electron imaging for samples (**2**, **4** and **8**) were done at 25 KV gun voltage, at a spot size 5.0 and magnifications of 1000x, 2000x and 4000x.

Preparation of $[Ge(OPr^i)_2\{ONC(Me)C_5H_4N\text{-}2\}_2]$*:* A benzene solution (~ 25 ml) of $Ge(OPr^i)_4$ (1.70 g; 5.5 m mol) was added to a benzene solution (~15 ml) of $[HONC(Me)C_5H_4N\text{-}2]$ (1.50 g; 11.0 m mol). The contents were refluxed for ~ 4 h and the progress of the reaction was monitored by the determination of the isopropanol, liberated azeotropically with benzene, by the oxidimetric method. A light yellow, clear solution was obtained. After stripping off the solvent under reduced pressure, a yellow solid was obtained in quantitative yield (98% yield).

Preparation of $[Ge(OPr^i)_3\{ONC(Me)C_5H_4N\text{-}2\}]$*:* Typically, 2-acetyl pyridyloxime (0.93 g; 6.8 m mol) was added to a benzene solution (~30 ml) of $Ge(OPr^i)_4$ (2.1 g; 6.8 m mol) and the reaction mixture was refluxed on a fractionating column for ~4 h. The isopropanol in the reaction was collected azeotropically with benzene. The progress as well as the completion of the reaction was checked by the estimation of the liberated isopropanol in the azeotrope. A pink, clear solution was obtained. After stripping off the excess solvent under reduced pressure, a pink semi solid was obtained in quantitative yield (96% yield).

Hydrolysis of complexes $[Ge(OPr^i)_2\{ONC(Me)C_4H_3O\text{-}2\}_2]$ **(2),** $[Ge(OPr^i)_2\{ONC(Me)C_4H_3S\text{-}2\}_2]$ **(4)** *and* $[Ge\{OCH(CH_3)_2\}_2\{ONC(H)C_4H_3O\text{-}2\}_2]$ **(8)**: Compound **8** (~2.6 g) was dissolved in isopropanol (~30 ml; used as supplied, E. Merck). and stirred for 24 h. Gelation occurred after 1 h. The whole mixture was dried in an oven (at 110°C) for 4 h. A creamish powder (xerogel) was obtained. This was washed several times with n-hexane and acetone (1:1) and sintered at 300°C for 2 h to give a white powder, which was characterised as pure GeO_2 obtained from **8** [C, 0.02; H, 0.07; N, 0%]. This sample was again sintered at 550°C for 3 h to ensure the retention of hexagonal phase at higher temperatures. The other complexes (**2, 4**) were also hydrolysed using the similar procedure.

All other complexes were prepared by a similar route and the details are summarised in Table 3.

Conclusion

On the basis of the molecular weight determination, IR, NMR (^1H and $^{13}C\{^1H\}$) and FAB mass spectral studies, a tetrahedral geometry around germanium atom has been proposed in solution for the above germanium (IV) compounds derived from internally functionallized oximes. Complete hydrolysis of some of the derivatives in isopropanol, followed by sintering at 550°C afforded pure nano-crystalline hexagonal (α-quartz) GeO_2 as reflected by their powder X-ray diffraction pattern, IR and SEM studies. It may be inferred from the above results that the Ge(IV) complexes with internally functionalised oximes are potential precursors for material synthesis by sol-gel technology at low temperature.

Mass spectral fragmentation patterns and detailed XRD and SEM data may be obtained on application to the authors.

We are grateful to UGC, DST and CSIR, New Delhi for financial support. We thank Prof. Anjali Krishnamurti for carrying out XRD analyses.

Received 2 August 2007; accepted 18 December 2007
Paper 07/4777 doi: 10.3184/030823407X271229

References

1 S. Shibata, T. Kitagawa, F. Hanawa and M. Horiguchi, *J. Non-Crystalline Sol.*, 1986, **88**, 345.
2 K. Kojima, K. Tsuchiya and N. Wada, *J. Sol-Gel Sci. Technol*., 2000, **19**, 511.
3 D.B. Mitzi, *Inorg. Chem*., 2005, **44**, 3755.
4 Z. Yin, P.E. Jessop and B.K. Garside, *Appl. Opt*., 1983, **22**, 4088.
5 S. Sakaguchi and S. Todoroki, *Appl. Opt*., 1997, **36**, 6809.
6 (a) O. Yamaguchi, K. Kotera, M. Asano and K. Shimizu, *J. Chem. Soc. Dalton Trans.*,1982,1907; *J. Jap.Soc. Powder Powder Met*., 1977, **24**, 157; *J. Am. Ceram. Soc*., 1987, **20**, 94; (b) Z. Jiang, T. Xie, G.Z. Wang, X.Y. Yuan, C.H. Ye, W.P. Cai, G.W. Meng, G.H. Li and L.D. Zhang, *Mat. Lett*., 2005, **59**, 416.
7 (a) Y.H. Tang, Y.F. Zhang, N. Wang, I. Bello, C.S. Lee and S.T. Lee, *Appl. Phys. Lett*., 1999, **74**, 3824; (b) P. Hidalgo, B. Mendez and J. Piqueras, *Nanotechnology*, 2005, **16**, 2521.
8 G. Brusatin, M. Guglielmi and A. Martucci, *J. Am. Ceram. Soc*., 1997, **80,** 3139**.**
9 Charles K.F. Ho, K. Pita, N.Q. Ngo and C.H. Kam, *Opt. Expr.,* 2005, **13**, 1049.
10 C.J. Brinker and G.W. Scherer, *The Physics and Chemistry of Sol-Gel Processing*, Academic Press. Inc., San Diego, 1990.
11 H. Shen and S. Mathur, *J. Phys. IV France,* 2002, **12**, Pr 4-1.
12 V.G. Kessler, G.I. Spijksma, G.A. Seisenbaeva, S. Hakansson, D.H.A. Blank and H.J.M. Bouwmeester, *J. Sol-Gel Technol.,* 2006, **40**, 163.
13 V. Dhayal, N. Sharma, V. Sharma, R. Bohra, J.E. Drake and C.L.B. MacDonald, *Polyhedron,* 2007, **26**, 3168.
14 V. Sharma, S. Agrawal, R. Bohra and V.K. Jain, *J. Chem., Res.*, 2004, 273.
15 N. Sharma, V. Sharma, R. Bohra and V.S. Raju, *Appl. Organomet. Chem*., 2007, 21.
16 M. Pathak, R. Bohra and R.C. Mehrotra, *J. Chem. Res. (S),* 2003, 567.
17 J.E. Drake, A.G. Mislankar and J. Yang, *Inorg. Chem*., 1992, **31**, 5543.
18 D.H. Chen, H.C. Chiang and C.H. Ueng, *Inorg. Chim. Acta*., 1993, **208**, 99.
19 R.C. Mehrotra and G. Chandra, *J. Chem. Soc*., 1963, 2804.
20 M. Pathak, R. Bohra, R.C. Mehrotra, I-P. Lorenz and H. Piotrowski, *J. Chem. Res*., 2004, 377.
21 H.Y. Kim, P. Viswanathamurthi, N. Bhattarai and D.R. Lee, *Rev. Adv. Mater*, 2003, **5**, 220.
22 S. Agrawal, V. Sharma and R. Bohra, *J. Chem. Res.*, 2006, 426.
23 V. Sharma, S. Agrawal, R. Bohra, R. Ratnani, J.E. Drake, A.L. Bingham, M.B. Hursthouse and M.E. Light, *Inorg. Chim. Acta*, 2006, **359**, 1404.
24 A. Singh, A.K. Rai and R.C. Mehrotra, J.*Organomet. Chem*., 1973, **57**, 301.
25 A. Vyas, N. Sharma, R.K. Sharma and R. Bohra; *Main Group Met. Chem*., 2001, **24**, 373.
26 (a) P.V. Teredesai, D.T. Anderson, N. Hauser, K. Lantzky and J.L. Yager, *Phys. Chem. Glasses*, 2005, **46**, 345; (b) A. Martucci, G. Brusatin and M. Guglicllmi, C. Strohhofer, J. Fick, S. Pelli and G.C. Righini, *J. Sol-Gel Sci. Technol*., 1998, **13**, 535.
27 D.L. Tabern, W.R. Orndorff and L.M. Dennis, *J. Am. Chem. Soc.,* 1925, **47***,* 2039.
28 A. Gupta, R.K. Sharma, R. Bohra, R. Ratnani, V.K. Jain, J.E. Drake, M.B. Hursthouse and M.E. Light, *J. Organomet. Chem*., 2002, **645**, 118.
29 D.C. Bradley, L. Kay and W. Wardlaw, *J. Chem. Soc*., 1956, 4916.
30 D.C. Bradley, F.M.A. Halim and W. Wardlaw, *J. Chem. Soc*., 1950, 3450.

Zirconium tetrachloride catalysed synthesis of symmetric and unsymmetric ethers from secondary benzylic alcohols†

Biswanath Das*, Maddeboina Krishnaiah, Boyapati Veeranjaneyulu, Yallamalla Srinivas and Yerra Koteswara Rao

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad-500 007, India

Secondary benzylic alcohols are coupled in the presence of zirconium tetrachloride to afford the corresponding symmetrical ethers in good yields. Unsymmetric ethers are obtained with good selectivity by condensation of two different secondary benzylic alcohols under the action of the same catalyst.

Keywords: symmetric ethers, unsymmetric ethers, $ZrCl_4$, secondary benzylic alcohol

Etherification by direct coupling of alcohols is a useful method in organic synthesis.[1] The reaction is generally carried out by using a small amount of an inorganic or organic acid. The Williamson ether synthesis,[2] one of the most commonly used methods, requires the conversion of alcohols to halides or tosylates. Various Lewis acids such as $FeCl_3$,[3] $BiBr_3$,[4] $ZnCl_2$,[6] $GaCl_3$,[6] methylrhenium trioxide[7] and rare earth metal triflates[8] can also catalyse the etherification. However, many of these methods suffer from drawbacks such as the use of expensive reagent or stiochiometric amount of catalyst, harsh reaction conditions, longer reaction times, high temperature and low yields.

In continuation of our synthetic work,[9] we have discovered a suitable method for the direct preparation of symmetric and unsymmetric ethers by using a catalytic amount of $ZrCl_4$ under reflux. Various secondary benzylic alcohols having electron-donating groups underwent the reaction smoothly to furnish the ethers in good yields (Scheme 1) while the substrates having electron withdrawing groups afforded the products with lower yields.

The reaction was complete within 1–3 h (Table 1). Unsymmetrical ethers were also formed with good selectivity by coupling of two different benzylic alcohols in the presence of the catalyst (Table 2). However, in the case of cyclic benzylic alcohols, olefins are produced in high yields at room temperature (Scheme 2, Table 3). The structures of the products were determined from their spectral (^{1}H NMR and MS) data.

Recently, $ZrCl_4$ has been used in various chemical transformations as it possesses an interesting reactivity, is less costly and is less toxic than some alternatives.[10] The reagent has been employed in the synthesis of nitriles,[11] oxidation of alcohols,[12] selective tosylation of alcohols,[13] tetrahydropyranylation and detetrahydropyranylation of alcohols and phenols.[14] Here we describe the catalytic activity of $ZrCl_4$ in the etherification of secondary benzylic alcohols.

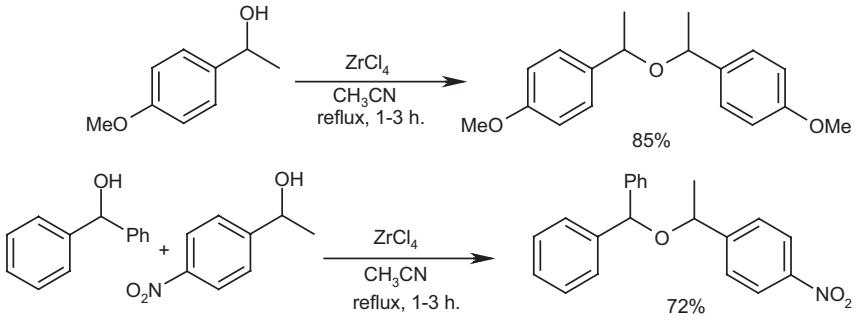
We have developed a mild and efficient method for direct preparation of symmetrical and unsymmetrical ethers using catalytic amount of zirconium tetrachloride. The major advantages of this protocol include short reaction times, availability of the catalyst, high yields, good selectivity and simple experimental procedure.

Experimental

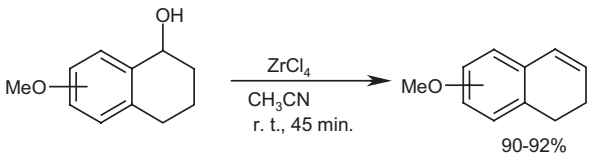
The spectra were determined with the following instruments: Melting points were measured on a Büchi 510 instrument and are uncorrected. IR, Perkin Elmer spectrophotometer; NMR, Varian Gemini 200 MHz and MS: Micromass VG 7070 H (70 eV), Column chromatography was performed over silica gel (BDH, 100–200 mesh) and TLC with silica gel GF_{254}.

General procedure for the synthesis of symmetric and unsummetric ethers

To a mixture of a secondary benzylic alcohol (1 mmol) (or two different secondary benzylic alcohols [0.5 mmol each]) in acetonitrile (5 ml), $ZrCl_4$ (0.2 mmol) was added. The mixture was stirred at reflux and the reaction was monitored by TLC. After completion,



Scheme 1

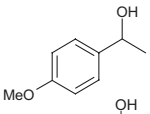
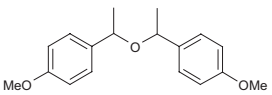
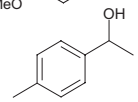
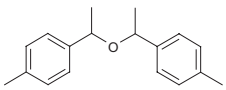
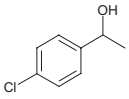
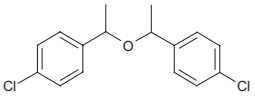
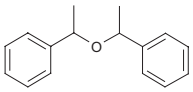
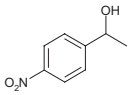
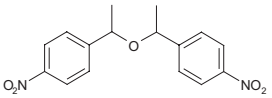
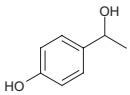
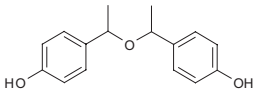
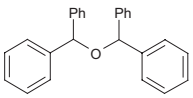


Scheme 2

* Correspondent. E-mail: biswanathdas@yahoo.com

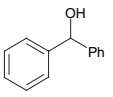
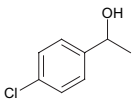
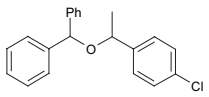
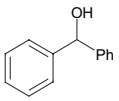
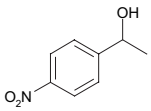
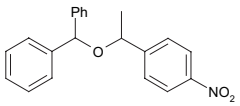
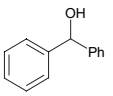
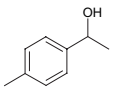
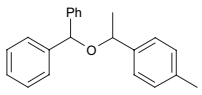
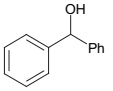
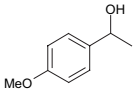
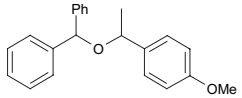
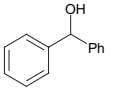
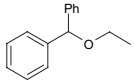
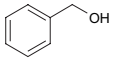
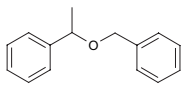
† Part 155 in the series, "Studies on novel synthetic methodologies".

Table 1 Formation of symmetric ethers from sec-benzylic alcohols catalysed by $ZrCl_4$[a]

Entry	Substrate	Product	Time/h	Isolated yield/%	M. p./°C (reported)[lit]
1			1	85	Liquid
2			1.5	80	Liquid
3			1.5	85	Liquid
4			2	86	Liquid (liquid)[6]
5			3	55	146–148
6			2	78	92–94
7			1	95	90–92 (89–91)[6]

[a]All the products were characterised from spectral (^{1}H NMR and MS) data.

