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SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 3759–3762

Unusual sulfanylation through ring transformation of arene-tethered 2*H*-pyran-2-ones by in situ built Michael adduct ☆

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Received 30 January 2006; revised 7 March 2006; accepted 17 March 2006

Abstract—A novel synthesis of highly functionalized alkylsulfanylmethyl arenes **8a**–**m** through the ring transformation of 6-aryl-4-methyl/ethylsulfanyl-2*H*-pyran-2-one-3-carbonitriles **1a**–**j**, by reaction with methyl vinyl ketone **2**, is delineated and illustrated. To ascertain the course of reaction, 3-arylsulfanylmethyl-2-methyl-6-methylsulfanyl-4-phenylbenzonitriles **8k**–**m** were also prepared from the reaction of **1** with 4-arylsulfanyl-butan-2-ones **7c**,**d**.

The biaryl system serves as a central building block in various natural products of therapeutic significance.[1] The synthesis of highly congested biaryls, particularly those with hindered rotation, is highly demanding not only in the construction of natural products, but also in asymmetric syntheses,[2] crown ethers,[3] chiral liquid crystals,[4] chiral phases for chromatography[5] and agrochemicals.[6]

Earlier, biaryls have been synthesized by coupling of aromatic moieties using a variety of expensive metal catalysts.[7–20] Villemin et al.[21] synthesized asymmetrical biaryls efficiently by microwave irradiation of an aromatic halide and a tetraaryl borate in DMF. These have also been prepared[22] by dihydrooxazole-mediated coupling, but with a limitation on the substituent in the phenyl ring and difficulty in obtaining some Grignard reagents. Very recently, we have reported[23] the synthesis of non-sulfanylated biaryls from the reaction of suitably functionalized 2*H*-pyran-2-ones and malonodinitrile.

The wide-ranging applications of biaryl systems necessitated the development of an easy access to the synthesis of alkyl/arylsulfanylmethylbiaryls **8a**–**m** through the ring transformation of suitably functionalized 2*H*-pyran-2-one-3-carbonitriles[24] **1a**–**j** with methyl vinyl ketone **2**.

Our attempt to construct hindered biaryls **3** with an aryl or heteroaryl linked to a styrenyl group through the ring transformation of 2*H*-pyran-2-ones **1a**–**j** with methyl vinyl ketone **2**, failed. The isolated product, showed three singlet signals in the ^{1}H NMR due to CH_3, SCH_3 and CH_2 protons, but no vinyl signals. The molecular ion and mass spectral fragmentation pattern also did not match with the anticipated product **3**. The structure of the isolated compound **8a** was unambiguously confirmed by single crystal X-ray diffraction analysis as 2-methyl-6-methylsulfanyl-3-methylsulfanylmethyl-4-phenylbenzonitrile. The formation of products **8a**–**m** is only possible if the ring transformation of **1** involves 4-alkyl/arylsulfanyl-butan-2-one **7**, formed by Michael addition of alkylthiol or thiophenol to methyl vinyl ketone.

The liberation of alkylthiol in situ could occur in two ways: via a substitution reaction at position 4 of the pyran ring by a carbanion, generated from methyl vinyl ketone to form **4**, or through the ring transformation of 2*H*-pyran-2-one by **2** with ring opening followed by Michael addition of an enolate to C-3-C-4 of the pyran ring, with the elimination of alkylthiol and formation of pyran-2-ylidene **6**. Our best efforts to isolate either of the envisaged products **4** or **6** failed. Based on our past observations on the ring transformations of 2*H*-pyran-2-ones, the reaction is possibly initiated by

