COMMUNICATION

ChemComm www.rsc.org/chemcomm

First example of ring expansion of activated quinolines and isoquinolines: novel benzoazepines†

J. S. Yadav,*[a] B. V. Subba Reddy,[a] Manoj Kumar Gupta,[a] A. Prabhakar[b] and B. Jagadeesh[b]

[a] *Division of Organic Chemistry, Hyderabad-500 007, India. E-mail: yadavpub@iict.res.in; Fax: +91-40-7160512; Tel: +91-40-27193030*

[b] *Centre for Nuclear Magnetic Resonance, Indian Institute of Chemical Technology, Hyderabad-500 007, India. E-mail: yadavpub@iict.res.in; Fax: +91-40-7160512; Tel: +91-40-27193030*

Received (in Cambridge, UK) 6th April 2004, Accepted 25th June 2004
First published as an Advance Article on the web 2nd August 2004

Activated quinoline and isoquinoline undergo unexpected ring expansion by diazocarbonyl compounds *via* C–C insertion in the presence of 5 mol% of copper triflate to produce ethyl 1*H*-benzo[*b*]azepine-1-carboxylate and ethyl 3*H*-benzo[*d*]azepine-3-carboxylate, respectively, in excellent yields with a high degree of selectivity

Benzoazepine derivatives act as potent antagonists of the glycine binding site associated with *N*-methyl-D-aspartate (NMDA). They have been used as NMDA antagonists and NMDA channel blockers.[1] Activated aza-aromatics are useful building blocks in organic synthesis, especially for the synthesis of various biologically active nitrogen containing alkaloids.[2] Generally, aza-aromatic compounds can be activated by chloroformates or acyl chlorides.[3] Recently, copper(II) triflate has emerged as a mild and efficient catalyst for effecting various organic transformations.[4] Compared to conventional Lewis acids, copper(II) triflate has the advantages of low catalyst loading, moisture stability, low cost and catalyst recycling.[5]

In this article, we report for the first time an unprecedented ring expansion of activated quinolines and isoquinolines. Initially, we attempted the alkylation of activated 3-methylquinoline with ethyl diazoacetate using 5 mol% of copper(II) triflate. The reaction went to completion in a short time (~1.0 h) and the product 1*H*-benzo[*b*]azepine, **3a** (Fig. 1) was obtained in 85% yield. The structure of the product **3a** was established by incisive NMR studies using HSQC and HMBC experiments. The HSQC and ^{13}C spectra clearly showed the presence of 17 carbons with 3 methyl, 2 methylenes, 6 methines and 6 quaternary carbons. The minimum energy structure for **3a** obtained from the molecular mechanics calculation is also shown in Fig. 1.

Similarly various substituted quinolines reacted efficiently with a variety of diazocarbonyl compounds to produce 1*H*-benzo[*b*]-azepine derivatives (entries b–f, Table 1, Scheme 1).‡

Encouraged by the results obtained with quinolines, we turned our attention to isoquinolines. Interestingly, several activated isoquinolines underwent smooth ring expansion with diazocarbonyl compounds to give 3*H*-benzo[*d*]azepine derivatives (entries g–k, Table 1, Scheme 2).

In the case of isoquinoline also, the structure of the product was determined by HSQC and HMBC experiments. HSQC and ^{13}C

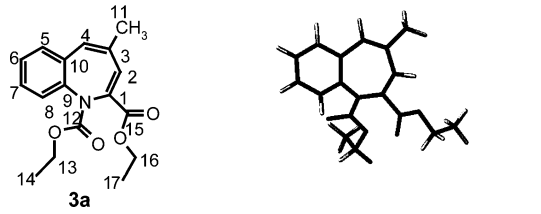
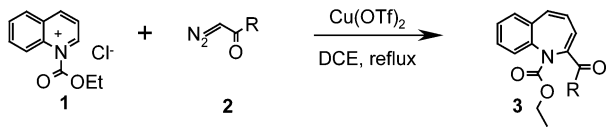


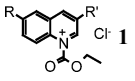
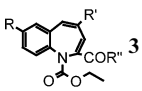
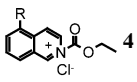
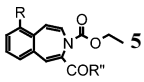
Fig. 1 Chemical and energy-minimized structure of **3a**.