Table 2 Formation of unsymmetric ethers by coupling of different alcohols catalysed by $ZrCl_4$[a]

Entry	Alcohol A	Alcohol B	Product	Time/h	Isolated yield/%[b]	M. p./°C (reported)[lit]
8				1.5	74[b]	Liquid
9				2	72[b]	117–119
10				2.5	70[b]	Liquid
11				2	75[b]	Liquid
12				3	76	Liquid
13				3	64	Liquid (liquid)[6]

[a]All the products were characterised from spectral (^{1}H NMR and MS) data.
[b]Symmetric bis (diphenyl)methyl ether was formed in small quantity (7–10%) as determined by ^{1}H NMR spectrum of the crude product.

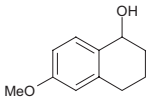
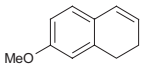
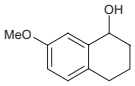
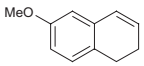
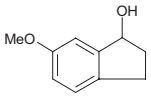
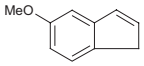
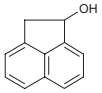
the mixture was diluted with EtOAc (10 ml) and washed with brine (20 ml) and water (2 × 10 ml). The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (silica gel, hexane: EtOAc) to afford the pure ether.

The spectral data of some of the representative ethers (Table 1–3) are given below.

(**1**): Colourless liquid IR (KBr): 2926, 1602, 1258, 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.27–7.10 (m, 2H), 6.82–6.65 (m, 6H), 4.46 (q, J = 6.7 Hz, 1H), 4.18 (q, J = 6.7 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 1.44 (d, J = 6.7 Hz, 3H), 1.34 (d, J = 6.7 Hz, 3H); FABMS: m/z 309 [M + Na]$^+$; Anal. Calc. for $C_{18}H_{22}O_3$: C, 75.5; H, 7.7%. Found: C, 75.5; H, 7.5%.

(**2**): Colourless liquid IR (KBr): 3021, 1486, 1350, 1086 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.15–699 (m, 8H), 4.41 (q, J = 6.5 Hz, 1H), 4.13 (q, J = 6.5 Hz, 1H), 2.23 (s, 3H), 2.16 (s, 3H), 1.35 (d,

Table 3 Formation of alkenes from cyclic benzylic alcohols catalysed by $ZrCl_4$[a]

Entry	Substrate	Product	Time/min	Isolated yield/%[b]	M. p. (°C) (reported)[lit]
14			45	92(5)	Liquid
15			45	90(6)	Liquid (liquid)[8]
16			70	73(10)	Liquid (liquid)[8]
17			40	89	80–82 (79–81)[8]

[a]All the products were characterised from spectral (^{1}H NMR and MS) data.
[b]Yield reported in parentheses is for corresponding symmetrical ether.

J = 6.4 Hz, 3H), 1.32 (d, *J* = 6.4 Hz, 3H); FABMS: *m/z* 277 [M + Na]$^+$; Anal. Calc. for $C_{18}H_{22}O$: C, 85.0; H, 8.7%. Found: C, 85.1; H, 8.6%.

Compound (**3**): Colourless liquid IR (KBr): 3061, 1496, 1450, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.35–7.12 (m, 8H), 4.40 (q, *J* = 6.5 Hz, 1H), 4.12 (q, *J* = 6.5 Hz, 1H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.32 (d, *J* = 6.8 Hz, 3H); FABMS: *m/z* 317, 319, 321 [M + Na]$^+$; Anal. Calc. for $C_{16}H_{16}Cl_2O$: C, 64.9; H, 5.4%. Found: C, 64.8; H, 5.3%.

(**5**): White solid; m. p. 146-148°C; IR (KBr): 2925, 2854, 1522, 1347, 1236, 1066 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): 8.21 (m, 4H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 5.86 (q, *J* = 6.5 Hz, 1H), 4.25 (q, *J* = 6.5 Hz, 1H), 1.58 (d, *J* = 6.4 Hz, 3H), 1.42 (d, *J* = 6.4 Hz, 3H); FABMS: *m/z* 339 [M + Na]$^+$; Anal. Calc. for $C_{16}H_{16}N_2O_5$: C, 60.7; H, 5.1; N, 8.86%. Found: C, 60.8; H, 5.1; N, 8.8%.

(**6**): White solid; m.p. 92–94 °C; IR (KBr); 3246, 1630, 1520, 1086 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.21–7.12 (m, 2H), 6.65–6.75 (m, 6H), 4.46 (q, *J* = 6.5 Hz, 1H), 4.12 (q, *J* = 6.5 Hz, 1H), 1.43 (d, *J* = 6.5 Hz, 3H) 1.32 (d, *J* = 6.5 Hz, 3H); FABMS: *m/z* 281 [M + Na]$^+$; Anal. Calc. for $C_{16}H_{18}O_3$: C, 74.4; H, 7.0%. Found: C, 74.3; H, 6.8%.

(**8**). Colourless liquid; IR (KBr); 3028, 1600, 1492, 1450, 1086 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.38–7.12 (m, 14H), 5.15 (s, 1H), 4.39 (q, *J* = 6.0 Hz, 1H), 1.45 (d, *J* = 6.0 Hz, 3H); FABMS: *m/z* 345, 347 [M + Na]$^+$; Anal. Calc. for $C_{21}H_{19}ClO$: C, 78.0; H, 5.9%. Found: C, 77.7; H, 5.9%.

(**9**)**:** Light yellow solid; m.p. 117–119°C; IR (KBr); 2923, 2852, 1514, 1343, 1091 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): 8.20 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.34–7.12 (m, 10H), 5.17 (s, 1H), 4.51 (q, *J* = 6.3 Hz, 1H), 1.50 (d, *J* = 6.3, Hz 3H); FABMS: *m/z* 356 [M + Na]$^+$; Anal. Calc. for $C_{21}H_{19}O_3N$: C, 75.67; H, 5.70; N, 4.20%. Found: C, 75.54; H, 5.66; N, 4.10%.

(**10**): Colourless liquid; IR (KBr); 2932, 1532, 1436, 1085 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.31–7.06 (m, 14H), 5.16 (s, 1H), 4.30 (q, *J* = 6.5, Hz 1H), 2.35 (s, 3H), 1.45 (d, *J* = 6.5 Hz, 3H); FABMS: *m/z* 325 [M + Na]$^+$; Anal. Calc. for $C_{22}H_{22}O$: C, 87.41; H, 7.28%. Found: C, 87.58; H, 7.36%.

(**11**): Colourless liquid; IR (KBr); 3028, 1601, 1489, 1258, 1086 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.40–7.15 (m, 12H), 6.80 (d, *J* = 8.2 Hz, 2H), 5.2 (s, 1H), 4.40 (q, *J* = 6.4 Hz, 1H), 3.72 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H); FABMS: *m/z* 341 [M + Na]$^+$; Anal. Calc. for $C_{22}H_{22}O_2$: C, 83.01; H, 6.91%. Found: C, 83.24; H, 6.98%.

(**12**): Colourless liquid; IR (KBr); 2974, 2866, 1453, 1493, 1096 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.35–7.14 (m, 10H), 5.38 (s, 1H), 3.45 (q, *J* = 7.2 Hz, 2H), 1,25 (t, *J* = 7.2 Hz, 3H); FABMS: *m/z* 235 [M + Na]$^+$; Anal. Calc. for $C_{15}H_{15}O$: C, 85.30; H, 7.10%. Found: C, 85.22; H, 7.24%.

(**14**): Colourless liquid; IR (KBr); 3032, 2996, 1480, 1453, 1245, cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): 6.90 (d, *J* = 8.0, 1H), 6.66–6.57 (m, 2H), 6.35 (d, *J* = 9.0, 1H), 5.85 (m, 1H), 3.75 (s, 3H), 2.76 (t, *J* = 7.0, 2H), 2.31–2.20 (m, 2H); FABMS: *m/z* 183 [M + Na]$^+$; Anal. Calc. for $C_{11}H_{12}O$: C, 82.50; H, 7.50%. Found: C, 82.46; H, 7.61%.

The authors thank CSIR, New Delhi for financial assistance.

Received 22 November 2007; accepted 13 December 2007
Paper 07/4958 doi: 10.3184/030823407X270392

References

1 M.B. Smith and J. March, *Advanced Organic Chemistry* 5th edn, Wiley-Interscience, New York, 2001, pp. 479-480.
2 D. Barton and W.D. Ollis, *Comprehensive Organic Chemistry*, Pergamon: Elmsford, 1979; Vol. 1, p 819.
3 P. Salehi, N. Iranpoor and F.K. Behbahani, *Tetrahedron,* 1998, **54**, 943.
4 B. Boyer, E.M. Keramane, J.P. Roque and A.A. Pavia, *Tetrahedron Lett*., 2000, **41**, 2891.
5 S. Kim, K.N. Chung and S. Yang, *J. Org. Chem*., 1987, **52**, 3917.
6 J. Choi and Y. Kang, *Bull. Korean Chem. Soc*., 2005, **26,** 343.
7 Z. Zhu and J.H. Espenson, *J. Org. Chem.,* 1996, **61**, 324.
8 (a) A. Kawada, K. Yasuda, H. Abe and T. Harayama, *Chem. Pharm. Bull*., 2002, **50**, 380; (b) G.V.M. Sharma and A.K. Mahalingam, *J. Org. Chem*., 1999, **64**, 8943.
9 (a) B. Das, R. Ramu, B. Ravikanth and K.R. Reddy, *Tetrahedron Lett*., 2006, **47**, 779; (b) B. Das, P. Thirupathi, V.S. Reddy, Y.K. Rao, *J. Mol. Catal. A: Chem.* 2006, **247**, 233; (c) B. Das, A. Majhi, J. Banerjee, N. Chowdhury, K.H. Kishore and U.S.N. Murthy, *Chem. Pharm. Bull.,* 2006, **54**, 403; (d) B. Das, M. Krishnaiah and K. Venkateswarlu, *Tetrahedron Lett*., 2006, **47**, 4457.
10 J.E. Huheey, Inorganic Chemistry, 3rd edn. Roger and Harper Row, Singapore, Chap. 18, 1990.
11 C. Tsuji, E. Miyazawa, T. Sakamoto and Y. Kikugawa, *Synth. Commun*., 2002, **32**, 871.
12 F. Shirini, M.A. Zolfigol and A. Pourhabib *J. Chem. Res (S*), 2001, 476.
13 B. Das, M.R. Reddy, V.S. Reddy and R. Ramu, *Chem Lett*., 2004, **33**, 1526.
14 N. Rezai, F. Alsadat Meybodi and P. Salehi, *Synth. Commun*., 2000, **30**, 1799.

Simple and convenient synthesis of 1,3,5-triarylbenzenes from ketones

Huanan Hu[a,b,c], Anjiang Zhang[a,c,d*], Lisheng Ding[a,b], Xinxiang Lei[a,c] and Lixue Zhang[c]

[a]*Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China*

[b]*Graduate School of Chinese Academy of Sciences, Beijing 100049, China*

[c]*College of Chemistry and Material Engineering, Wenzhou University, Wenzhou 325027, China*

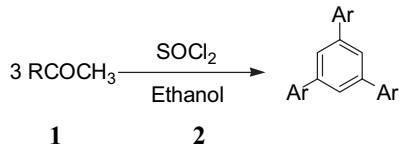
[d]*Ningbo Institute of Material Technology and Engineering, Chinese Academy of Sciences, Ningbo 315211, China*

A new and efficient synthesis of a series of 1,3,5-triarylbenzenes was accomplished in good yields via the triple condensation of aryl methyl ketones promoted by thionyl chloride in anhydrous ethanol. The method is simple and convenient.

Keywords: 1,3,5-triarylbenzene, thionyl chloride, aryl methyl ketone

The properties of molecules or molecular complexes with a high degree of symmetry are of interest in a large number of research areas.[1] 1,3,5-Triarylbenzenes are important C_3-symmetrical aromatic compounds and can be converted into a series of triphenylbenzene-cored dendrimers,[2,3] a conducting polymer and polymers for nonlinear optical applications.[4] A simple method yielding these compounds involves the triple condensation of aryl methyl ketones (**1**), as shown in Scheme 1. The reported methods of inducing condensation involve mainly one of the following catalysts: strong acids,[5] aniline and aniline hydrochloride,[6] or Lewis acids, such as lanthanide chlorides,[7] tetrachlorosilane,[8] aluminium chloride,[9] tin tetrachloride[10] and so on. These methods are both inconvenient and unsuitable for synthesis because they are very difficult to manipulate, need elevated temperatures or take a long time.

We therefore sought a more efficient and general method to convert (**1**) into (**2**) and now report that the triple condensation of aryl methyl ketones promoted by thionyl chloride in anhydrous ethanol at reflux temperature for no more than one hour afforded good yields of 1,3,5-triarylbenzenes.



Scheme 1 Ar = (a) C_6H_5; (b) 4-MeC_6H_4; (c) 4-$MeOC_6H_4$; (d) 4-ClC_6H_4; (e) 3- ClC_6H_4; (f) 4-BrC_6H_4; (g) 3-BrC_6H_4; (h) 4-$CF_3C_6H_4$; (i) 4-$NO_2C_6H_4$.

Results and discussion

For the investigation of reaction conditions for the triple condensation of aryl methyl ketones (**1**) using thionyl chloride as catalyst in anhydrous ethanol, we chose the synthesis of 1,3,5-triphenylbenzene (**2a**) as a model reaction. In the experiments, we first investigated the effect of molar ratios of acetophenone, anhydrous ethanol and catalyst on the yields at reflux temperature for 60 min, and found that we could obtain the best yields under the conditions of n(**1a**):n(ethanol): n($SOCl_2$) = 3:15:5. The results are shown in Table 1.

We also surveyed the effect of reflux time on the yields with the best molar ratio of reaction reagents and found that we could obtain the best yields at reflux temperature for 60 min. The results are given in Table 2.

The reaction mechanism involves the triple condensation of aryl methyl ketones: firstly, the intermediate chalcones were synthesised by the double condensation of aryl methyl ketones, and then 1,3,5-triarylbenzenes were synthesised by the condensation of the intermediate chalcones with aryl methyl ketones in moderate to good yields regardless of whether ketones contained electron-withdrawing or electron-donating groups. The results are summarised in Table 3. However, 1,3,5-trinitrophenylbenzene (**2i**) was not obtained because the chalcone formed from 4-nitroacetophenone was insoluble in anhydrous ethanol, and on precipitating from the reaction mixture, stopped the condensation before the 1,3,5-trinitrophenylbenzenes (**2i**) was formed.[9] On the other hand, the triple condensation of aryl methyl ketones needs a reaction time of more than 10 days and gives moderate yields (50–60%) only using hydrogen chloride as catalyst.[9] It may be concluded that the triple condensation using thionyl chloride as catalyst is not catalysed by hydrogen chloride, but that hydrogen chloride produced from thionyl chloride can speed up the reaction. Further studies on the reaction mechanism are in progress.

Experimental

All melting points were determined on an XT-4A apparatus and are uncorrected. TLC was performed using precoated silica gel GF_{254} (0.25 mm) and column chromatography was performed using silica gel (200-300 meshs). ^1H and ^{13}C NMR spectra were measured on a Bruker Advance 300 spectrometer using TMS as internal standard. *J*-values are given in Hz.For AA'XX' systems in ^1H $J^* = J_{23} + J_{25}$ The IR spectra were taken on a Bruker Vector 55 spectrometer. Elemental analyses were carried out with an EA 1112 elemental analyser. All the reagents used were AR grade.

Synthesis of 1,3,5-trialkylbenzenes **2a–h:** *general procedure*
Thionyl chloride (1.82 ml, 25 mmol) was added slowly by a syringe to a stirred solution of (**1**) (15 mmol) in anhydrous ethanol (4.4 ml,

Table 1 Effect of molar ratio of reaction reagents to catalyst on the yields

n(**1a**):n(ethanol):n($SOCl_2$)	3:4:4	3:10:4	3:14:4	3:15:4	3:15:5	3:15:6
Yield/%	37	58	64	72	85	79

Table 2 Effect of reflux time on the yields

Time/min	10	30	45	60	90	120
Yield/%	55	61	79	85	81	75

* Correspondent. E-mail: anjiangzhang@gmail.com

Table 3 Yields of 1, 3, 5-triarylbenzenes from ketones

Entry	Product	Mp/°C	Yield/%[a]
1	**2a**	172	85
2	**2b**	179–180	84
3	**2c**	143	78
4	**2d**	246	82
5	**2e**	170–171	76
6	**2f**	262–263	81
7	**2g**	167–168	75
8	**2h**	158–159	69
9	**2i**	153	Trace

[a]Isolated yields.