Keywords: Sulfanylated arenes; 2*H*-Pyran-2-one; Ring transformation reactions.
☆ Communication No. 6721.
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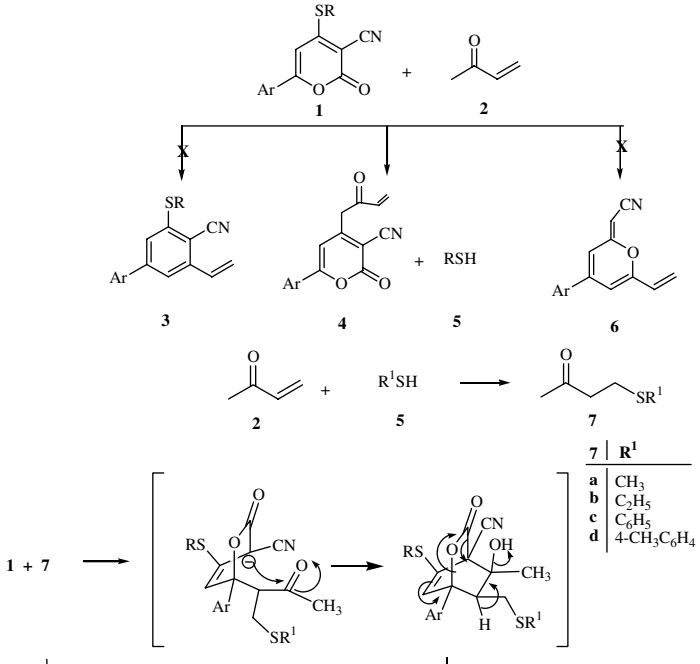
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.03.119

substitution at C-4 with liberation of alkylthiol followed by an unusual in situ Michael addition to methyl vinyl ketone **2**, which in turn acts as a source of a carbanion for the further ring transformation reactions. The carbanion formation could occur at either C-1 or C-3 of 4-alkylsulfanyl-butan-2-one **7**, but C-3 is more susceptible due to the combined inductive effects of the acetyl and methylsulfanylmethyl groups. The formation of products **8a**–**i** is only possible if the ring transformation involves a carbanion generated at C-3 from **7a**. In support of our previous findings, an independent ring transformation reaction from 4-ethylsulfanyl-6-phenyl-2*H*-pyran-2-one-3-carbonitrile **1j** with methyl vinyl ketone was carried out under similar reaction conditions and an analogous product, 6-ethylsulfanyl-3-ethylsulfanylmethyl-2-methyl-4-phenylbenzonitrile **8j**, was isolated.

This experiment indicated that the liberated alkylthiol acts as a nucleophile to form an adduct in situ on reaction with **2**. The reason for the moderate yields of the isolated compounds **8a**–**j** in the range of 37–48% is possibly due to the limited availability of methyl vinyl ketone for the formation of the Michael adduct. In another set of experiments, we prepared Michael adducts **7c** and **7d** independently from the reaction of methyl vinyl ketone with thiophenol and 4-thiocresol, respectively.[25]

The reaction of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles **1a**,**d** with **7c** and **7d** separately led to the expected analogous products **8k**–**m** in moderate yields because of the competitive reactions of the Michael adducts **7c**,**d** at the C-4 and C-6 electrophilic centres of 2*H*-pyran-2-ones **1**. In support of our proposed mechanism, an independent reaction was carried out stirring a mixture of 4-methylsulfanyl-6-phenyl-2*H*-pyran-2-one-3-carbonitrile **1a**, methyl vinyl ketone **2** and ethanethiol in the presence of powdered KOH in DMF at room temperature for 24 h. On usual work up and chromatographic purification, a mixture of two cross-over products was isolated and distinguished by ^{1}H NMR spectra as 6-ethylsulfanyl-2-methyl-3-methylsulfanylmethyl-4-phenylbenzonitrile and 3-ethylsulfanylmethyl-2-methyl-6-methylsulfanyl-4-phenylbenzonitrile in a ratio of almost 40:60. These experiments further support our view that the liberated alkylthiol is used up in the formation of the Michael adduct from methyl vinyl ketone, which then participates in the ring transformation reactions.



