A Novel and Simple Route for the Synthesis of 3,4-Disubstituted Pyrroles

Venkatapuram Padmavathi*, Boggu Jagan Mohan Reddy and Adivireddy Padmaja

Department of Chemistry, Sri Venkateswara University, Tirupati 517 502, India

Received June 14, 2004

A new class of 3,4-disubstituted pyrroles has been prepared by the reaction of 1-aroyl-2-arylsulfonylethenes and 1,2-diarylsulfonylethenes with tosyl methyl isocyanide.

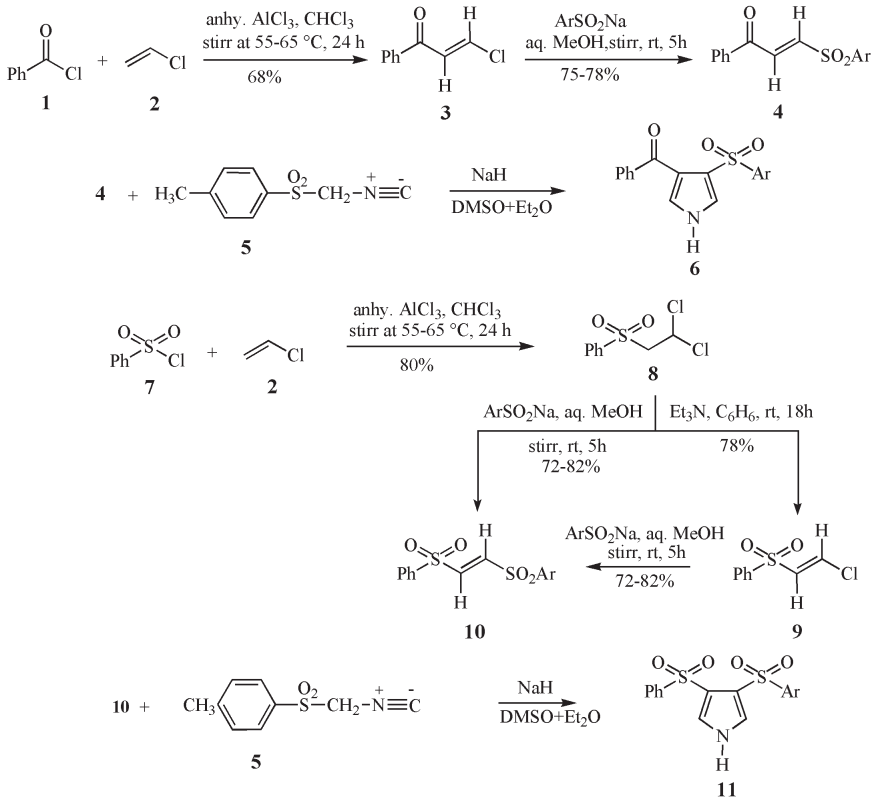
J. Heterocyclic Chem., **42**, 333 (2005).

Introduction.

Pyrroles are of pharmacological relevance due to their antiinflammatory and analgesic activities. The prominent examples are ketorolac, tolmetin and indomethacin [1]. In view of the importance of these compounds substantial attention has been paid to their synthesis, which proceeds mainly *via* cycloaddition or cycloisomerization of acyclic precursors [2-5]. Besides, the conjugate addition of nucleophiles to α,β-unsaturated compounds is one of the most powerful bond forming strategies and has been widely utilized in the field of heterocyclic chemistry. The Barton-Zard pyrrole synthesis based on the reaction of nitro alkenes with ethyl isocyanate also provides an ideal method for β-substituted pyrroles [6-12]. Tosyl methyl isocyanide (TosMIC) has also been used as a reagent for the synthesis of pyrroles [13-15]. However, to the best of our knowledge there are no reports of the synthesis of 3,4-disubstituted pyrroles from α,β-unsaturated sulfones. In a preliminary communication, we have recently reported the synthesis of 3,4-disubstituted pyrroles by cyclocondensation of aryl styryl sulfones and benzyl styryl sulfones with tosyl methyl isocyanide. On the other hand, phenyl vinyl sulfones under similar conditions produced 3- and 3,5-disubstituted pyrroles [16].