75 mmol). The mixture was stirred for 1 h at reflux temperature and then neutralised with a saturated sodium carbonate solution. The solid obtained on cooling was filtered, washed with cold water, ether and ethanol, and dried under reduced pressure to give the title compound (**2a**–**h**).

1,3,5-Triphenylbenzene (**2a**): Light yellowish solid. M.p. 171–172°C (lit.[10] 172°C). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 7.78 (s, 3H), 7.67–7.71 (m, 6H), 7.44–7.50 (m, 6H), 7.35–7.41 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.4 (3C), 141.2 (3C), 128.8 (6C), 127.5 (6C), 127.4 (3C), 125.2 (3C). IR (KBr) ν: 3032, 1595, 1570, 1491, 1460, 1380, 750 cm^{-1}. Anal. Calcd. for $C_{24}H_{18}$ (306.4): C, 94.08; H, 5.92. Found: C, 94.12; H, 5.89%.

1,3,5-Tri(4-methylphenyl)benzene (**2b**): Light yellowish solid. M.p. 179–180°C (lit.[9] 178°C). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 7.73 (s, 3H), 7.57–7.61 (m, 6H), 7.25–7.29 (m, 6H), 2.42 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.2 (3C), 138.4 (3C), 137.2 (3C), 129.5 (6C), 127.2 (6C), 124.6 (3C), 21.1 (3C). IR (KBr) ν: 3036, 2916, 2862, 1596, 1514, 1466, 1392, 870, 750 cm^{-1}. Anal. Calcd. for $C_{27}H_{24}$ (348.5): C, 93.06; H, 6.09. Found: C, 94.1; H, 6.2%.

1,3,5-Tri(4-methoxyphenyl)benzene (**2c**): Light yellowish solid. M.p. 143°C (lit.[10] 143°C). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 7.62–7.67 (m, 9H), 7.02 (m, J^* = 8.7 Hz, 6H), 3.88 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.9 (3C), 137.6 (3C), 128.9 (3C), 128.4 (6C), 125.2 (3C), 114.6 (6C), 56.0 (3C). IR (KBr) ν: 3035, 2923, 2872, 1596, 1572, 1516, 1465, 1240, 1180, 860, 760 cm^{-1}. Anal. Calcd.for $C_{27}H_{24}O_3$ (396.5): C, 81.79; H, 6.10. Found: C, 81.8; H, 6.2%.

1,3,5-Tri(4-chlorophenyl)benzene (**2d**): Light yellowish solid. M.p. 246°C (lit.[10] 246°C). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 7.70 (s, 3H), 7.60 (m, J^* = 8.4 Hz, 6H), 7.46 (m, J^* = 8.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.8 (3C), 139.2 (3C), 134.0 (3C), 129.6 (6C), 128.5 (6C), 125.0 (3C). IR (KBr) ν: 3033, 1600, 1570, 1510, 1464, 870, 756 cm^{-1}. Anal. Calcd. for $C_{24}H_{15}Cl_3$ (409.7): C, 70.35; H, 3.69. Found: C, 70.3; H, 3.7%.

1,3,5-Tri(3-chlorophenyl)benzene (**2e**): Light yellowish solid. M.p. 170–171°C (lit.[9] 171°C). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 7.73 (s, 3H), 7.57–7.63 (m, 3H), 7.38–7.43 (m, 3H), 7.28–7.32 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.4 (3C), 139.5 (3C), 136.4 (3C), 130.6 (3C), 130.2 (3C), 128.6 (3C), 125.8 (3C), 125.2 (3C). IR (KBr) ν: 3032, 1598, 1564, 1510, 1480, 880, 750 cm^{-1}. Anal. Calcd. for $C_{24}H_{15}Cl_3$ (409.7): C, 70.35; H, 3.69. Found: C, 70.4; H, 3.75%.

1,3,5-Tri(4-bromophenyl)benzene (**2f**): Light yellowish solid. M.p. 262–263°C (lit.[10] 263°C). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 7.66 (s, 3H), 7.49 (m, J^* = 8.4 Hz, 6H), 7.37 (m, J^* = 8.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.6 (3C), 135.6 (3C), 132.3 (6C), 128.3 (6C), 125.2 (3C), 124.1 (3C). IR (KBr) ν: 3030, 1592, 1560, 1510, 1470, 860, 755 cm^{-1}. Anal. Calcd. for $C_{24}H_{15}Br_3$ (543.1): C, 53.08; H, 2.78. Found: C, 53.1; H, 2.9%.

1,3,5-Tri(3-bromophenyl benzene (**2g**): Light yellowish solid. M.p. 167–168°C. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 7.73 (s, 3H), 7.63–7.67 (m, 3H), 7.37–7.43 (m, 6H), 7.25–7.28 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.6 (3C), 135.6 (3C), 132.3 (3C), 130.1 (3C), 128.3 (3C), 127.6 (3C), 125.2 (3C), 124.1 (3C). IR (KBr) ν: 3033, 1589, 1561, 1506, 1465, 880, 750 cm^{-1}. Anal. Calcd. for $C_{24}H_{15}Br_3$ (543.1): C, 53.08; H, 2.78. Found: C, 53.3; H, 2.8%.

1,3,5-Tri(4-trifluoromethylphenyl)benzene (**2h**): Light yellowish solid. M.p. 158–159°C. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ: 7.75–7.83 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.9 (3C), 141.4 (3C), 129.8 (q, J = 32.6 Hz, 3C), 127.6 (6C), 126.0 (6C), 125.9 (3C), 124.3 (q, J = 270.6 Hz, 3C). IR (KBr) ν: 3035, 1590, 1566, 1512, 1460, 872, 760 cm^{-1}. Anal. Calcd. for $C_{27}H_{15}F_9$ (510.4): C, 63.54; H, 2.96. Found: C, 63.6; H, 2.9%.

Received 15 October 2007; accepted 29 December 2007
Paper 07/4887 doi: 10.3184/030823407X275946

References

1 W. Verbouwe, M. Van der Auweraer, F.C. De Schryver, J.J. Piet and J.M. Warman, *J. Am. Chem. Soc.,* 1998, **120**, 1319.
2 T.M. Miller, T.X. Neenan, R. Zayas and E.B. Harvey. *J. Am. Chem. Soc.,* 1992, **114**, 1018.
3 O. Mongin, J. Brunel, L. Porres and M. Blanchard-Desce, *Tetrahedron Lett*., 2003, **44**, 2813.
4 J. Brunel, O. Mongin, A. Jutand, I. Ledoux, J. Zyss and M. Blanchard-Desce, *Chem. Mater.,* 2003, **15**, 4139.
5 E. Weber, M. Hecker, E. Koepp and W. Orlia, *J. Chem. Soc., Perkin, Trans.*, 1988, 1251.
6 W.L. Robert, *J. Org. Chem.,* 1981, **46**, 4552.
7 K.J. Cheng and S.H. Wu, *Acta Chim. Sinica,* 1999, **57**, 1162.
8 S.S. Elmorsy, A. Pelter and K. Smith, *Tetrahedron Lett.,* 1991, **32**, 4175.
9 E.L. Robert, J.D. Elmer, M.N. Nancy and C. Wallace, *J. Am. Chem. Soc*., 1953, **75**, 5959.
10 X.B. Jing, F. Xu, Q.H. Zhu, X.F. Ren, C.G. Yan, L. Wang and J.R. Wang, *Synth. Commun.*, 2005, **35**, 3167.

A first homogeneous gold(III)-catalysed epoxidation of aromatic alkenes

Xiao-Qiang Li, Chen Li, Fan-Bo Song and Chi Zhang*

The State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China

The first example of a homogeneous gold(III)-catalysed epoxidation of aromatic alkenes at room temperature using sodium chlorite as the stoichiometric oxidant in a homogeneous trisolvent system of 2-methoxyethanol/acetonitrile/water (volume ratio: 1/3/1) is reported. A radical-trapping experiment suggested that the reaction might proceed via a radical pathway.

Key words: alkenes, epoxidations, homogeneous catalysis, gold, sodium chlorite

Homogeneous cationic gold-catalysed organic transformations have been a focus of attention in recent years due to their novelty and high efficiency.[1] In most cases, cationic gold acts as a soft Lewis acid to activate alkynes and allenes towards either carbon-carbon bond or carbon-heteroatom bond formation. Owing to the lower electron density in a carbon–carbon double bond,[1b] reports concerning the activation of alkenes have been limited and only appeared quite recently with the nucleophilic addition of phenols,[2,3] active methylene compounds,[4] and alcohols[5] to unactivated alkenes. Homogeneous gold-catalysed oxidation reactions have attracted interest as well,[1a] including oxidation of sulfides to sulfoxides,[6] alcohols to carbonyl compounds,[7] methane to methanol,[8] alkanes to alkyl hydroperoxides[9] and the Baeyer–Villiger oxidation of ketones.[10] Moreover, the homogeneous gold-catalysed oxidation of alkenes such as the nitrene transfer reaction[11] and the oxidative cleavage of a C–C double bond[12] have also been studied. To the best of our knowledge, the homogeneous epoxidation of alkenes using a simple gold salt as a catalyst,[13] has not been reported. Hence, we report the first example of a homogeneous gold(III)-catalysed epoxidation of aromatic alkenes with sodium chlorite ($NaClO_2$) as the stoichiometric oxidant in a trisolvent system of $CH_3OCH_2CH_2OH/CH_3CN/H_2O$ at room temperature.

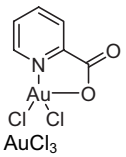
Initially, the epoxidation reaction of *trans*-stilbene was tested using gold trichloride as a catalyst and sodium chlorite[14] as an oxidant in CH_3CN/H_2O (4/1, v/v). This reaction provided *trans*-stilbene oxide in 42% yield at room temperature (Table 1, entry 1).[15] However, the background reaction (without $AuCl_3$) also gave the *trans*-stilbene oxide in 35% yield. In order to increase the catalytic activity of $AuCl_3$, various types of ligands including *N,N*-bidentate ligands such as neocuprione; *N,O*-mixed tetracoordinating ligands such as *N,N′*-bis(salicylidene)-1,2-phenylenediamine and the *O, O*-bidentate ligand, acetylacetone (acac) were tried. Of these, only acac was successful (Table 1, entry 2 *vs* entry 1).[16] With this in mind, six oxygen-containing organic solvents were screened as a third solvent along with CH_3CN/H_2O without the use of any ligands (entries 3-8). It was observed that the use of $CH_3OCH_2CH_2OH/CH_3CN/H_2O$ (volume ratio: 1/3/1) as the solvent system gave the best result, with conversion of *trans*-stilbene being 91% and the isolated yield of *trans*-stilbene oxide being 81% (entry 4). Noticeably, there was no background epoxidation reaction in this trisolvent system. This was distinct from the CH_3CN/H_2O bisolvent system where background reaction occurred to a great extent. The catalytic activity of gold trichloride in the epoxidation of *trans*-stilbene in this trisolvent system was evident. 1,2-Dimethoxyethane, ethanol and *i*-propanol were inferior solvent components to 2-methoxyethanol (entries 3, 6 and 7). Though the same yield of *trans*-stilbene oxide was obtained in a trisolvent of *t*-BuOH/CH_3CN/H_2O as that in $CH_3OCH_2CH_2OH/CH_3CN/H_2O$ (entry 4 vs. 8), only 14% epoxide yield was produced for the epoxidation of *trans*-4-chlorostilbene in *t*-BuOH/CH_3CN/H_2O. Consequently, the trisolvent of $CH_3OCH_2CH_2OH/CH_3CN/H_2O$ was the choice of solvent for further optimisation.

Table 1 Optimisation of reaction components[a]

Entry	Ligand or the third solvent	Yield/%[b]	Conversion /%
1	None	42	47
2	acac[c]	66	84
3	DME[d]	59	66
4	$CH_3OCH_2CH_2OH$[e]	81	91
5	$HOCH_2CH_2OH$[e]	–	no reaction
6	EtOH[e]	34	43
7	*i*-PrOH[e]	51	61
8	*t*-BuOH[e]	81	86

[a]Unless otherwise indicated, the reaction was conducted with 1 mmol of *trans*-stilbene, 5 mol% of $AuCl_3$, 3 mmol of $NaClO_2$ in the bisolvent of CH_3CN (12 ml) and H_2O (3 ml) at room temperature for 24 hours. [b]Isolated yields. [c]20 mol% of acac was added into the reaction system illustrated in note *a*. [d]3 ml of DME was added into the reaction system illustrated in note a, correspondingly, volume of CH_3CN was reduced to 9 ml from 12 ml and volume of H_2O kept unchanged. No ligand was used. [e]All other parameters were identical to those of entry 3 except that 3 ml of alcohol was employed instead of DME.

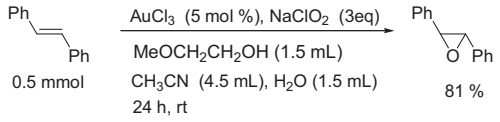
Table 2 Screened gold catalysts[a]

Entry	Gold catalyst	Yield/%
1[b]	$(PPh_3)AuCl$	< 5
2[b,c]	$(PPh_3)AuCl/AgOTf$	< 5
3[d]	 $AuCl_3$	80
4[d]	$AuCl_3$	81

[a]Reaction conditions: 0.5 mmol of *trans*-stilbene, 0.025 mmol of gold catalyst, and 1.5 mmol of $NaClO_2$ in a trisolvent of $CH_3OCH_2CH_2OH$ (1.5 ml), CH_3CN (4.5 ml), and H_2O (1.5 ml). [b]95% of *trans*-stilbene was recovered. [c]Molar ratio of $(PPh_3)AuCl$ to AgOTf was 1 : 1. [d]The conversion of *trans*-stilbene was 91%.

Other gold(I) and gold(III) complexes were screened with results summarised in Table 2. Chloro(triphenylphosphine) gold(I)[17] has no catalytic activity since more than 95% of the starting material was recovered, and its catalytic activity did not improve on the addition of AgOTf (Table 2, entries 1 and 2). Dichloro(pyridine-2-carboxylato)gold(III)[18] showed equal catalytic activity to $AuCl_3$ when *trans*-stilbene was used as the substrate (entries 3 and 4). However, in the case of *trans*-4-chlorostilbene, $AuCl_3$ was more reactive since yields of the corresponding epoxide using $AuCl_3$ and dichloro(pyridine-2-carboxylato)gold(III) were 87% and 76%, respectively. Therefore, the optimal reaction system was composed of 5 mol% $AuCl_3$, 3 equivalents of sodium chlorite, and a trisolvent $CH_3OCH_2CH_2OH/CH_3CN/H_2O$ (1/3/1, volume ratio)

* Correspondent. E-mail: zhangchi@nanai.edu.cn



Scheme 1 Optimal epoxidation system of *trans*-stilbene.

(see Scheme 1). Under the optimal conditions, there was no precipitate of metallic gold during the course of the reaction, which supports a homogeneous gold-catalysed epoxidation reaction.