7	R^1
a	CH_3
b	C_2H_5
c	C_6H_5
d	4-$CH_3C_6H_4$

8	Ar	R^1	Yield (%)
a	phenyl	CH_3	40
b	4-methylphenyl	CH_3	38
c	4-fluorophenyl	CH_3	45
d	4-chlorophenyl	CH_3	47
e	4-bromophenyl	CH_3	47
f	4-methoxyphenyl	CH_3	40
g	3,4-dichlorophenyl	CH_3	45
h	2-furanyl	CH_3	37
i	2-thienyl	CH_3	37
j	phenyl	C_2H_5	48
k	phenyl	C_6H_5	40
l	phenyl	4.CH_3.C_6H_4	48
m	4-chlorophenyl	C_6H_5	45

R = C_2H_5 for **8j** otherwise CH_3

Scheme 1.

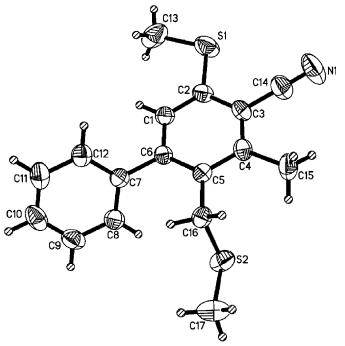


Figure 1. The ORTEP (30% probability) diagram of **8a** with the atomic numbering scheme.

2*H*-Pyran-2-one **1** has three electrophilic centres at C-2, C-4 and C-6 in which the latter is highly vulnerable to nucleophilic attack owing to extended conjugation and the presence of an electron withdrawing substituent (CN) at position 3 of the pyran ring. Thus, the carbanion generated in situ from 4-alkyl/arylsulfanyl-butan-2-one attacks at C-6 with ring closure followed by the elimination of carbon dioxide and water affording **8**, as shown in Scheme 1. Thus, a mixture of 2*H*-pyran-2-one **1**, methyl vinyl ketone **2** and powdered KOH in DMF was stirred at room temperature for 24 h to give **8a**–**j**. All the synthesized compounds were characterized[26] by spectroscopic and elemental analysis.

Figure 1 shows the crystal structure of **8a**.[26] The molecule consists of two phenyl rings with one twisted at C-6 by 54.2(1)° from the least-squares mean plane through the substituted phenyl ring. The crystal packing reveals the presence of weak intermolecular S···Ar interactions between S2 and the centroid of the substituted phenyl ring [$1-x$, $1-y$, $1-z$; S2···Cg: 3.857 Å].

Our procedure provides an easy access for the synthesis of sulfanylated asymmetrical hindered biaryls in a single step.

Acknowledgement

D.S. is thankful to CSIR for Senior Research Fellowship.

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26. Typical procedure for the synthesis of **8**: A mixture of 2*H*-pyran-2-one **1** (1 mmol), methyl vinyl ketone **2** (1.5 mmol) and powdered KOH (1.5 mmol) in dry DMF was stirred for 24 h at room temperature. The reaction mixture was poured onto ice water and neutralized with 10% HCl. The separated solid was filtered, washed with water and dried. The crude product was purified by silica gel column chromatography to afford **8** in moderate yield. Compound **8a**: Yield 40%; mp 106–108 °C; IR (KBr) ν 2213 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.95 (s, 3H, CH_3), 2.51 (s, 3H, SCH_3), 2.72 (s, 3H, SCH_3), 3.59 (s, 2H, CH_2), 6.98 (s, 1H, ArH), 7.42–7.44 (m, 5H, ArH); MS (FAB) 300 (M^++1). Anal. Calcd for $C_{17}H_{17}NS_2$: C, 68.18; H, 5.72; N, 4.68. Found: C, 68.40; H, 5.66; N, 4.44. Compound **8b**: Yield 38%; mp 104–106 °C; IR (KBr) ν 2212 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.96 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.50 (s, 3H, SCH_3), 2.71 (s, 3H, SCH_3), 3.60 (s, 2H, CH_2), 6.97 (s, 1H, ArH), 7.23–7.33 (m, 4H, ArH); MS (FAB) 314 (M^++1). Anal. Calcd for $C_{18}H_{19}NS_2$: C, 68.96; H, 6.11; N, 4.47. Found: C, 69.29; H, 5.86; N, 4.35. Compound **8c**: Yield 45%; mp 110–112 °C; IR (KBr) ν 2214 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.99 (s, 3H, CH_3), 2.51 (s, 3H, SCH_3), 2.71 (s, 3H, SCH_3), 3.56 (s, 2H, CH_2), 6.95 (s, 1H, ArH), 7.10–7.19 (m, 2H, ArH) 7.37–7.44 (m, 2H, ArH); MS (FAB) 318 (M^++1). Anal. Calcd for $C_{17}H_{16}FNS_2$: C, 64.32; H, 5.08; N, 4.41. Found: C, 63.85; H, 4.91; N, 3.96. Compound **8j**: Yield 48%; mp 77–79 °C; IR (KBr) ν 2216 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.09 (t, $J = 7.40$ Hz, 3H, CH_3), 1.35