In continuation of our studies for the preparation of 3,4-disubstituted pyrroles we wish to report the use of different Michael acceptors for the efficient conversion into pyrroles, using TosMIC. Recently we have reported the synthesis of Michael acceptors, unsaturated oxo sulfones and bis sulfones by the reaction between vinyl chloride and aroyl/aryl sulfonyl chloride under Friedel Craft's reaction conditions [17]. These activated unsaturated systems have been used as

Scheme



Ar = **a)** Ph **b)** 4-OMe•Ph **c)** 4-Cl•Ph **d)** 3,4-Cl_2Ph

dipolarophiles and condensed with various 1,3-dipolar reagents to get a variety of heterocycles [18,19].

In our present approach, the synthesis of 3,4-disubstituted pyrroles is envisaged by a simple and common route using these Michael acceptors. When 1-benzoyl-2-aryl sulfonyl ethene (**4**) is treated with TosMIC (**5**) in the presence of sodium hydride in a mixture of ether and DMSO, 3-benzoyl-4-arylsulfonyl-1*H*-pyrrole (**6**) is obtained (Scheme and Table 1). The ^{1}H NMR spectrum of **6a** showed two singlets at δ_H 8.05 and 7.09 for C_2-H and C_5-H. The ^{13}C NMR spectrum of **6a** displayed signals at 139.6, 118.7, 109.8 and 120.9 for C_2, C_3, C_4 and C_5, respectively apart from signals due to carbonyl and aromatic carbons (Table 2). Similar reaction of 1,2-diarylsulfonylethene (**10**) with TosMIC (**5**) resulted in 3,4-bisarylsulfonyl-1*H*-pyrrole (**11**), whose structure is confirmed by ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **11a** displayed singlets at δ_H 7.06 and 7.06 for C_2-H and C_5-H where as in the ^{13}C NMR spectrum signals are observed at 119.6, 110.9, 110.9 and 119.6 for C_2, C_3, C_4 and C_5 (Table 2).

In summary we have developed an effective and simple route for the synthesis of 3,4-disubstituted pyrroles from 1-benzoyl-2-arylsulfonylethene and 1,2-diarylsulfonylethene using TosMIC.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. IR spectra (KBr disc) were recorded on Beckmann IR-18 spectrophotometer. ^{1}H NMR spectra were

Table 1

Physical Properties and IR data of Compounds **6** and **11**

Compd.	m.p. (°C)	Yield (%)	Mol. Formula (Mol.Wt.)	Calcd. (Found) (%) C	H	N	SO_2	IR (cm^{-1}) C=O	C=C	NH
6a	128-129	52.3	$C_{17}H_{13}NO_3S$ (311.36)	65.58 (65.52)	4.21 (4.26)	4.50 (4.57)	1134 1320	1658	1589	3378
6b	132-134	68.4	$C_{18}H_{15}NO_4S$ (341.38)	63.33 (63.37)	4.43 (4.39)	4.10 (4.17)	1128 1342	1664	1593	3365
6c	149-151	72.3	$C_{17}H_{12}ClNO_3S$ (345.80)	59.05 (59.10)	3.50 (3.53)	4.05 (4.11)	1120 1324	1654	1589	3378
6d	142-144	75.6	$C_{17}H_{11}Cl_2NO_3S$ (380.25)	53.70 (53.66)	2.92 (2.95)	3.68 (3.74)	1148 1306	1650	1596	3391
11a	198-200	55.2	$C_{16}H_{13}NO_4S_2$ (347.41)	55.32 (55.28)	3.77 (3.79)	4.03 (4.07)	1142 1318	-	1596	3368
11b	221-223	64.6	$C_{17}H_{15}NO_5S_2$ (377.44)	54.10 (54.22)	4.01 (4.08)	3.71 (3.64)	1128 1324	-	1589	3354
11c	216-218	63.8	$C_{16}H_{12}ClNO_4S_2$ (381.86)	50.33 (50.31)	3.17 (3.14)	3.67 (3.73)	1132 1341	-	1594	3358
11d	234-236	67.6	$C_{16}H_{11}Cl_2NO_4S_2$ (416.30)	46.16 (46.12)	2.66 (2.64)	3.36 (3.41)	1146 1325	-	1598	3385