Various olefins were tested using this homogeneous gold-catalysed epoxidation reaction. The reaction of *cis*-stilbene was much slower than *trans*-stilbene as only 39% of *cis*-stilbene was transformed to give *trans*-stilbene oxide as the major epoxidation product (ratio of *trans*- *to cis*-stilbene oxide: 20/1) after 48 h (Table 3, entry 2). The nonstereospecificity of the epoxidation reaction implied that the reaction proceeds stepwise. As for mono *para*-halogen substituted *trans*-stilbenes, the yields of the corresponding epoxides decreased from excellent to poor in the order of F > Cl > Br (entries 3, 4, 6). Different solubility observed in experiments among these three halogen-substituted *trans*-stilbenes might account for the observed yield order. A trisubstituted aromatic olefin, triphenylethylene gave triphenylethylene oxide in 62% yield (entry 10). When *trans*-α-methyl stilbene and 1-phenylcyclohexene were tested, however, the oxidation products obtained were 2,2-phenyl propanal and α-phenylcyclopentanecarboxaldehyde, which derived from the rearrangement of two epoxides intermediates, *trans*-α-methyl stilbene oxide and 1-phenylcyclohexene oxide respectively.[19] A control experiment showed that *trans*-α-methyl stilbene oxide readily rearranged to 2,2-phenylpropanal in quantitative yield in the presence of 5 mol% $AuCl_3$ in dichloromethane at room temperature within 30 min. 1,2-Dialkyl-substituted alkenes and terminal olefins were poor substrates under the standard conditions. During the study of substrate scope, it was observed that metallic gold precipitated after several minutes if the epoxidation reaction proceeded poorly, whereas, if the epoxidation reaction went on well, there was no precipitated metallic gold until the completion of the reaction.

A preliminary study has been done to probe the mechanism of the present $AuCl_3$-catalysed epoxidation reaction. The fact that *cis*-stilbene yielded *trans*-stilbene oxide as the major epoxidation product implied that free radical species might be involved in the reaction. This was the case since the addition of 20 mol% of 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO), a widely used radical scavenger, inhibited the epoxidation reaction dramatically, with conversion of *trans*-stilbene being only 22% after 30 h.

In summary, the first homogeneous gold(III)-catalysed epoxidation of aromatic olefins has been developed. A novel redox catalytic reactivity of cationic gold(III) has been discovered. Further studies to understand the mechanism and develop a gold-catalysed enantioselective epoxidation reaction are underway.

Experimental

Sodium chlorite (80% purity) was purchased and used without further purification. CH_3CN, H_2O and $CH_3OCH_2CH_2OH$ were distilled before use. The known epoxide products were identified by comparison of their ^{1}H- and ^{13}C NMR spectra with those reported in literature. The ^{1}H NMR spectra were recorded at 400 MHz (^{13}C NMR at 100 MHz), using $CDCl_3$ as the solvent.

Epoxidation of trans-stilbene; typical procedure

To a stirred mixture of *trans*-stilbene (90 mg, 0.5 mmol) and gold(III) chloride (7.6 mg, 0.025 mmol) in a homogeneous solvent of CH_3CN (4.5 ml), $CH_3OCH_2CH_2OH$ (1.5 ml) and water (1.5 ml) was added sodium chlorite (170 mg, 1.5 mmol, 80% purity) at room temperature. The reaction mixture turned to yellow immediately. After 24 h, the reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ solution (15 ml), and the mixture was extracted with EtOAc (30 ml × 3). The combined organic layers were washed with water (10 ml) and brine (10 ml) once, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (2% EtOAc in petroleum ether) on silica gel to give *trans*-stilbene oxide[14] (159 mg, 81%) as a white solid: m.p. 66–67°C (lit.[14] 63–65°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.37 (m, 10H), 3.88 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.07, 128.53, 128.29, 125.47, 62.80. IR (KBr) 1452, 1278, 860, 837, 745, 690 cm^{-1}; EI-MS (M^+): 196.

Table 3 Epoxidation of olefins catalysed by $AuCl_3$[a]

Entry	Olefin	Yield /%[b]	Conversion /%
1	*trans*-Stilbene	81	91
2	*cis*-Stilbene	35[c]	39
3	*trans*-4-Fluorostilbene	92	97
4	*trans*-4-Chlorostilbene	87	91
5[d]	*trans*-4-Bhlorostilbene	76	85
6	*trans*-4-Bromostilbene	56	58
7[e]	*trans*-4-Cyanostilbene	50	70
8	*trans*-4-Methylstilbene	55	92
9	*trans*-4,4′-Dimethylstilbene	50	90
10	Triphenylethylene	62	84
11	*trans*-α-Methylstilbene	56[f]	71
12	1-Phenylcyclohexene	58[g]	100
13	β-Methylstyrene	37	100

[a]Unless otherwise noted, reactions were conducted under the standard conditions shown in Scheme 1. [b]Isolated yields. [c]*trans*/*cis*-stilbene oxide = 20:1, determined by ^{1}H NMR. [d]5 mol% of dichloro(pyridine-2-carboxylato)gold(III) was used as the catalyst instead of $AuCl_3$. [e]Reaction time was 48 h. [f]The yield of 2,2-phenyl propanal. [g]The yield of α-phenylcyclopentanecarboxaldehyde.

Oxidation of 1-phenylcyclohexene

1-Phenylcyclohexene was treated with the above procedure, except that flash column chromatography was conducted with 1% EtOAc in petroleum ether on silica gel, giving 50 mg α-phenylcyclopentanecarboxaldehyde[20] in 58% yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.28–7.16 (m, 5H), 2.47–2.41 (m, 2H), 1.83–1.54 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.59, 140.20, 128.67, 127.58, 127.08, 63.61, 32.24, 24.13. IR(KBr) 3036, 2805, 2715, 2212, 1720 1587, 1488, 754, 659 cm^{-1}. ESI-MS (M^+): 174.

trans-*4-Fluorostilbene oxide* (Table 3, entry 3)

M.p. 75–76°C (lit.[21] 76–77°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.04 (m, 9H), 3.85 (d, J = 2.4 Hz, 1H), 3.83 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.72 (d, J = 244.9 Hz), 136.82, 132.81, 128.55, 128.37, 127.14 (d, J = 8.2 Hz), 125.44, 115.55 (d, J = 21.5 Hz), 62.76, 62.18. IR(KBr) 3062, 3033, 2987, 1602, 1509, 1459, 1430, 1234, 1093, 829, 775, 738, 694, 563, 520 cm^{-1}. ESI-MS (M^+): 214.

trans-*4-Chlorostilbene oxide* (Table 3, entry 4)

M.p. 99–100°C (lit.[21] 100.4–101.5°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 9H), 3.85 (d, J = 2.4 Hz, 1H), 3.82 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.67, 135.69, 134.01, 128.70, 128.55, 128.41, 126.79, 125.44, 62.82, 62.09. IR(KBr) 3046, 2979, 2917, 1650, 1589, 1488, 1457, 1274, 1087, 1010, 817, 748, 696, 516 cm^{-1}. ESI-MS (M^+): 230.

trans-*4-Bromostilbene oxide* (Table 3, entry 6)

M.p. 83–85°C (lit.[22] 83–85°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.21 (m, 9H), 3.84 (d, J = 2.4 Hz, 1H), 3.82 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.63, 136.11, 131.63, 128.55, 128.42, 127.09, 125.43, 122.12, 62.79, 62.13. IR(KBr) 3045, 2985, 1671, 1587, 1484, 1457, 1423, 1105, 1068, 1006, 815, 748, 698, 617, 514 cm^{-1}. ESI-MS (M^+): 274.

trans-*4-Cyanostilbene oxide* (Table 3, entry 7)

M.p. 76–77°C (lit.[21] colourless oil, in view of our other evidence we believe the literature description to be in error). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.70–7.26 (m, 9H), 3.92 (d, J = 1.6 Hz, 1H), 3.83 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.40, 136.11, 132.33, 128.62, 126.08, 125.46, 125.35, 118.53, 111.95, 63.16, 61.74. IR(KBr) 3041, 3010, 2225, 1602, 1494, 1459, 1423, 1280, 1170, 1091, 825, 759, 725, 694, 611, 551 cm^{-1}. ESI-MS (M^+): 221.

trans-*4-methylstilbene oxide* (Table 3, entry 8) [21]
M.p. 59–61°C (lit.[21] 59–60°C).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.18 (m, 9H), 3.85 (d, J = 2.4 Hz, 1H), 3.83 (d, J = 2.4 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.11, 137.19, 134.06, 129.21, 128.50, 128.20, 125.43, 62.83, 62.71, 21.19. IR(KBr) 3049, 2984, 1494, 1457, 1427, 1218, 1108, 1049, 817, 732, 696, 607, 509 cm^{-1}. EI-MS (M^+): 210.

trans-*4,4'-Dimethylstilbene oxide* (Table 3, entry 9)
M.p. 80–82°C (lit.[14] 75–77°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.18 (m, 9H), 3.82 (s, 2H), 2.36 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.01, 134.19, 129.18, 125.39, 62.74, 21.18. IR(KBr) 3032, 2896, 1608, 1523, 1278, 1010, 882, 839, 801 cm^{-1}. EI-MS (M^+): 224.

Triphenylethylene oxide (Table 3, entry 10)
M.p. 75–76°C (lit.[14] 75–77°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–6.93 (m, 15H), 4.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.92, 135.73, 135.40, 129.13, 128.66, 128.56, 128.30, 127.79, 127.73, 127.65, 127.59, 127.50, 126.70, 126.28, 68.62, 67.98. IR (KBr) 3027, 1605, 1460, 1394, 1280, 756, 690 cm^{-1}. EI-MS (*m/z*) (M^+): 272.

2,2-diphenyl propanal (Table 3, entry 11)[19a]
Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.35–7.25 (m, 10H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.48, 141.74, 128.68, 128.11, 127.17, 59.78, 22.53. IR(KBr) 3046, 2980, 1720, 1605, 1491, 1450 860, 832, 741, 693 cm^{-1}. ESI-MS (M^+): 210.

trans-β-*methylstyrene oxide* (Table 3, entry 13)[14]
Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (m, 5H), 3.57 (d, J = 1.6 Hz, 1H), 3.03 (dq, J = 4.8, 1.6 Hz, 1H), 1.45 (d, J = 4.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.67, 128.35, 127.94, 125.47, 59.43, 58.94, 17.84. IR(KBr) 3033, 2924, 1691, 1447, 1246, 1067, 687 cm^{-1}. EI-MS: *m/z* 134 (M^+).

This work was financially supported by The National Natural Science Foundation of China (No. 20572046 and No. 20421202), the 111 Project (B06005), and the Ministry of Education of China.

Received 26 September 2007; accepted 19 December 2007
Paper 07/4951 doi: 10.3184/030823407X275937

References

1 For reviews on gold-catalysed transformations see: (a) A.S.K. Hashmi, *Gold Bull.,* 2004, **37**, 51; (b) A.S.K. Hashimi, *Gold Bull.,* 2003, **36**, 3; (c) A. Hoffmann-Roder and N. Krause, *Org. Biomol. Chem.,* 2005, **3**, 387; (d) G. Dyker, *Angew. Chem., Int. Ed.* 2000, **39**, 4237; (e) A.S.K. Hashimi, *Angew. Chem., Int. Ed.,* 2005, **44**, 6990; (f) S. Ma, S. Yu and Z. Gu, *Angew. Chem., Int. Ed.,* 2006, **45**, 200; (g) E. Jimenez-Nunez, and A.M. Echavarren, *Chem. Commun.,* 2007, 333; (h) A.S.K. Hashmi and G.J. Hutchings, *Angew. Chem., Int. Ed.,* 2006, **45**, 7896; (i) L. Zhang, J. Sun and S.A. Kozmin, *Adv. Synth. Catal.,* 2006, **348**, 2271; (j) R.A. Widenhoefer and X. Han, *Eur. J. Org. Chem.,* 2006, 4555; (k) N. Marion and S.P. Nolan, *Angew. Chem., Int. Ed.,* 2007, **46**, 2750; (l) A.S.K. Hashimi, *Chem. Rev.,* 2007, **107**, 3180.
2 C.-G. Yang and C. He, *J. Am. Chem. Soc.,* 2005, **127**, 6966.
3 (a) J. Zhang, C.-G. Yang and C. He, *J. Am. Chem. Soc.,* 2006, **128**, 1798; (b) C. Brouwer and C. He, *Angew. Chem. Int. Ed.,* 2006, **45**, 1744.
4 (a) X.-Q. Yao and C.-J. Li, *J. Am. Chem. Soc.*, 2004, **126**, 6884; (b) R.V. Nyuyen, X.-Q. Yao, D.S. Bohle and C.-J. Li, *Org. Lett.,* 2005, **7**, 673; (c) R.V. Nyuyen, X.-Q. Yao and C.-J. Li, *Org. Lett.,* 2006, **8**, 2397; (d) C.-Y Zhou and C.-M. Che, *J. Am. Chem. Soc.,* 2007, **129**, 5828.
5 X. Zhang and A. Corma, *Chem. Commun.,* 2007, 3080.
6 (a) F. Gasparrini, M. Giovannoli, D. Misiti, G. Natile and G. Palmieri, *Tetrahedron,* 1983, **39**, 3181; (b) F. Gasparrini, M. Giovannoli, D. Misiti, G. Natile and G. Palmieri, *Tetrahedron,* 1984, **40**, 165; (c) F. Gasparrini, M. Giovannoli and D. Misiti, *J. Org. Chem.,* 1990, **55**, 1323; (d) E. Boring, Y.V. Geletti and C.L. Hill, *J. Am. Chem. Soc.,* 2001, **123**, 1625.
7 B. Guan, D. Xing, G. Cai, X. Wan, N. Yu, Z. Fang, L. Yang and Z. Shi, *J. Am. Chem. Soc.,* 2005, **127**, 18004.
8 C.J. Jones, D. Taube, R.A. Periana, R.J. Nielsen, J. Oxgaard and W.A. Goddard III, *Angew. Chem. Int. Ed.,* 2004, **43**, 4626.
9 G.B. Shul'pin, A.E. Shilov and G. Süss-Fink, *Tetrahedron Lett.,* 2001, **42**, 7253.
10 A. von. Baeyer and V. Villiger, Ber. *Dtsch. Chem. Ges.*, 1899, **32**, 3622.
11 Z. Li, X. Ding and C. He, *J. Org. Chem.,* 2006, **71**, 5876.
12 D. Xing, B. Guan, G. Cai, Z. Fang, L. Yang and Z. Shi, *Org. Lett.,* 2006, **8**, 693.
13 For selected heterogeneous epoxidation reactions of propene, see: (a) T. Hayshi, K. Tanaka and M. Haruta, *J. Catal.* 1998, **178**, 566; (b) B. Chowdhury, J.J. Bravo-Suarez, M. Dare, S. Tsubota and M. Haruta, *Angew. Chem., Int. Ed.,* 2006, **45**, 412; (c) T.A. Nijhuis and B.M. Weckhuysen, *Catal. Today,* 2006, **117**, 84; For heterogeneous epoxidation reactions of styrene, see: (d) N.S. Patil, B.S. Uphade, P. Jana, S.K. Bharagava and V.R. Choudhary, *J. Catal.,* 2004, **223**, 236; For heterogeneous epoxidation reactions of *trans*-stilbene, see: (e) P. Ligner, F. Morfin, S. Mangematin, L. Massin, J.-L. Rousset and V. Caps, *Chem. Commun.* 2007, 186.
14 X. -L. Geng, Z. Wang, X.-Q. Li and C. Zhang, *J. Org. Chem.,* 2005, **70**, 9610.
15 Other oxidants such as H_2O_2, Oxone, NaOCl, and PhIO did not give epoxidation product, only trace amount of C-C double bond cleavage products were detected.
16 See Supplementary Data for details.
17 For the preparation of chloro(triphenylphosphine)gold(I), see: K. Burgess, B.F.G. Johnson, J. Lewis and P.R. Raithby *J. Chem. Soc., Dalton Trans.,* 1983, 1661.
18 For the preparation of dichloro(pyridine-2-carboxylato)gold(III), see: (a) A. Dar, K. Moss, S. M. Cottrill, R.V. Parish, C.A. McAuliffe, R.G. Pritchard, B. Beagley and J. Sandbank, *J. Chem. Soc., Dalton Trans.,* 1992, 1907; For applications of dichloro(pyridine-2-carboxylato)gold(III), see: (b) S. Wang and L. Zhang, *J. Am. Chem. Soc.,* 2006, **128**, 8414; (c) S. Wang and L. Zhang, *J. Am. Chem. Soc.,* 2006, **128**, 14274; (d) A.S.K. Hashimi, J.P. Weyrauch, M. Rudolph and E. Kurpejovic, *Angew. Chem., Int. Ed.,* 2004, **43**, 6545.
19 For selected examples of simple metal salts induced rearrangement of epoxides, see: (a) $InCl_3$: B.C. Ranu and U. Jana, *J. Org. Chem.,* 1998, **63**, 8212; (b) $Er(OTf)_3$: A. Procopio, R. Dalpozzo, A.N. Nino, M. Nardi, G. Sindona and A. Tagarelli, *Synlett,* 2004, **14**, 2633; (c) $Bi(OTf)_3$: K.A. Bhatia, K.J. Eash, N.M. Leoard, M.C. Oswald and R.S. Mohan, *Tetrahedron Lett.,* 2001, **42**, 8129; (d) $IrCl_3$: I. Karame, L.M. Tommasino and M. Lemaire, *Tetrahedron Lett.,* 2003, **44**, 7687.
20 (a) K. Maruoka, N. Murase, R. Bureau, T. Ooi and H. Yamamoto, *Tetrahedron,* 1994**,** **50**, 3663; (b) T. Imama, M. Ogawa, T. Kataoka, O. Muraoka and G. Tanabe, *Tetrahedron,* 1998**,** **54**, 8941.
21 S. Oudeyer, E. Léonel, J.P. Paugam and J. -Y. Nédélec, *Synthesis,* 2004, **3**, 389.
22 Y. Okazaki, F. Ando and J. Koketsu, *Bull. Chem. Soc. Jpn*., 2003, **76**, 2155.

