JOURNAL OF CHEMICAL RESEARCH 2008 MAY, 287–288 **RESEARCH PAPER** 287

Synthesis of indolones and quinolones by reductive cyclisation of *o*-nitroaryl acids using zinc dust and ammonium formate

Bhima Reddy Dinesh[a], A. Ramesha Baba[a], K. Udaya Sankar[b] and D. Channe Gowda[a]*

[a]*Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore-570 006, Karnataka, India*

[b]*Food Engineering Department, Central Food Technological Research Institute, Mysore-570 013, India*

A novel protocol for the synthesis of indolone and quinolone derivatives from *o*-nitroaryl acids was developed using Zn and HCO_2NH_4 under supercritical fluid carbon dioxide ($scCO_2$) medium. The process involves the reduction of the nitro group to an amino group followed by in situ cyclisation.

Keywords: reductive cyclisation, indolones, quinolones, supercritical fluid carbon dioxide

Indolones and quinolones are important pharmaceutical intermediates and continue to receive the attention of synthetic organic chemists.[1,2] Reductive cyclisation of nitroarenes is a powerful means of obtaining indolones and quinolones,[2-4] like sigmatrophic rearrangement, nucleophillic cyclisation and electrophilic cyclisation. The reductive cyclisation of substituted *o*-nitroaryl acids or esters was effected by employing H_2/Pd,[3] $Et_3N.HCO_2H$/Pd,[4] Fe/AcOH[5] or Sn/HCl.[6] These systems are generally intolerant to many functional groups as they result in a mixture of products, also time consuming and low yields. In addition, the use of palladium on carbon requires stringent precautions because of its flammable nature and the use of Fe and Sn results in the generation of a large amount of spent metal waste. Ammonium formate/zinc dust is a cost effective system which is widely used in catalytic transfer hydrogenation for many functional group transformations.[7,8] In addition, aromatic nitro compounds on reduction with ammonium formate and zinc dust yield the corresponding anilines.[9] Therefore, we thought that the intramolecular reductive cyclisation of suitably substituted acid of *o*-nitroaryl acids with zinc and ammonium formate might provide a method for the synthesis of indolones and quinolones.

During the last decade, $scCO_2$ has been increasingly exploited for performing a variety of hydrogenation reactions[10,11] because of its versatile properties like, (i) solubilising immiscible reactants in a single supercritical phase thereby eliminate interphase resistances, (ii) ease of product separation or catalyst recovery from the reaction mixture by stage wise pressure reduction and (iii) environmentally benign reaction medium when compared to organic reaction media, which is very important aspect. Commonly, Rh/C, Pd/C, Pt/C, *etc*., have been used as catalysts for various heterogeneous hydrogenations.[10,12] But, over the period of reaction time, exercising with carbonaceous catalyst can afford deactivation of the catalyst by coking. This may be suppressed by changing the working conditions such as change in the gas phase to dense supercritical medium[13] and extraction of fouling products.[14] Consequently, in the present study our effort is also towards utilisation of silica gel as a metal active ingredient in association with inexpensive Zn dust to provide larger surface area.

Results and discussion

In order to optimise the reaction conditions, the synthesis of 1,3-dihydro-2-indolone (**2a**) from *o*-nitrophenylacetic acid was chosen as a model and the reaction was carried out at different temperature and pressure of CO_2 (Table 1). In the presence of CO_2 at atmospheric pressure and temperature, only the reduction of $–NO_2$ to $–NH_2$ was observed and further cyclisation was not observed to obtain the desired product. A continuous increase in the temperature and pressure of CO_2 to a critical condition resulted in the formation of **2a**. Therefore, it is noteworthy to identify that CO_2 at supercritical condition, not only accelerates the rate of the reaction but also acts as a medium for the reaction. As it can be seen in Table 1, the reaction time, temperature and the pressure of CO_2 obviously influence the yields of indolones. Further, it was noticed that the use of silica gel not only provides surface area, but also intensifies the reductive cyclisation process by heat transfer between the components of the reaction mixture to give the expected product. However, it can easily be separated (and reused) at the end of a process, which is a logical and versatile approach for simplifying the process. In contrast, a control reaction was carried out without adding the catalyst, which resulted in starting material, indicating that silica gel does not catalyse the reaction. In addition, we also examined the influence of water as solvent and/or hydrogen source, because water could be a desirable transport medium in $scCO_2$ system for the water-soluble compounds. But it does not stabilise in carbon dioxide and failed to keep up the reaction. However, water can be used as hydrogen source during cyclisation at a very high temperature.[15]