Scheme 1

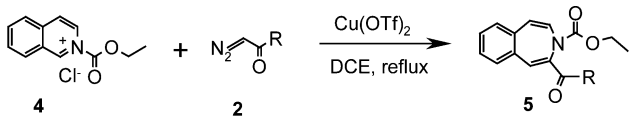
† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b4/b405100a/

Table 1 $Cu(OTf)_2$-catalyzed ring expansion of activated quinolines and isoquinolines with diazo compounds

Entry	Quinoline/isoquinoline salt	Diazo compound	Product[a]	Time (h)	Yield (%)[b]
	 **1**	N_2=CHCOR″ **2**	 **3**		
a	**(1a)** R = H; R′ = CH_3	R″ = OEt	**(3a)** R = H; R′ = CH_3; R″ = OEt	0.5	85
b	**(1b)** R = R′ = H	R″ = OEt	**(3b)** R = R′ = H; R″ = OEt	1.0	82
c	**(1c)** R = H; R′ = Br	R″ = OEt	**(3c)** R = H; R′ = Br; R″ = OEt	1.0	80
d	**(1d)** R = CH_3; R′ = H	R″ = OEt	**(3d)** R = CH_3; R′ = H; R″ = OEt	1.0	88
e	**(1e)** R = OCH_3; R′ = H	R″ = OEt	**(3e)** R = OCH_3; R′ = H; R″ = OEt	1.0	86
f	**(1f)** R = R′ = H	R″ = 2-chlorophenyl	**(3f)** R = R′ = H; R″ = 2-chlorophenyl	1.5	90
	 **4**		 **5**		
g	**(4g)** R = H	R″ = OEt	**(5g)** R = H; R″ = OEt	1.0	92
h	**(4h)** R = NO_2	R″ = OEt	**(5h)** R = NO_2; R″ = OEt	0.5	95
i	**(4i)** R = H	R″ = phenyl	**(5i)** R = H; R″ = phenyl	0.5	98
j	**(4j)** R = H	R″ = 2-chlorophenyl	**(5j)** R = H; R″ = 2-chlorophenyl	0.5	96
k	**(4k)** R = H	R″ = *n*-$C_{13}H_{27}$	**(5k)** R = H; R″ = *n*-$C_{13}H_{27}$	1.0	88

[a] All products were characterized by ^1H, ^{13}C NMR, IR spectra and mass spectrometry. [b] Yield refers to pure products isolated by column chromatography.

DOI: 10.1039/b405100a



Scheme 2

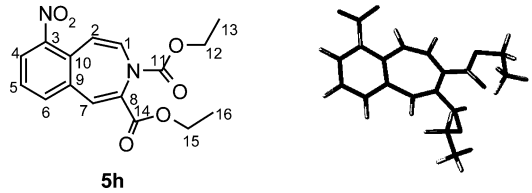


Fig. 2 Chemical and energy-minimized structure of **5h**.

spectra clearly showed the presence of 16 carbons with 2 methyl, 2 methylenes, 6 methines and 6 quaternary carbons for 3*H*-benzo[*d*]azepine structure, **5h** (Fig. 2). The cross peaks in HMBC between H2–C3 and H1–C10 confirmed the **5h**. The minimum energy structure obtained from the molecular mechanics calculation is also shown in Fig. 2.

When compared to quinolines, isoquinolines afforded higher yields. Further, diazoesters gave lower yields than diazoketones. As a solvent, dichloroethane appeared to give the best results. No reaction was observed with other metal triflates such as $Sc(OTf)_3$, $Yb(OTf)_3$ and $In(OTf)_3$. However, similar results were observed using 10 mol% of $Rh_2(OAc)_4$. Further, most of the acid catalysts such as BF_3OEt_2, $InCl_3$, $CeCl_3$, KSF clay failed to produce the desired product.