Synthesis and characterisation of Hg (II) and Ag (I) complexes of 4-fluorobenzoylmethylenetriphenylphosphorane and 4-chlorobenzoyl methylenetriphenylphosphorane, with spectroscopic studies

Kazem Karami*

Department of Chemistry Isfahan University of Technology, Isfahan, 84156/83111, Iran

4-flourobenzyloxymethylenetriphenylphosphorane ylide [$Ph_3PCHCOC_6H_4F$], (FBPPY), and 4-chlorobenzyl-oxymethylenetriphenylphosphorane ylide [$Ph_3PCHCOC_6H_4Cl$],(CBPPY), have been synthesised. The reactions of the title ylides with HgX_2 (X =Cl,I) in equimolar ratios using dry acetone as solvent, have yielded [{$HgCl_2$(FBPPY)}$_2$](**1**), [{HgI_2(FBPPY)}$_2$](**2**), [{$HgCl_2$(CBPPY)}$_2$](**3**) and [{HgI_2 (CBPPY)}$_2$](**4**) respectively. The reactions of the title ylides with $AgNO_3$ in molar ratios (2:1) using dry acetone as solvent have yielded [Ag(FBPPY)$_2$]NO_3 (**5**) and [Ag(CBPPY)$_2$]NO_3 (**6**). The analytical data, IR and ^{1}H and ^{31}P NMR data of the products were obtained.

Keywords: Hg(II), Ag(I), α-ketostabilised phosphorus ylide

The α-ketostabilised phosphorus ylide $Ph_3PCH{=}C(H)COR$ (R = Me, Ph, OMe) has been found to be an interesting ligand in organometallic chemistry and a useful intermediate for organic synthesis.[1-4] In general, carbonyl-stabilised phosphorus ylides are interesting ligands because they can behave as C- or O- donors owing to the delocalisation of the ylidic electron pair.[5] This delocalisation also makes these ylides weak nucleophiles, but this does not reduce their interest as ligands, and surprisingly, it was their weak donor ability that allowed other workers to prepare new types of ylide complexes.[5] This ambidentate character facilitates the preparation of stable metal complexes in which the ylide could be O- (forms *cisoid* and *transoid*, **B**, Scheme 1)[6] or C-coordinated (**A,** Scheme 1),[7] with both modes rationalised in terms of the resonance forms **a**–**c** together with the isomeric forms (*cisoid* and *transoid*, **c**).

In the compounds reported to date, the chemical behaviour of the α-ketostabilised phosphorus ylide has been clearly dominated by the C-coordinated form,[8-11] and very few examples of O-coordinated ylides are known.[6,12-15] In this work, we report stabilised phosphorus ylides (FBPPY and CBPPY) and metal complexes with HgX_2 (X = Cl, I) and $AgNO_3$.

Experimental

Physical measurements and materials

Diethyl ether (Et_2O) was distilled over sodium benzophenone ketyl just before use. All other solvents were reagent grade and used without further purification. Solution-state ^{1}H and ^{31}P NMR spectra at 300 K were obtained in $CDCl_3$ using a 400 MHz Bruker spectrometer operating at 400.13 MHz for ^{1}H and 161.97 MHz for ^{31}P. Melting points were measured on a SMPI apparatus. Elemental analysis for C, H and N were performed using a PE 2400 series analyser. IR spectra were recorded on a FT-IR JASCO 680 spectrophotometer and the measurements were made by the KBr disk method.

Mercury halides, 4-flouroacetophenone, 4-chloroacetophenone and triphenyl phosphine were purchased from Merck. The ylides were synthesised by the reaction of triphenylphosphine with a chloroform solution of 2-bromo-4-flouroacetophenone or 2-bromo-4-chloroacetophenone and dehydrogenated by NaOH.[16] All solvents were dried by the reported methods.[17]

Synthesis of FBPPY and CBPPY

To chloroform solution (15 ml) of triphenylphosphine (1 mmol) was added 2-bromo-4-flouroacetophenone or 2-bromo-4-chloroacetophenone (1 mmol) and the resulting mixture was stirred for 12 h. The solution was filtered off, and the precipitate washed with diethyl ether and air-dried. Further treatment with aqueous NaOH solution (0.5 M) led to elimination of HBr, giving the free ligand precursors FBPPY or CBPPY.

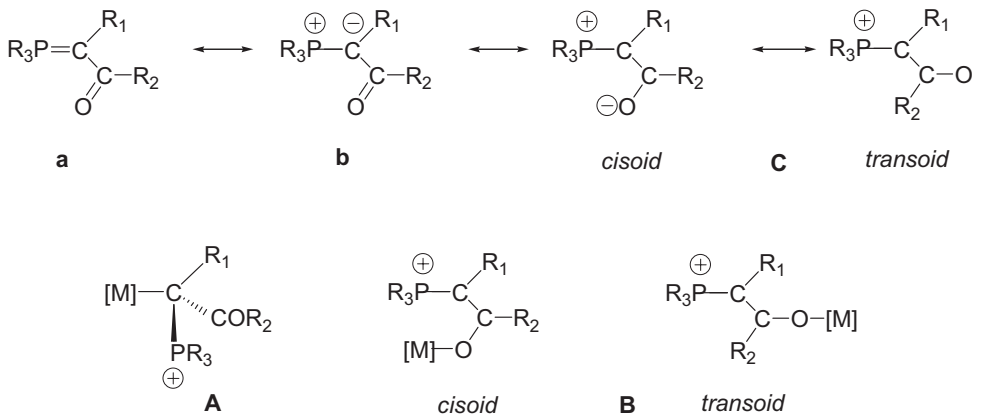
FBPPY: M.p. 142°C, Anal. Calc for $C_{26}H_{20}OPF$: C, 78.4; H, 5.1 Anal Found: C, 78.2; H, 5.0%.

CBPPY: M.p. 137–138°C Anal. Calc for $C_{26}H_{20}OPCl$: C, 75.3; H, 4.9 Anal Found: C, 75.0; H, 4.9%

Synthesis of the complexes

[{$HgCl_2$ (FBPPY)}$_2$] (**1**): To a solution (5 ml) of FBPPY (0.198 g, 0.5 mmol) in acetone (5 ml) was added mercury(II) chloride (0.134 g, 0.5 mmol). The mixture was stirred for 4 h. The white solid product was separated by filtration and washed with diethyl ether. Yield: 92.0%, M.p. 214°C, Anal. Calc for $C_{52}H_{40}Cl_4F_2Hg_2O_2P_2$: C, 46.6; H, 3.0 Anal Found: C, 46.45; H, 2.95% ^{1}H NMR: 5.51(d, 1H, CH, $^2J_{PH}$ = 10.25 Hz), 7.1–8.2 (m, 19H, Ph) ppm and ^{31}P NMR: 21.79 ppm.

[{HgI_2(FBPPY)}$_2$] (**2**): To a solution of FBPPY (0.100 g, 0.25 mmol) in acetone (5 ml) was added mercury (II) iodide (0.114 g, 0.25 mmol). The mixture was stirred for 12 h. On concentration



Scheme 1

* Correspondent. E-mail: karami@cc.iut.ac.ir

by removing the solvent by vacuum, a pale yellow precipitate was obtained. The products were washed with benzene and dried *in vacuo*. Yield: 81%, M.p. 214°C, Anal. Calc for $C_{52}H_{40}F_2Hg_2I_4O_2P_2$: C, 36.6; H, 2.4 Anal Found: C, 36.45; H, 2.3% ^{1}H NMR: 4.62(d, 1H, CH, $^2J_{PH}$ = 5.5 Hz), 7.1–8 (m, 19H, Ph) ppm and ^{31}P NMR: 20.34 ppm.

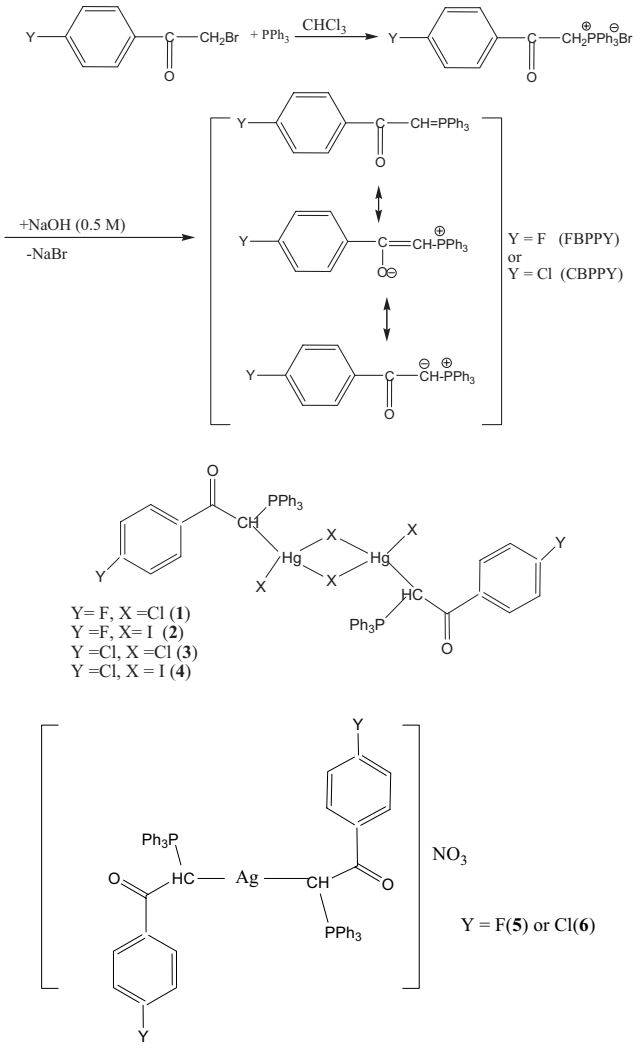
[{HgCl$_2$(CBPPY)}$_2$] (**3**): To a solution (5 ml) of CBPPY (0.207 g, 0.5 mmol) in acetone (5 ml) was added mercury(II) chloride (0.134 g, 0.5 mmol). The mixture was stirred for 4 h. The white solid product was separated by filtration and washed with diethyl ether. Yield: 92.0%, M.p. 204°C (dec), Anal. Calc for $C_{52}H_{40}Cl_6Hg_2O_2P_2$: C, 45.5; H, 2.9 Anal Found: C, 45.35; H, 2.8%.

^{1}H NMR: 5.48(s br, 1H, CH), 7.0–8.1 (m, 19H, Ph) ppm and ^{31}P NMR: 21.86 ppm.

[{HgI$_2$(CBPPY)}$_2$] (**4**): To a solution of CBPPY (0.104 g, 0.25 mmol) in acetone (5 ml) was added mercury (II) iodide (0.114 g, 0.25 mmol). The mixture was stirred for 12 h. On concentration by removing the solvent by vacuum, a pale yellow precipitate was obtained. The products were washed with diethyl ether and dried *in vacuo*. Yield: 81%, M.p. 219°C (dec), Anal. Calc for $C_{52}H_{40}Cl_2Hg_2I_4O_2P_2$: C, 35.9; H, 2.3 Anal Found: C, 36.05; H, 2.4% ^{1}H NMR: 5.49(s br, 1H, CH), 7.1–8.2 (m, 19H, Ph) ppm and ^{31}P NMR: 21.85 ppm.

[Ag(FBPPY)$_2$]NO$_3$ (**5**): The ylide FBPPY (0.470 g, 1.18 mmol) was added to a solution of $AgNO_3$ (0.100 g, 0.59 mmol) in acetone (10 ml). The solution was stirred, whilst protected from the light, for 1 h and then filtered through $MgSO_4$. The volume of solvent was reduced under vaccum to about 2 ml. Diethyl ether (25 ml) was added to precipitate [Ag{CH(PPh$_3$) C(O) C$_6$H$_4$–F}]NO$_3$ (**5**) as a white powder. M.p. 185°C (dec), Anal. Calc for $C_{52}H_{40}AgF_2NO_5P_2$: C, 64.6; H, 4.2 Anal Found: C, 64.5; H, 4.2% ^{1}H NMR: 5.06(s br, 1H), 7.1–8.1 (m, 19H, Ph) ppm and ^{31}P NMR: 22.13 ppm.

[Ag(CBPPY)$_2$]NO$_3$ (**6**) The ylide CBPPY (0.489 g, 1.18 mmol) was added to a solution of $AgNO_3$ (0.100 g, 0.59 mmol) in acetone (10 ml). The solution was stirred, whilst protected from the light for 1 h and then filtered through $MgSO_4$. The volume of solvent was reduced under vaccuum to about 2 ml. Diethyl ether (25 ml) was added to precipitate [Ag{CH(PPh$_3$)C(O)C$_6$H$_4$-Cl}]NO$_3$ (**6**) as a white powder. M.p. 179°C, Anal. Calc for $C_{52}H_{40}AgCl_2NO_5P_2$: C, 62.5; H, 4.0 Anal Found: C, 62.5; H, 3.9% ^{1}H NMR: 6.06(s br, 1H, CH), 7.2–8.2 (m, 19H, Ph) ppm and ^{31}P NMR: 21.79 ppm.



Results and discussion

Synthesis

The ligand was synthesised by treating 2-bromo-4'-flouroacetophenone or 2-bromo-4'-chloroacetophenone with triphenylphosphine and removal of the proton from the phosphonium salt.

Reactions of HgX_2 (X = Cl, I) with the ylide in a 1 : 1 stoichiometry afforded the C-coordinated complexes (**1–4**), with a halo-bridged dimeric structure, and reaction with $AgNO_3$ in a 2 : 1 stoichiometry afforded the C-coordinated complexes (**5**) and (**6**).