On the basis of these results, we further investigated this reductive cyclisation process with different *o*-nitroaryl acids at similar condition. As shown in Table 2, *o*-nitroaryl acids could be conveniently converted into corresponding indolones (**2a–g**) or quinolones (**4a–d**) with good yields (70–82%). In the case of *o*-nitrocinnamic acid, it is not only undergoing cyclisation, but also undergoes hydrogenation to give corresponding 3,4-dihydroquinolone with good yield. However, other functionalities such as halogens and methoxide are tolerated.

In conclusion, we have developed a highly efficient Zn/HCO_2NH_4 under $scCO_2$ protocol for the smooth reductive cyclisation of suitable *o*-nitroaryl acids to the corresponding indolones and quinolones. On the other hand, this protocol offers several advantages such as environmentally benign,

Table 1 Reduction of *o*-nitrophenyl acetic acid to 1,3-dihydro-2-indolone under various conditions[a]

Entry	P/MPa	T/h	T/°C	Yield[b]/%
1[c]	0	1	30	0
2[c]	0	1	50	Trace
3	8	0.5	50	24
4	8	1	50	56
5[d]	12	1	50	62
6	12	1	50	74
7[e]	12	1	50	15

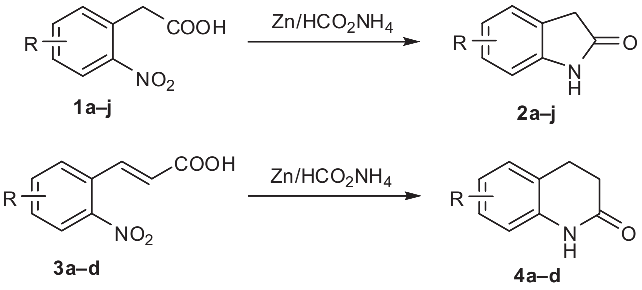
[a]*o*-nitrophenyl acetic acid (10 mmol), zinc dust (20 mmol), ammonium formate (20 mmol). [b]Isolated. [c]In presence of carbon dioxide. [d]Without silica gel. [e]Addition of water as co-solvent (2–3 ml).

---

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

Table 2 Reductive cyclisation of ***o***-nitroaryl acids using zinc/ammonium formate under $scCO_2$.

$scCO_2$.



Product	R	Yield/%	Melting point/°C		Ref.
			Found	Literature	
2a	H	74	125–127	126–127	16
2b	4-Cl	71	216–218	215–216	5
2c	5-Cl	75	196–198	195–197	5
2d	6-Br	80	214–215	213–214	5
2e	7-Cl	73	218–219	218–220	17
2f	5-F	76	143–144	142–143	5
2 g	6-NH_2	65	195–196	194–195	18
4a	H	79	162–164	163.5	19
4b	6,7-OMe	75	88–90	[a]	-
4c	6-OH	74	235–238	236–240	20
4d	7-OH	78	234–237	233–237	21

[a] Not found in literature.

easy product isolation, high yield, and minimisation of undesired toxic wastes. Moreover, utilisation of silica gel as a solid support obviously influences the progress of the reaction.

Experimental

Materials

The substrates were either commercially available or prepared by standard methods. Zinc dust was purchased from SISCO Research Laboratories Pvt. Ltd., Bombay (India) and was treated with 0.01N hydrochloric acid for about 2 min. It was filtered through a sintered glass funnel and washed with water, dry methanol and dry ether. Thus obtained zinc was vacuum dried and stored. Ammonium formate and 60–120-mesh silica gel (for column chromatography) were purchased from E. Merck (India) Ltd. All of the solvents used were analytical grade or were purified according to standard procedures. Thin layer chromatography was carried out on silica gel plates obtained from Whatman Inc. The melting points were determined by a Thomas–Hoover melting point apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AQS-500 spectrometer at 500 and 125 MHz in $CDCl_3$ solutions and IR spectra were recorded on a Jasco FTIR- 4100 spectrometer.