(t, $J = 7.40$ Hz, 3H, CH_3), 2.39 (q, $J = 7.32$ Hz, 2H, SCH_2), 2.73 (s, 3H, CH_3), 3.01 (q, $J = 7.32$ Hz, 2H, SCH_2), 3.62 (s, 2H, CH_2), 7.09 (s, 1H, ArH), 7.42–7.44 (m, 5H, ArH), MS (FAB) 328 (M^++1). Anal. Calcd for $C_{19}H_{21}NS_2$: C, 69.68; H, 6.46; N, 4.28. Found: C, 69.86; H, 6.84; N, 4.01. Compound **8l**: Yield 48%; mp 90–92 °C; IR (KBr) ν 2214 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 2.31 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 2.70 (s, 3H, SCH_3), 3.94 (s, 2H, CH_2), 6.97 (s, 1H, ArH), 7.01–7.11 (m, 4H, ArH), 7.37–7.39 (m, 5H, ArH); MS (FAB) 376 (M^++1). Anal. Calcd for $C_{23}H_{21}NS_2$: C, 73.56; H, 5.64; N, 3.73. Found: C, 73.18; H, 5.52; N, 4.06. Crystal data of Compound **8a**: $C_{17}H_{17}NS_2$, $M = 299.44$, monoclinic, $P2_1/n$, $a = 9.874(1)$, $b = 8.183(1)$, $c = 20.009(3)$, $\beta = 90.1(1)°$, $V = 1616.7(4)$ Å^3, $Z = 4$, $D_c = 1.230$ g cm^{-3}, μ (Mo-Kα) = 0.319 mm^{-1}, $F(000) = 632$, colourless rectangular crystal, size = $0.3 \times 0.15 \times 0.125$ mm, 4150 reflections measured ($R_{int} = 0.027$), 2856 unique, $R_w = 0.131$ for all data, conventional $R = 0.053$ [$(\Delta/\sigma)_{max} = 0.000$] on F values of 1369 reflections with $I > 2\sigma(I)$, $S = 0.997$ for all data and 184 parameters, $\Delta\rho_{max} = 0.231$ and $\Delta\rho_{min} = -0.178$. Unit cell determination and intensity data collection ($2\theta = 50°$) was performed on a Bruker P4 diffractometer at 293(2) K. Structure solution by direct methods and refinements by full-matrix-least-squares methods on F^2. Programs: *XSCANS* [Siemens Analytical X-ray Instruments Inc.: Madison, Wisconsin, USA 1996] was used for data collection and data processing, *SHELXTL-NT* [Bruker AXS Inc.: Madison,Wisconsin, USA 1997] was used for structure determination, refinements and molecular graphics. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC deposit No: 275438).