Spectroscopy

The ν(CO) values, which are sensitive to complexation, occur at 1516 and 1521 cm^{-1} in the parent ylides, as in the case of other resonance stabilised ylides.[11] Coordination of the ylide through carbon causes an increase in ν(CO), while for O-coordination a lowering of ν(CO) is expected (Table 1). The IR absorption bands observed for all complexes show an increase in ν(CO), indicative of coordination of the ylide through carbon. The ν(P$^+$–C$^-$), which is also diagnostic for the coordination, occurs at 897 cm^{-1} in Ph$_3$P$^+$–C$^-$H$_2$ and at 883 and 881 cm^{-1} in FBPPY and CBPPY respectively. In the present study, the ν (P$^+$–C$^-$) values for all complexes were shifted to lower frequencies (Table 1), suggesting some removal of electron density in the P–C bond. The ^{1}H NMR data for the mercury (II) complexes, along with those of the parent ylide, are listed in (Table 2). The NMR signal due to the methine proton, when recorded in $CDCl_3$, was broad for complexes **3**, **4**, **5** and **6**. This indicates that probably the ylide dissociates in solution. Compounds wherein the ylide is C-coordinated exhibit a $^2J_{(PH)}$ value of 10 Hz or less.[11,13]

The ^{31}P NMR resonances of the complexes were observed to occur at a lower field with respect to the free ylide (Table 2). The expected downfield shifts of ^{31}P and ^{1}H signals for the PCH group

Table 1 ν (CO) of selected phosphoranes and their metal complexes

Compound	ν (CO)	Δ(CO)	ν (P–C)	Ref.
$Ph_3PCHCOCH_3$ (APPY)	1530	–		18
$Ph_3PCHCOPh$ (BPPY)	1520	–	878	18
$Ph_3PCHCOC_6H_4$-F(= FBPPY)	1516	–	883	This work
$Ph_3PCHCOC_6H_4$-Cl(= CBPPY)	1521	–	881	This work
C-coordination				
[{HgCl$_2$(FBPPY)}$_2$] (**1**)	1638	+ 122	818	This work
[{HgI$_2$(FBPPY)}$_2$] (**2**)	1626	+ 110	808	This work
[{HgCl$_2$(CBPPY)}$_2$] (**3**)	1635	+ 114	816	This work
[{HgI$_2$(CBPPY)}$_2$] (**4**)	1622	+ 101	811	This work
[Ag(FBPPY)$_2$]NO$_3$ (**5**)	1613	+ 97	880	This work
[Ag(CBPPY)$_2$]NO$_3$ (**6**)	1616	+ 95	875	This work
O-coordination				
[Sn(CH$_3$)$_3$(APPY)]Cl	1480	–40		12
[Pd{C$_6$F$_5$)(PPh$_3$}$_2$(APPY)]ClO$_4$	1513	–17		7d

Table 2 ^{1}H and ^{31}P NMR data of FBPPY and its complexes with mercury (II), Ag (I) and Pd (II)

Compound	^{1}H chemical shifts (CH) (δ ppm)	$^{2}J_{(PH)}$ (Hz)	^{31}P chemical shifts (δ ppm)
FBPPY	4.37 (d)	23.99	16.8
CBPPY	4.4(d)	23.87	16.7
$[\{HgCl_2(FBPPY)\}_2]$ (**1**)	5.51(d)	10.25	21.79
$[\{HgI_2(FBPPY)\}_2]$ (**2**)	4.62(d)	5.48	20.34
$[\{HgCl_2(CBPPY)\}_2]$ (**3**)	5.48 (s br)	–	21.86
$[\{HgI_2(CBPPY)\}_2]$ (**4**)	5.49 (s br)	–	21.85
$[Ag(FBPPY)_2]NO_3$ (**5**)	5.06 (s br)	–	22.13
$[Ag(CBPPY)_2]NO_3$ (**6**)	6.06 (s br)	–	21.79

upon complexation were observed in their corresponding spectra. The appearance of single signals for the PCH group in both the ^{31}P and ^{1}H spectra at ambient temperature indicates the presence of only one molecule for all the complexes as expected for C-coordination. It must be noted that O-coordination of the ylide sometimes leads to the formation of *cis*- and *trans*-isomers giving rise to two different signals in the ^{31}P and ^{1}H NMR.[6b,17] ^{1}H and $^{31}P\{^{1}H\}$ NMR data are presented in Table 2. Although two diasteroisomer (RR/SS and RS) are possible for each complex (because the methane carbons are chiral) NMR spectroscopy does not distinguish them at room temperature. The methine resonances are intermediate between, and ^{2}J(PH) values smaller than, those in the free ylides and phosphonium salts; this was observed for other C-coordinated carbonyl-stabilised phosphorus ylide complexes and is due to the hybridisation change in the ylidic carbon (SP^2-SP^3) in the C-coordination mode.[7b,15,16] Values of ^{2}J(PH) much larger (*ca* 20 Hz) have been observed in complexes where coordination is through the oxygen atom.[12] Neither H–Ag and H–Hg nor P–Ag and P–Hg coupling was observed at room temperature in the spectra of our complexes; the same was the case for $[Ag(C_6F_5)CH(PPh_3)CO_2Me]$.[18] It is possible that a fast equilibrium between complexes and free ylides is responsible for the failure observed either the NMR couplings or presence of two diastereoisomers

Received 17 October 2007; accepted 31 December 2007
Paper 07/4897 doi: 10.3184/030823407X275955

References

1 Y. Shen, *Acct. Chem. Res*., 1998, **31**, 584.
2 C. Puke, G. Erker, N.C. Aust, E.U. Wurthweine and R. Frohich, *J. Am. Chem. Soc*.,1998, **120**, 4863.
3 O.I. Kolodiazhnyi, *Russ. Chem. Rev*., 1997, **66**, 225.
4 D.E.C. Cobridge, Phosphorus an Outline of Chemistry, Biochemistry and Uses, 5th edn, Elsevier, Amsterdam, 1995.
5 J. Vicente, M.T. Chicote, M.C. Lagunas and P.G. Jones*, J. Chem. Soc., Dalton Trans*.,1991, 2579.
6 J. Buckle and P.G. Harrison, *J. Organomet. Chem.*, 1973, **49**, C17.
7 (*a*) H. Nishiyama, K. Itoh and Y. Ishii, *J. Organomet. Chem.*, **87**, 129 (1975); (*b*) E.T. Weleski, J.L. Silver, M.D. Jansson and J.L. Burmeister, *J. Organomet. Chem.*,1975, **102**, 365; (*c*) P. Bravo, G. Fronza and T. Ticozzi, *J. Organomet. Chem.*, 1976**, 111**, 361; (*d*) H. Koezuka, G. Matsubayashi and T. Tanaka, *Inorg. Chem.*, 1976, **15**, 417; (*e*) G. Fronza, P. Bravo and C. Ticozzi, *J. Organomet. Chem.*,1978, **157**, 299; (*f*) G. Facchin, R. Bertani, M. Calligaris, G. Nardin and M. Mari, *J. Chem. Soc*., *Dalton Trans*,1987, 1381.
8 H. Nishiyama, K. Itoh and Y. Ishii, *J. Organomet. Chem*., 1975, **87**, 129.
9 J. Vicent, M.T. Chicote and J. Fernandez-Baeza, *J. Organomet. Chem*.,1989, **364**, 407.
10 M. Onishi, Y. Ohama, K. Hiraki and H. Shintani, *Polyhedron,* 1982, **1**, 539.
11 J. Vicent, M.T. Chicote, M.C. Lagunas and P.G. Jones, *J. Chem. Soc., Dalton Trans.,* 1991, 2579.
12 J. Buckle, P.G. Harrison, T.J. King and J.A. Richards, *J. Chem. Soc., Chem. Commun., 1104,* 1972.
13 J.A. Albanese, D.A. Staley, A.L. Rheingold and J.L. Burmeister, *Inorg. Chem*., 1990, 2209.
14 I. Kawafune and G. Matsubayashi, *Inorg. Chim. Acta,*1983, **70**, 1.
15 R. Uson, J. Fornies, R. Navarro, P. Espinet and C.J. Mendivil, *Organomet. Chem.,*1985**, 290**, 125.
16 J. Vicent, M.T. Chicote, J.A. Cayuelas, J. Fernandez-Baeza, P.G.Jones, G.M. Sheldrick and P. Espinet, *J. Chem. Soc., Dalton Trans*., 1985**,** 1163.
17 J.L. Burmeister, J.L. Silver, E.T. Weleski, E.E. Schweizer and C.M. Kopay, Synth. *Inorg. Met. Org. Chem*., 1973, **3**, 339.
18J. Vicent, M.T. Chicote, J. Fernandez-Baeza, J. Martin and I. Saura-Llamas, *J. Organomet. Chem*., 1987, **331**, 409.

A novel and efficient synthesis of terminal arylacetylenes via Sonogashira coupling reactions catalysed by MCM-41-supported bidentate phosphine palladium(0) complex

Yue Wang, Bin Huang, Shouri Sheng and Mingzhong Cai*

Department of Chemistry, Jiangxi Normal University, Nanchang 330022, P. R. China

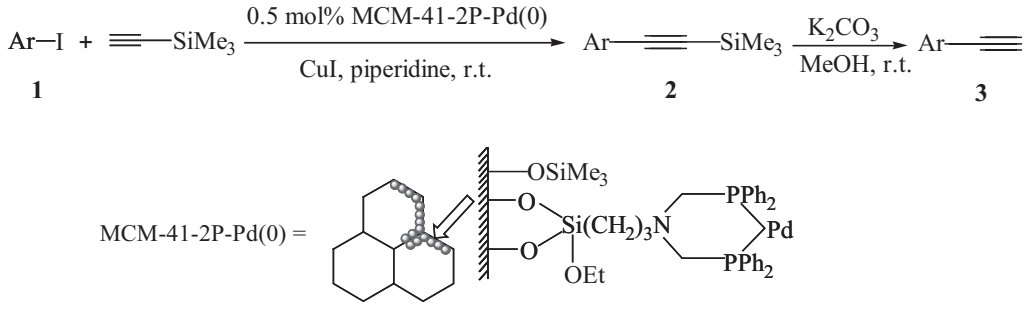
A variety of terminal arylacetylenes have been conveniently synthesised in good to high yields via Sonogashira coupling of aryl iodides with (trimethylsilyl)acetylene catalysed by a MCM-41-supported bidentate phosphine palladium(0) complex, followed by desilylation. The polymeric palladium catalyst can be reused many times without any decrease in activity.

Keywords: Sonogashira coupling, MCM-41-supported catalyst, bidentate phosphine palladium complex, heterogeneous catalysis, terminal arylacetylene

Terminal arylacetylenes are an important synthetic intermediates[1] and are usually prepared by classical procedures such as the Vilsmeier method,[2] the halogenation-dehydrohalogenation sequence of vinyl aromatics[3] and ketones,[4] and the dehydrohalogenation of β,β-dihaloolefins.[5] However, these methods involve a tedious multistep synthetic procedure and the yields are poor to moderate. The palladium-catalysed cross-coupling of terminal alkynes with aryl halides is known as the Sonogashira reaction[6] and has become an extremely powerful tool for the formation of carbon–carbon bonds. This coupling reaction has been widely applied in organic synthesis since a wide variety of functionality can be tolerated on either partner and the yields of coupled products are high. Lau *et al*.[7] reported that terminal arylacetylenes could be conveniently synthesised in good yields by palladium(0)-catalysed Sonogashira coupling of aryl halides with (trimethylsilyl)acetylene, followed by desilylation under mild conditions. However, the Sonogashira reaction generally proceeds in the presence of a homogeneous palladium catalyst, which makes the catalyst recovery a tedious operation and may result in unacceptable palladium contamination of the product. From the standpoint of green chemistry, the development of more environmentally benign conditions for the reaction, for example the use of a heterogeneous palladium catalyst would be desirable.[8] So far, polymer-supported palladium catalysts have successfully been used for the Heck reaction,[9] the Suzuki reaction,[10] and the Sonogashira reaction.[11] However, to the best of our knowledge, no report for the Sonogashira coupling of aryl halides with (trimethylsilyl)acetylene has been reported using supported palladium catalysts. Recent developments on the mesoporous material MCM-41 provided a possible new candidate for a solid support for immobilisation of homogeneous catalysts.[12] MCM-41 has a regular pore diameter of *ca*.5 nm and a specific surface area > 700 m^2 g^{-1}.[13] Its large pore size allows passage of large molecules such as organic reactants and metal complexes through the pores to reach the surface of the channel.[14] Very recently, we have reported the synthesis of the first MCM-41-supported bidentate phosphine palladium(0) complex [abbreviated as MCM-41-2P-Pd(0)] and found that this complex is a highly active and recyclable catalyst for the heterogeneous Suzuki reaction.[15] Herein we wish to report that a variety of terminal arylacetylenes could be conveniently synthesised in good to high yields via Sonogashira coupling of aryl iodides with (trimethylsilyl)acetylene catalysed by MCM-41-2P-Pd(0), followed by desilylation under mild conditions (Scheme 1).

The MCM-41-supported bidentate phosphine palladium(0) complex [MCM-41-2P-Pd(0)] was prepared by our previous procedure.[15] The phosphine and palladium contents were 1.15 and 0.52 mmol/g, respectively. The influences of bases, solvents and amounts of the catalyst on the catalytic property of the MCM-41-2P-Pd(0) complex were investigated by using the coupling reaction of iodobenzene with (trimethylsilyl) acetylene. The results are shown in Table 1. It was found that among the bases tested, piperidine proved to be the most efficient. Among the solvents used, piperidine was also the best choice. Increasing the amount of palladium catalyst could shorten the reaction time, but did not increase the yield of 1-phenyl-2-(trimethylsilyl)ethyne (entry 12). The low palladium concentration usually led to a long period of reaction, which was consistent with our experimental results (entries 13, 14). Taken together, excellent results were obtained when the coupling reaction was carried out with 0.5 mol% of MCM-41-2P-Pd(0) and 5 mol% of CuI in piperidine at room temperature (entry 9).

The results of MCM-41-2P-Pd(0)-catalysed cross-coupling of a variety of aryl iodides with (trimethylsilyl)acetylene are summarised in Table 2. As shown in Table 2, the coupling reaction of aryl iodides having electron-withdrawing or electron- donating substituents with (trimethylsilyl)acetylene



Scheme 1

* Correspondent. E-mail: caimzhong@163.com

Table 1 Sonogashira reaction of iodobenzene with (trimethylsilyl)acetylene in the presence of several bases and solvents[a]

Entry	Base	Solvent	MCM-41-2P-Pd(0) (mol%)	Time/h	Yield [b]/%
1	Et_3N	Toluene	0.5	9	73
2	Et_3N	DMF	0.5	6	79
3	Et_3N	Dioxane	0.5	6	78
4	Et_3N	Et_3N	0.5	3	82
5	$BuNH_2$	DMF	0.5	6	80
6	$BuNH_2$	Dioxane	0.5	6	75
7	$BuNH_2$	$BuNH_2$	0.5	3	83
8	Piperidine	DMF	0.5	5	85
9	Piperidine	Piperidine	0.5	2	96
10	Pyrrolidine	DMF	0.5	5	83
11	Pyrrolidine	Pyrrolidine	0.5	2	92
12	Piperidine	Piperidine	1.0	1	95
13	Piperidine	Piperidine	0.1	8	90
14	Piperidine	Piperidine	0.05	24	85

[a]All reactions were performed using 1.0 mmol of iodobenzene, 1.5 mmol of (trimethylsilyl)acetylene, 0.05 mmol of CuI and 3.0 mmol of base in 3 ml of solvent at room temperature under Ar. [b]Isolated yield based on the iodobenzene used.

Table 2 Synthesis of 1-aryl-2-(trimethylsilyl)ethynes **2a–n**[a]

Entry	Ar-X	Product	Yield[b]/%
1	Ph-I	**2a**	96
2	4-BrC_6H_4-I	**2b**	97
3	4-ClC_6H_4-I	**2c**	96
4	4-$MeOC_6H_4$-I	**2d**	93
5	4-$O_2NC_6H_4$-I	**2e**	95
6	4-MeC_6H_4-I	**2f**	93
7	4-HOC_6H_4-I	**2g**	90
8	4-$MeCOC_6H_4$-I	**2h**	97
9	4-$MeOCOC_6H_4$-I	**2i**	96
10	3-$O_2NC_6H_4$-I	**2j**	98
11	3-MeC_6H_4-I	**2k**	94
12	3-NCC_6H_4-I	**2l**	96
13	1-Iodonaphthalene	**2m**	92
14	2-Iodothiophene	**2n**	88

[a]All reactions were performed using 1.0 mmol of aryl iodide, 1.5 mmol of (trimethylsilyl)ethyne, 0.005 mmol of palladium catalyst and 0.05 mmol of CuI in 3 ml of piperidine at room temperature under Ar for 2 h.
[b]Isolated yield based on the aryl iodide **1** used.