Typical procedure

A 25 ml stainless steel high-pressure reactor vessel was loaded with the reaction mixture containing suitably substituted *o*-nitro acids (10 mmol) and ammonium formate (20 mmol, 1.26 g) adsorbed over silica gel (4 g). Then Zn dust (1.3 g) was added to catalyse the reaction. The vessel was sealed and $scCO_2$ pre-maintained at the temperature 50 °C and pressure 12 MPa was introduced slowly. The reaction mixture was stirred and the vessel was maintained at the same condition of temperature and pressure during the progress of the reaction. When the reaction was complete (monitored by TLC) the vessel was cooled and pressure was released slowly to atmospheric pressure. The residue was extracted, separated and crystallised. The products were characterised by IR, ^1H and ^{13}C NMR, elemental analysis

*Spectral data of 6,7-dimethoxy-3,4-dihydroquinolin-2(1*H*)-one* (**4b**, Table 2): IR (KBr): 3198, 1665, 1460, 1345, 1308, 725 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.63 (t, 3-CH_2–), 2.91 (t, 4-CH_2–), 3.87 (s, 6-OCH_3 & 7-OCH_3), 6.4 (s, ArH), 6.7 (s, ArH), 8.9 (s, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 24.72, 30.60, 55.89, 55.09, 100.13, 111.40, 114.56, 130.32, 144.51, 148.13, 171.52 ppm; Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.8; H, 6.3; N, 6.8; Found: C, 63.8; H, 6.3; N, 6.8.

The authors wish to thank University Grants Commission, New Delhi, India for providing financial assistance.

Received 24 March 2008; accepted 1 May 2008
Paper 08/5178 doi: 10.3184/030823408X320647

References

1 G.W. Gribble, *J. Chem. Soc., Perkin Trans.1*, 2000, 1045.
2 J.E. Saxton, *The chemistry of heterocyclic compounds*: *indoles*, Wiley-Interscience, New York, 1983 Vol. 25, Part IV.
3 T.V.R. RanjanBabu, B.L. Chenard and M.A. Petti, *J. Org. Chem*., 1986**, 51**, 1704.
4 N.A. Cortese and R.F. Heck, *J. Org. Chem*., 1977, **42**, 3491.
5 G.J. Quallich and P.M. Morrissey, *Synthesis*., 1993, 51.
6 L. Simet, *J. Org. Chem*., 1963, **28**, 3580.
7 G.R. Srinivasa, L. Nalina, K. Abiraj and D.C. Gowda, *J. Chem. Res. (S)*., 2003, 630.
8 S. Gowda, K. Abiraj and D.C. Gowda, *Tetrahedron Lett*., 2002, **43**, 1329.
9 D.C. Gowda, B. Mahesh and S. Gowda, *Indian J. Chem*., 2001, **40(B)**, 75.
10 A. Baiker, *Chem. Rev*., 1999, **99**, 453.
11 D. Prajapati and M. Gohain, *Tetrahedron*., 2004, **60**, 815.
12 C.V. Rode, U.D. Joshi, O. Sato and M. Shirai, *Chem. Commun*., 2003, 1960.
13 B. Subramanian and B.J. MaCoy, *J. Ind. Eng. Chem. Res*., 1994, **33**, 504.
14 B. Subramanian and A. Torma, *Innovations in supercritical fluids science and technology*; ACS Symposium Series No. 608; K.W. Hutchenson and N.R. Foster, (ed) American Chemical Society, Washington DC, 1995, p.246.
15 C. Boix, J.M de la Fuente and M. Poliakoff, *New J. Chem*., 1999, **23**, 641.
16 W.C. Sumpter, *Chem. Rev*. 1945, **37**, 443.
17 E.H. Goetz,, *US pat*. 1979, 4,160,032.
18 E.C. Michael, and M.K. Gary, *US pat*. 1993, 5,252,536.
19 http://chem.sis.nlm.nih.gov/chemidplus, CAS Registry No. 553-03-7, accessed in Jan 2008.
20 http://www.sigmaaldrich.com/catalog/search/productdetail/ALDRICH/675350
21 http://www.sigmaaldrich.com/catalog/search/productdetail/ALDRICH/675369