In summary, we describe a novel route for the construction of the seven-membered azepine ring system from readily accessible aza-aromatics and diazocarbonyl compounds. It is an entirely new approach for the conversion of activated quinolines and isoquinolines into a novel azepine framework.

MKG thanks the Council of Scientific and Industrial Research, New Delhi for the award of a fellowship.

Notes and references

‡ Typical procedure: a mixture of quinoline or isoquinoline (1 mmol), ethyl chloroformate (1.1 mmol), diazocarbonyl compound (1.2 mmol), and copper triflate (5 mol%) was stirred in 1,2-dichloroethane at 75 °C for the appropriate time (Table). After completion of the reaction, as monitored by TLC, the mixture was diluted with water and extracted with dichloromethane (2 × 10 mL). Removal of solvent followed by purification by silica gel column chromatography afforded pure benzoazepine. **3a**: Liquid, IR (KBr): ν_{max} 2982, 2934, 1922, 1713, 1640, 1602, 1575, 1493, 1444, 1397, 1373, 1322, 1248, 1185, 1113, 1072, 1052, 1033, 833, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.16 (m, 5H), 6.75 (br. s, 1H), 4.20 (q, 4H, J = 7.0 Hz), 2.29 (s, 3H), 1.29 (t, 6H, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 153.6, 140.9, 139.7, 135.0, 133.8, 131.2, 128.9, 128.1, 127.3, 126.8, 126.5, 62.4, 60.8, 23.0, 14.3, 14.0. EIMS: *m*/*z*: 301 (M^+, 75), 256 (55), 229 (100), 201 (45), 154 (30), 144 (25), 117 (20), 84 (7), 49 (22). **3h**: Yellowish solid, mp = 82–85 °C. IR (KBr): ν_{max} 2984, 2931, 1789, 1733, 1714, 1672, 1629, 1528, 1486, 1372, 1336, 1308, 1235, 1173, 1152, 1119, 1051, 1016, 941, 895, 866, 815, 766 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.68–7.30 (m, 4H), 6.51 (d, 1H, J = 9.0 Hz), 6.25 (d, 1H, J = 9.0 Hz), 4.30 (q, 4H, J = 7.1 Hz), 1.34 (t, 6H, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 152.7, 148.7, 147.6, 136.7, 136.1, 134.8, 129.4, 127.1, 123.5, 120.2, 113.5, 63.6, 61.4, 14.2, 14.0. FAB Mass: *m*/*z*: 333 (M^+, 10), 303 (5), 287 (5), 243 (5), 229 (5), 215 (5), 201 (5), 185 (5), 133 (40), 109 (22), 95 (35), 81 (45), 69 (70), 55 (100).

1 R. D. Fabio, F. Micheli, D. Baraldi, B. Bertani, N. Conti, G. D. Forno, A. Feriani, D. Donati, C. Marchioro, T. Messeri, A. Missio, A. Pasquarello, G. Pentassuglia, D. A. Pizzi, S. Provera, A. M. Quaglia and F. M. Sabbatini, *Il Farmaco*, 2003, **58**, 723–738.
2 (*a*) A. R. Katritzky, S. Rachwal and S. Rachwal, *Tetrahedron*, 1996, **52**, 15031; (*b*) D. M. Stout and A. I. Meyers, *Chem. Rev.*, 1982, **82**, 223; (*c*) T. Itoh, M. Miyazaki, K. Nagata and A. Ohsawa, *Tetrahedron*, 2000, **56**, 4383.
3 R. Yamaguchi, T. Nakayasu, B. Hatano, T. Nagura, S. Kozima and K.-I. Fujitha, *Tetrahedron*, 2001, **57**, 109.
4 M. P. Sibi, G. R. Cook, in *Lewis Acids in Organic Synthesis*; H. Yamamoto, Ed., Wiley-VCH, New York, 2000, Chapter 12, p. 543.
5 J. S. Yadav, B. V. S. Reddy and G. Satheesh, *Tetrahedron Lett.*, 2003, **44**, 8331.