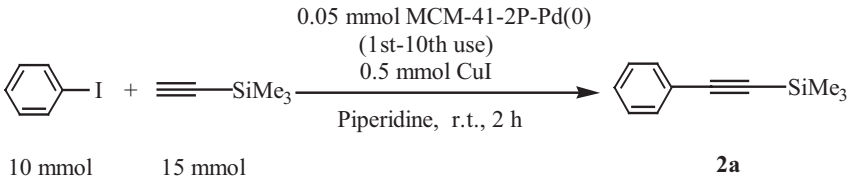


Table 3 Sonogashira reaction of iodobenzene with (trimethylsilyl)acetylene catalysed by recycled catalyst

Entry	Catalyst cycle	Isolated yield/%	TON
1	First	96	192
2	Tenth	93	186
3	First to tenth consecutive	94	Total of 1880

proceeded smoothly at room temperature in piperidine giving a variety of 1-aryl-2-(trimethylsilyl)ethynes in excellent yields after 2 h of reaction time. The coupling reactions of aryl bromides with (trimethylsilyl)acetylene did not occur at 25°C or 60°C under the same conditions. The cross-coupling reaction of 4-bromoiodobenzene with (trimethylsilyl)-acetylene afforded selectively 1-(4-bromophenyl)-2-(trimethylsilyl) ethyne **2b** in 97% yield; no 1,4-bis(trimethylsilylethynyl) benzene was formed (entry 2). The coupling reaction of aryl iodides with (trimethylsilyl)acetylene also proceeded in the absence of copper iodide, but a longer reaction time (24 h) was required and the yield was moderate. The Sonogashira coupling reactions of 1-iodonaphthalene and heteroaryl iodides such as 2-iodothiophene with (trimethylsilyl)acetylene could also proceed smoothly under the same conditions affording the corresponding coupled products in high yields (entries 13, 14). The optimised catalyst system is quite general in application and tolerant of a wide range of functional groups such as nitro, cyano, halogen, methoxy, carbonyl, hydroxy. In all reactions, only 0.5 mol% of MCM-41-2P-Pd(0) based on the aryl iodides was used, the molar turnover numbers (TON) were larger than those in the corresponding coupling reaction catalysed by the homogeneous palladium catalysts.[6,7]

The MCM-41-supported bidentate phosphine palladium(0) catalyst can be easily recovered by simple filtration. We next examined the reuse of the catalyst by using the Sonogashira coupling of iodobenzene with (trimethylsilyl)acetylene. In general, the continuous recycle of resin-supported palladium catalysts is difficult owing to leaching of the palladium species from the polymer supports. However, when the coupling reaction of iodobenzene with (trimethylsilyl)acetylene was

Table 4 Synthesis of terminal arylacetylenes **3a–n**[a]

Entry	ArC≡CH	Product	Yield[b]/%
1	PhC≡CH	**3a**	88
2	4-BrC_6H_4C≡CH	**3b**	90
3	4-ClC_6H_4C≡CH	**3c**	91
4	4-$MeOC_6H_4C$≡CH	**3d**	86
5	4-$O_2NC_6H_4C$≡CH	**3e**	92
6	4-MeC_6H_4C≡CH	**3f**	90
7	4-HOC_6H_4C≡CH	**3g**	85
8	4-$MeCOC_6H_4C$≡CH	**3h**	91
9	4-$MeOCOC_6H_4C$≡CH	**3i**	94
10	3-$O_2NC_6H_4C$≡CH	**3j**	89
11	3-MeC_6H_4C≡CH	**3k**	93
12	3-NCC_6H_4C≡CH	**3l**	94
13	1-Ethynylnaphthalene	**3m**	88
14	2-Ethynylthiophene	**3n**	86

[a]All reactions were performed using 1.0 mmol of **2**, 0.09 mmol of K_2CO_3 in 3 ml of MeOH at 25°C under Ar for 3 h.
[b]Isolated yield based on the **2** used.

run even with 0.5 mol% of MCM-41-2P-Pd(0), the catalyst could be recycled 10 times without any loss of activity. The reaction promoted by the tenth recycled catalyst afforded **2a** in 93% yield (Table 3, entry 2). The average yield of **2a** in consecutive reactions promoted by the 1-10 times recycled catalyst was 94% (entry 3). The result is important from a practical point of view.

Subsequent treatment of 1-aryl-2-(trimethylsilyl)ethynes **2** with anhydrous potassium carbonate in anhydrous methanol at 25°C for 3 h gave a variety of terminal arylacetylenes (Scheme 1). The experimental results are summarised in Table 4. From the Table 4, we can see that the desilylation reaction of a variety of 1-aryl-2-(trimethylsilyl)ethynes **2** in the presence of anhydrous potassium carbonate proceeded smoothly under mild conditions, affording the corresponding terminal arylacetylenes **3** in good to high yields.

In conclusion, we have developed a novel and efficient route for synthesis of terminal arylacetylenes by the Sonogashira coupling of aryl iodides with (trimethylsilyl) acetylene catalysed by a MCM-41-supported bidentate phosphine palladium(0) catalyst, followed by desilylation under mild conditions. Because (trimethylsilyl)acetylene can be easily prepared in high yield under mild conditions from acetylene and chlorotrimethylsilane according to the procedure developed by Brandsma and Verkruijsse,[16] the present method has the advantages of readily available starting materials, straightforward and simple procedures, mild reaction conditions, high yields, tolerance for a wide variety of functionality, and excellent reusability of the palladium catalyst.

Experimental

^{1}H NMR spectra were recorded on a Bruker AC-P400 (400 MHz) spectrometer with TMS as an internal standard using $CDCl_3$ as the solvent. ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AC-P400 (400 MHz) spectrometer using $CDCl_3$ as the solvent. IR spectra were determined on an FTS-185 instrument as neat films. Mass spectra were obtained on a Finigan 8239 mass spectrometer (EI, 70 eV). Microanalyses were measured using a Yanaco MT-3 CHN microelemental analyser. All reactions were carried out in pre-dried glassware (150°C, 4 h) and cooled under a stream of dry Ar. Piperidine was dried by KOH and distilled prior to use. For AA'XX' systems in ^{1}H NMR $J^* = J_{23} + J_{25}$.

General procedure for the synthesis of 1-aryl-2-(trimethylsilyl)ethynes **2a–n**

The aryl iodide (1.0 mmol), MCM-41-2P-Pd(0) (10 mg, 0.005 mmol Pd), piperidine (3 ml), and CuI (0.05 mmol) were added to a flask under argon, and the resulting mixture was stirred at room temperature for 5 min. To this suspension was added (trimethylsilyl) acetylene (1.5 mmol), and the reaction mixture was stirred at room temperature for 2 h. The mixture was dissolved in Et_2O (40 ml). The MCM-41- 2P-Pd(0) catalyst was separated from the mixture by filtration, washed with distilled water (2 × 10 ml), EtOH (3 × 10 ml) and Et_2O (2 × 10 ml) and reused in the next run. The ethereal solution was washed with water (2 × 10 ml) and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (light petroleum:ethyl acetate = 2:1 for **2g**; light petroleum for **2a, 2b, 2c, 2f, 2k, 2m, 2n**; light petroleum: ethyl acetate = 9:1 for **2d, 2e, 2h, 2i, 2j, 2l**) to give the desired product.

Compound **2a:** IR (film): ν (cm^{-1}) 3080, 2960, 2159, 1598, 1488, 1250, 843, 690; ^{1}H NMR ($CDCl_3$): δ 7.48–7.45 (m, 2H), 7.31–7.29 (m, 3H), 0.25 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 132.0, 128.5, 128.2, 123.1, 105.1, 94.1, 0.01; MS: *m/z* 174 (M^+, 19), 159 (68), 77 (57), 73 (100); Anal. Calc. for $C_{11}H_{14}Si$: C, 75.79; H, 8.10. Found: C, 75.92; H, 8.2%.

Compound **2b:** IR (film): ν (cm^{-1}) 2957, 2158, 1582, 1485, 1247, 846, 759; ^{1}H NMR ($CDCl_3$): δ 7.42 (m, J^* = 8.4 Hz, 2H), 7.32 (m, J^* = 8.4 Hz, 2H), 0.24 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 133.4, 131.5, 122.7, 122.1, 103.9, 95.6, 0.14; MS: *m/z* 254 (M^+, ^{80}Br, 2.6), (M^+, ^{78}Br, 2.5) 165 (51), 125 (56), 111 (77), 97 (100), 83 (80), 71 (70); Anal. Calc. for $C_{11}H_{13}SiBr$: C, 52.16; H, 5.17. Found: C, 51.9; H, 5.0%.

Compound **2c:** IR (film): ν (cm^{-1}) 3030, 2959, 2159, 1590, 1488, 1250, 844, 759, 685; ^{1}H NMR ($CDCl_3$): δ 7.38 (m, J^* = 8.4 Hz, 2H), 7.26 (m, J^* = 8.4 Hz, 2H), 0.24 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 134.6, 133.2, 128.6, 121.7, 103.9, 95.4, -0.07; MS: *m/z* 210 (M^+, ^{37}Cl, 3.8), 208(M^+, ^{35}Cl, 12) 193 (64), 73 (100); Anal. Calc. for $C_{11}H_{13}SiCl$: C, 63.27; H, 6.28. Found: C, 63.4; H, 6.1%.

Compound **2d:** IR (film): ν (cm^{-1}) 2960, 2156, 1606, 1508, 1249, 834, 699; ^{1}H NMR ($CDCl_3$): δ 7.41 (m, J^* = 8.8 Hz, 2H), 6.81 (m, J^* = 8.8 Hz, 2H), 3.81 (s, 3H), 0.24 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 159.7, 133.5, 115.3, 113.8, 105.2, 92.5, 55.3, 0.08; MS: *m/z* 204 (M^+, 31), 189 (76), 73 (100); Anal. Calc. for $C_{12}H_{16}SiO$: C, 70.53; H, 7.89. Found: C, 70.3; H, 8.1%.

Compound **2e:** IR (film): ν (cm^{-1}) 2960, 2160, 1593, 1521, 1348, 1250, 866; ^{1}H NMR ($CDCl_3$): δ 8.17 (m, J^* = 8.8 Hz, 2H), 7.60 (m, J^* = 8.8 Hz, 2H), 0.28 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 147.2, 132.7, 130.0, 123.5, 102.7, 100.6, -0.30; MS: *m/z* 219 (M^+, 33), 205 (47), 204 (100), 158 (73); Anal. Calc. for $C_{11}H_{13}NSiO_2$: C, 60.24; H, 5.98. Found: C, 60.4; H, 6.1%.

Compound **2f:** IR (film): ν (cm^{-1}) 2959, 2158, 1612, 1507, 1251, 871, 844, 816; ^{1}H NMR ($CDCl_3$): δ 7.35 (m, J^* = 8.0 Hz, 2H), 7.09 (m, J^* = 8.0 Hz, 2H), 2.34 (s, 3H), 0.24 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 138.6, 131.9, 128.9, 120.1, 105.4, 93.2, 21.5, 0.03; MS: *m/z* 188 (M^+, 13), 173 (84), 69 (66), 57 (100); Anal. Calc. for $C_{12}H_{16}Si$: C, 76.53; H, 8.56. Found: C, 76.3; H, 8.3%.

Compound **2g:** IR (film): ν (cm^{-1}) 3435, 2959, 2157, 1608, 1509, 1252, 868, 841; ^{1}H NMR ($CDCl_3$): δ 7.35 (m, J^* = 8.4 Hz, 2H), 6.75 (m, J^* = 8.4 Hz, 2H), 4.92 (s, 1H), 0.23 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 155.8, 133.7, 115.6, 115.3, 105.0, 92.5, 0.05; MS: *m/z* 190 (M^+, 91), 175 (100), 136 (84), 121 (94), 93 (77), 65 (58); Anal. Calc. for $C_{11}H_{14}SiO$: C, 69.42; H, 7.41. Found: C, 69.2; H, 7.5%.

Compound **2h:** IR (film): ν (cm^{-1}) 2961, 2159, 1688, 1600, 1558, 1263, 864, 843; ^{1}H NMR ($CDCl_3$): δ 7.88 (m, J^* = 8.4 Hz, 2H), 7.53 (m, J^* = 8.4 Hz, 2H), 2.60 (s, 3H), 0.27 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 197.3, 136.4, 132.1, 128.1, 128.0, 104.0, 98.1, 26.6, –0.18; MS: *m/z* 216 (M^+, 5.2), 149 (40), 111 (45), 97 (64), 71 (77), 57 (100); Anal. Calc. for $C_{13}H_{16}SiO$: C, 72.17; H, 7.45. Found: C, 71.9; H, 7.35%.

Compound **2i:** IR (film): ν (cm^{-1}) 2958, 2160, 1724, 1604, 1277, 1109, 860, 844, 770; ^{1}H NMR ($CDCl_3$): δ 7.96 (m, *J** = 8.4 Hz, 2H), 7.52 (m, *J** = 8.4 Hz, 2H), 3.91 (s, 3H), 0.26 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 166.5, 131.9, 129.7, 129.4, 127.8, 104.1, 97.7, 52.2, –0.17; MS: *m/z* 232 (M$^+$, 79), 218 (81), 217 (100), 201 (53), 158 (45); Anal. Calc. for $C_{13}H_{16}SiO_2$: C, 67.19; H, 6.94. Found: C, 67.35; H, 6.9%.

Compound **2j:** IR (film): ν (cm^{-1}) 2962, 2169, 1572, 1532, 1353, 1251, 845; ^{1}H NMR ($CDCl_3$): δ 8.31 (s, 1H), 8.17–8.14 (m, 1H), 7.76–7.73 (m, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 0.26 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 148.0, 137.5, 129.2, 126.8, 125.0, 123.1, 102.2, 97.6, -0.27; MS: *m/z* 219 (M$^+$, 11), 204 (100), 183 (57); Anal. Calc. for $C_{11}H_{13}NSiO_2$: C, 60.24; H, 5.98. Found: C, 59.95; H, 5.8%.

Compound **2k:** IR (film): ν (cm^{-1}) 2960, 2151, 1602, 1579, 1483, 1250, 843; ^{1}H NMR ($CDCl_3$): δ 7.30–7.25 (m, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 2.31 (s, 3H), 0.24 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 137.8, 132.5, 129.3, 128.9, 128.0, 122.8, 105.2, 93.6, 21.0, –0.12; MS: *m/z* 188 (M$^+$, 73), 173 (100); Anal. Calc. for $C_{12}H_{16}Si$: C, 76.53; H, 8.56. Found: C, 76.7; H, 8.4%.

Compound **2l:** IR (film): ν (cm^{-1}) 2957, 2236, 2151, 1594, 1571, 1476, 1248, 846; ^{1}H NMR ($CDCl_3$): δ 7.74 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 0.26 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 135.8, 135.2, 131.5, 129.0, 124.7, 117.9, 112.7, 102.2, 97.3, -0.36; MS: *m/z* 199 (M$^+$, 31), 83 (46), 71 (63), 57 (100); Anal. Calc. for $C_{12}H_{13}NSi$: C, 72.31; H, 6.57. Found: C, 72.1; H, 6.3%.

Compound **2m:** IR (film): ν (cm^{-1}) 2962, 2147, 1706, 1565, 1393, 1261, 843, 799; ^{1}H NMR ($CDCl_3$): δ 8.33 (d, *J* = 8.4 Hz, 1H), 7.85–7.81 (m, 2H), 7.71–7.69 (m, 1H), 7.58–7.51(m, 2H), 7.43–7.38 (m, 1H), 0.34 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 133.3, 133.0, 130.7, 128.9, 128.1, 126.7, 126.3, 126.1, 125.0, 120.7, 103.0, 99.4, 0.0; MS: *m/z* 224 (M$^+$, 3.8), 127 (26), 91 (51), 77 (62), 64 (100); Anal. Calc. for $C_{15}H_{16}Si$: C, 80.29; H, 7.19. Found: C, 80.0; H, 7.35%.

Compound **2n:** IR (film): ν (cm^{-1}) 2961, 2147, 1250, 1164, 844, 699; ^{1}H NMR ($CDCl_3$): δ 7.26–7.22 (m, 2H), 6.95 (t, *J* = 4.4 Hz, 1H), 0.25 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 132.7, 127.4, 127.0, 123.4, 98.9, 97.7, 0.13; MS: *m/z* 180 (M$^+$, 15), 165 (56), 73 (100); Anal. Calc. for $C_9H_{12}SSi$: C, 59.94; H, 6.71. Found: C, 59.7; H, 6.5%.

General procedure for the synthesis of terminal arylacetylenes **3a–n**
A mixture of 1-aryl-2-(trimethylsilyl)ethyne (1.0 mmol), anhydrous potassium carbonate (0.09 mmol) in anhydrous MeOH (3 ml) was stirred at 25°C under argon for 3 h. The solvent was evaporated under reduced pressure, and the residue was mixed with 2 ml of aqueous sodium bicarbonate and extracted with Et_2O (3 × 10 ml). The combined organic fractions were dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography on silica gel (light petroleum:ethyl acetate = 2:1 for **3g**; light petroleum for **3a, 3b, 3c, 3f, 3k, 3m, 3n**; light petroleum: ethyl acetate = 9:1 for **3d, 3e, 3h, 3i, 3j, 3l**).

Compound **3a:** IR (film): ν (cm^{-1}) 3292, 2110, 1598, 1574, 1488, 757, 691; ^{1}H NMR ($CDCl_3$): δ 7.51–7.48 (m, 2H), 7.35–7.32 (m, 3H), 3.08 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 132.1, 128.8, 128.3, 122.1, 83.7, 77.1. MS: *m/z* 102 (M$^+$, 43), 77 (65), 57 (100).

Compound **3b:** IR (film): ν (cm^{-1}) 3287, 2346, 1583, 1489, 1462, 758; ^{1}H NMR ($CDCl_3$): δ 7.46 (m, *J** = 8.8 Hz, 2H), 7.35 (m, *J** = 8.8 Hz, 2H), 3.12 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 133.6, 131.6, 123.1, 121.1, 82.6, 78.3. MS: *m/z* 182 (M$^+$, ^{80}Br, 1.9), 180 (M$^+$, ^{78}Br, 1.8), 156 (38), 101 (49), 71 (60), 57 (100). Anal. Calcd for C_8H_5Br: C, 53.05; H, 2.78. Found: C, 52.8; H, 2.6.

Compound **3c:** IR (film): ν (cm^{-1}) 3293, 2197, 1587, 1485, 1095, 822; ^{1}H NMR ($CDCl_3$): δ 7.42 (m, *J** = 8.4 Hz, 2H), 7.30 (m, *J** = 8.4 Hz, 2H), 3.10 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 134.9, 133.4, 128.7, 120.6, 82.5, 78.2; MS: *m/z* 138 (M$^+$, ^{37}Cl, 31), 136 (M$^+$, ^{35}Cl,100), 135 (88), 111 (59), 69 (46). Anal. Calcd for C_8H_5Cl: C, 70.33; H, 3.69. Found: C, 70.5; H, 3.6.

Compound **3d:** IR (film): ν (cm^{-1}) 3290, 2960, 2106, 1607, 1571, 1507, 1171, 1031, 832; ^{1}H NMR ($CDCl_3$): δ 7.42 (m, *J** = 8.8 Hz, 2H), 6.83 (m, *J** = 8.8 Hz, 2H), 3.80 (s, 3H), 3.00 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 160.0, 133.6, 114.2, 113.9, 83.7, 75.8, 55.3; MS: *m/z* 132 (M$^+$, 26), 123 (68), 111 (51), 109 (70), 97 (84), 95 (94), 69 (100), 57 (88), 55 (96). Anal. Calcd for C_9H_8O: C, 81.79; H, 6.10. Found: C, 81.5; H, 6.2.

Compound **3e:** IR (film): ν (cm^{-1}) 3253, 2107, 1594, 1513, 1492, 1344, 855, 752; ^{1}H NMR ($CDCl_3$): δ 8.20 (m, *J** = 8.8 Hz, 2H), 7.64 (m, *J** = 8.8 Hz, 2H), 3.36 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 146.2, 133.0, 128.9, 123.6, 82.3, 81.6; MS: *m/z* 147 (M$^+$, 100), 117 (86), 101 (97), 89 (78), 75 (95). Anal. Calcd for $C_8H_5NO_2$: C, 65.31; H, 3.43. Found: C, 65.1; H, 3.5.

Compound **3f:** IR (film): ν (cm^{-1}) 3290, 2923, 2341, 1631, 1598, 1574, 670; ^{1}H NMR ($CDCl_3$): δ 7.38 (m, *J** = 8.0 Hz, 2H), 7.12 (m, *J** = 8.0 Hz, 2H), 3.03 (s, 1H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 139.0, 132.0, 129.1, 119.0, 104.2, 83.8, 21.5; MS (EI): *m/z* 116 (M$^+$, 23), 101 (45), 97 (51), 91 (64), 71 (68), 69 (80), 57 (100). Anal. Calcd for C_9H_8: C, 93.06; H, 6.94. Found: C, 92.8; H, 6.75.

Compound **3g:** IR (film): ν (cm^{-1}) 3289, 2154, 1609, 1585, 1510, 1261, 1093, 836; ^{1}H NMR ($CDCl_3$): δ 7.41 (m, *J** = 8.4 Hz, 2H), 6.80 (m, *J** = 8.4 Hz, 2H), 4.93 (br, 1H), 3.02 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 156.3, 133.8, 115.5, 114.2, 104.3, 83.7; MS: *m/z* 118 (M$^+$, 100), 93 (89), 77 (56). Anal. Calcd for C_8H_6O: C, 81.34; H, 5.12. Found: C, 81.6; H, 5.35.

Compound **3h:** IR (film): ν (cm^{-1}) 3282, 2926, 2162, 1686, 1595, 1494, 761; ^{1}H NMR ($CDCl_3$): δ 7.91 (m, *J** = 8.4 Hz, 2H), 7.57 (m, *J** = 8.4 Hz, 2H), 3.25 (s, 1H), 2.61 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 197.3, 136.8, 132.3, 128.2, 126.9, 82.8, 80.3, 26.6; MS: *m/z* 144 (M$^+$, 86), 129 (100), 101 (91), 85 (64), 71 (75), 57 (85). Anal. Calcd for $C_{10}H_8O$: C, 83.31; H, 5.59. Found: C, 83.05; H, 5.3.

Compound **3i:** IR (film): ν (cm^{-1}) 3290, 2925, 1725, 1608, 1278, 1109, 696; ^{1}H NMR ($CDCl_3$): δ 7.99 (m, *J** = 8.4 Hz, 2H), 7.55 (m, *J** = 8.4 Hz, 2H), 3.92 (s, 3H), 3.23 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 166.4, 132.1, 130.2, 129.5, 126.8, 82.8, 80.0, 52.3; MS: *m/z* 160 (M$^+$, 57), 146 (32), 129 (100), 101 (71), 75 (34). Anal. Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 74.75; H, 4.8.

Compound **3j:** IR (film): ν (cm^{-1}) 3289, 2119, 1574, 1530, 1473, 1352, 807, 736; ^{1}H NMR ($CDCl_3$): δ 8.34 (s, 1H), 8.22–8.19 (m, 1H), 7.81–7.78 (m, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 3.22 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 148.1, 137.8, 129.4, 127.0, 124.0, 123.6, 81.1, 79.9; MS: *m/z* 147 (M$^+$, 89), 123 (34), 111 (42), 101 (100), 77 (45), 75 (65), 57 (48). Anal. Calcd for $C_8H_5NO_2$: C, 65.31; H, 3.43. Found: C, 65.45; H, 3.5.

Compound **3k:** IR (film): ν (cm^{-1}) 3291, 2922, 2381, 1631, 1463, 758; ^{1}H NMR ($CDCl_3$): δ 7.32–7.16 (m, 4H), 3.04 (s, 1H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 138.0, 132.7, 129.7, 129.2, 128.2, 121.9, 104.2, 83.8, 21.2; MS: *m/z* 116 (M$^+$, 19), 101 (54), 97 (61), 85 (67), 71 (84), 57 (100). Anal. Calcd for C_9H_8: C, 93.06; H, 6.94. Found: C, 93.2; H, 7.1.

Compound **3l:** IR (film): ν (cm^{-1}) 3293, 2233, 2109, 1641, 1594, 1573, 800; ^{1}H NMR ($CDCl_3$): δ 7.78–7.61 (m, 3H), 7.45 (t, *J* = 8.0 Hz, 1H), 3.19 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 136.2, 135.5, 132.1, 129.3, 123.8, 117.9, 113.0, 81.2, 79.8; MS: *m/z* 127 (M$^+$, 100), 101 (84), 75 (41). Anal. Calcd for C_9H_5N: C, 85.02; H, 3.96. Found: C, 84.8; H, 3.8.

Compound **3m:** IR (film): ν (cm^{-1}) 3292, 3058, 2102, 1586, 1508, 800, 773; ^{1}H NMR ($CDCl_3$): δ 8.37–8.35 (m, 1H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.75–7.72 (m, 1H), 7.59-7.40 (m, 3H), 3.47 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 133.5, 133.1, 131.2, 129.3, 128.3, 127.0, 126.5, 126.1, 125.1, 119.8, 81.9, 81.8; MS: *m/z* 152 (M$^+$, 23), 127 (68), 83 (59), 69 (64), 57 (100). Anal. Calcd for $C_{12}H_8$: C, 94.70; H, 5.30. Found: C, 94.5; H, 5.2.

Compound **3n:** IR (film): ν (cm^{-1}) 3290, 2143, 1631, 1463, 1117, 700; ^{1}H NMR ($CDCl_3$): δ 7.34–7.27 (m, 2H), 7.01–6.98 (m, 1H), 3.33 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 133.1, 128.9, 127.2, 122.5, 81.2, 77.4; MS: *m/z* 108 (M$^+$, 100), 83 (48). Anal. Calcd for C_6H_4S: C, 66.63; H, 3.73. Found: C, 66.4; H, 3.7.

Project 20462002 was supported by the National Natural Science Foundation of China.

Received 27 October 2007; accepted 31 December 2007
Paper 07/4917 doi: 10.3184/030823407X275928

References

1 (a) M. Masakatsu and K. Keiko, *Tetrahedron Lett.*, 1980, **21**, 4021; (b) E.D. Ames, *Synthesis*, 1981, 364; (c) N. Shinichi and K. Matsuda, *J. Chem. Soc. Perkin. Trans. 1*, 1992, 755; (d) M. Kotora and E.I. Negishi, *Synthesis*, 1997, 121; (e) C. Lai, C. Xi, Y. Jiang and R. Hua, *Tetrahedron Lett.*, 2005, **46**, 513.
2 (a) H.A. Staab and K. Neunhoffer, *Synthesis*, 1974, 424; (b) M. Rosenblum, N. Brawn, J. Papenmeier and M. Applebaum, *J. Organomet. Chem.*, 1966, **6**, 173.
3 W.L. Collier and R.S. Macomber, *J. Org. Chem.*, 1973, **38**, 1367.
4 (a) P.J. Kocienski, *J. Org. Chem.*, 1974, **39**, 3285; (b) J.B. Lambert and E.G. Larson, *J. Am. Chem. Soc.*, 1985, **107**, 5443.
5 (a) E.J. Corey and P.L. Fuchs, *Tetrahedron Lett.*, 1972, 3769. (b) J. Villieras, P. Pierrot and J.F. Normant, *Synthesis*, 1975, 458.
6 (a) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, 4467; (b) S. Takahashi, Y. Kuroyama, K. Sonogashira and N. Hagihara, *Synthesis*, 1980, 627; (c) R. Chinchilla and C. Najera, *Chem. Rev.*, 2007, **107**, 874.

7 W.B. Austin, N. Bilow, W.J. Kelleghan and K.S.Y. Lau, *J. Org. Chem.*, 1981, **46**, 2280.

8 (a) Y.R. de Miguel, *J. Chem. Soc., Perkin Trans. 1*, 2000, 4213; (b) S.J. Shuttleworth, S.M. Allin, R.D. Wilson and D. Nasturica, *Synthesis*, 2000, 1035; (c) J.A. Loch and R.H. Crabtree, *Pure Appl. Chem.*, 2001, **73**, 119; (d) B. Corain and M. Kralik, *J. Mol. Catal. A: Chem.*, 2001, **173**, 99.

9 (a) P.-W. Wang and M.A. Fox, *J. Org. Chem.*, 1994, **59**, 5358; (b) M.-Z. Cai, C.-S. Song and X. Huang, *Synthesis*, 1997, 521; (c) S.I. Khan and M.W. Grinstaff, *J. Org. Chem.*, 1999, **64**, 1077; (d) K. Yu, W. Sommer, J.M. Richardson, M. Week and C.W. Jones, *Adv. Synth. Catal.*, 2005, **347**, 161; (e) J.H. Clark, D.J. Macquarrie and E.B. Mubofu, *Green Chem.*, 2000, **2**, 53.

10 (a) S.-B. Jang, *Tetrahedron Lett.*, 1997, **38**, 1793; (b) I. Fenger and C.L. Drian, *Tetrahedron Lett.*, 1998, **39**, 4287; (c) Y.M.A. Yamada, K. Takeda, H. Takahashi and S. Ikegami, *J. Org. Chem.*, 2003, **68**, 7733; (d) E.B. Mubofu, J.H. Clark and D.J. Macquarrie, *Green Chem.*, 2001, **3**, 23; (e) N.T.S. Phan, D.H. Brown and P. Styring, *Tetrahedron Lett.*, 2004, **45**, 7915; (f) H.S. He, J.J. Yan, R. Shen, S. Zhuo and P.H. Toy, *Synlett*, 2006, 563.

11 (a) A. Corma, H. Garcia and A.J. Leyva, *J. Catal.*, 2006, **240**, 87; (b) E. Gonthier and R. Breinbauer, *Synlett*, 2003, 1049; (c) M.J. Gronnow, R. Luque, D.J. Macquarrie and J.H. Clark, *Green Chem.*, 2005, **7**, 552; (d) P.-H. Li and L. Wang, *Adv. Synth. Catal.*, 2006, **348**, 681; (e) M. Cai, J. Sha and Q. Xu, *Tetrahedron*, 2007, **63**, 4642; (f) M. Cai, Q. Xu and J. Sha, *J. Mol. Catal. A: Chem.*, 2007, **272**, 293; (g) M. Cai, Q. Xu and P. Wang, *J. Mol. Catal. A: Chem.*, 2006, **250**, 199.

12 C.T. Kresge, M.E. Leonowicz, W.J. Roth, J.C. Vartuli and J.S. Beck, *Nature*, 1992, **359**, 710.

13 J.S. Beck, J.C. Vartuli, W.J. Roth, M.E. Leonowicz, C.T. Kresge, K.D. Schmitt, C.T.-W. Chu, D.H. Olson, E.W. Sheppard, S.B. McCullen, J.B. Higgins and J.L. Schlenker, *J. Am. Chem. Soc.*, 1992, **114**, 10834.

14 (a) W. Zhou, J.M. Thomas, D.S. Shephard, B.F.G. Johnson, D. Ozkaya, T. Maschmeyer, R.G. Bell and Q. Ge, *Science*, 1998, **280**, 705; (b) T. Maschmeyer, F. Rey, G. Sankar and J.M. Thomas, *Nature*, 1995, **378**, 159; (c) C.-J. Liu, S.-G. Li, W.-Q. Pang and C.-M. Che, *Chem. Commun.*, 1997, 65.

15 M. Cai, J. Shao and Q. Xu, *J. Mol. Catal. A: Chem.*, 2007, **268**, 82.

16 L. Brandsma and H.D. Verkruijsse, *Synthesis*, 1999, 1727.

Author Index 2007

Keyword Index 2007

JOURNAL OF CHEMICAL RESEARCH

Change to reference style 2008

In order to make articles published on-line more accessible and available for cross-referencing purposes, the style for references will be need to be amended as from January 2008

All references must be numbered individually; parts (a), (b) etc. should not be used.

All experimental details and notes should be included within the text.

The style for references remains the same

1. D.N. Smith and A.D. Bond, *J. Org. Chem.*, 1983, **19**, 5997.
2. O. Arnet, P. Sanda and J.R. Stewart, *Aspects of Aromaticity*, 2nd edn, eds M. Charton and F. Hudson, Academic Press, New York, 1996. Vol. 1, pp. 185-189.