Table 2

Spectroscopic Data of Compounds of **6** and **11**

Compd.	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
6a	7.09 (s, 1H, C_5-H), 7.15-7.89 (m, 10H, Ar-H), 8.05 (s, 1H, C_2-H), 10.39 (bs, 1H, NH)	109.8 (C_4), 118.7 (C_3), 120.9 (C_5), 139.6 (C_2), 188.5 (C=O), 126.8, 128.5, 129.7, 130.5, 132.6, 133.4, 133.6, 138.9 (Aromatic carbons)
6b	3.75 (s, 3H, OCH_3), 7.08 (s, 1H, C_5-H), 7.15-7.89 (m, 9H, Ar-H), 8.09 (s, 1H, C_2-H), 10.52 (bs, 1H, NH)	56.2 (OCH_3), 110.9 (C_4), 116.8 (C_3), 120.7 (C_5), 141.6 (C_2), 188.2 (C=O), 115.4, 127.7, 128.8, 130.1, 131.2, 132.8, 133.6, 167.5 (Aromatic carbons)
6c	7.11 (s, 1H, C_5-H), 7.25-8.01 (m, 9H, Ar-H), 8.14 (s, 1H, C_2-H), 10.52 (bs, 1H, NH)	110.6 (C_4), 117.9 (C_3), 121.3 (C_5), 140.7 (C_2), 188.4 (C=O), 128.4, 128.9, 130.4, 131.0, 133.9, 132.6, 136.7, 139.5 (Aromatic carbons)
6d	7.13 (s, 1H, C_5-H), 7.26-7.99 (m, 8H, Ar-H), 8.12 (s, 1H, C_2-H), 10.55 (bs, 1H, NH)	110.4 (C_4), 121.8 (C_3), 127.3 (C_5), 141.9 (C_2), 188.3 (C=O), 128.3, 129.1, 129.8, 130.6, 131.3, 132.4, 133.0, 135.4, 137.4, 138.3 (Aromatic carbons)
11a	7.06 (s, 2H, C_2-H & C_5-H), 7.30-7.93 (m, 10H, Ar-H), 10.38 (bs, 1H, NH)	110.9 (C_3 & C_4), 119.6 (C_2 & C_5), 126.8, 129.7, 133.9, 138.6 (Aromatic carbons)
11b	3.76 (s, 3H, OCH_3), 7.10 (s, 2H, C_2-H & C_5-H), 7.30-7.93 (m, 9H, Ar-H), 10.41 (bs, 1H, NH)	56.2 (OCH_3), 111.5 (C_3 & C_4), 120.6 (C_2 & C_5), 115.4, 126.6, 127.8, 129.7, 130.9, 134.0, 139.0, 167.4 (Aromatic carbons)
11c	7.12 (s, 2H, C_2-H & C_5-H), 7.30-7.93 (m, 9H, Ar-H), 10.39 (bs, 1 H, NH)	111.3 (C_3 & C_4), 121.4 (C_2 & C_5), 126.7, 127.8, 129.6, 130.0, 134.1, 136.9, 139.2, 139.9 (Aromatic carbons)
11d	7.09 (s, 2H, C_2-H & C_5-H), 7.12-7.93 (m, 8H Ar-H), 10.44 (bs, 1 H, NH)	112.4 (C_3 & C_4), 121.8 (C_2 & C_5), 126.5, 126.8, 128.9, 130.4, 131.5, 133.8, 135.6, 138.5, 139.2, 140.0 (Aromatic carbons)

recorded in $CDCl_3$ at 300 MHz on a Varian EM-360 spectrophotometer. ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian VXR spectrometer operating at 75.5 MHz. All chemical shifts were reported in ppm relative to TMS as an internal standard. The mass spectra were recorded on Joel JMS-D 300 instrument operating at 70 eV. Elemental analyses were obtained from the University of Pune, Pune, India. The starting compounds 1-benzoyl-2-arylsulfonylethenes (**4**) and 1,2-diarylsulfonylethenes (**10**) were prepared by literature procedure [17].

3-Benzoyl-4-arylsulfonyl-1*H*-pyrroles (**6**).

A mixture of 1 mmol of TosMIC (**5**) and 1 mmol of 1-benzoyl-2-arylsulfonyl ethene (**4**) in Et_2O/DMSO (2:1) is added drop wise to a stirred suspension of NaH (50 mg) in 10 mL dry Et_2O at room temperature. The reaction mixture is stirred for 24 hours and diluted with water, then extracted with Et_2O and the organic phase dried over anhydrous Na_2SO_4. Concentration of the solvent gave crude product, which is purified by filtration through a column of silica gel (60-120) mesh, BDH with hexane / EtOAc, 4:1 as eluent.

3-Benzenesulfonyl-4-arylsulfonyl-1*H*-pyrroles (**11**).

A mixture of 1 mmol of TosMIC (**5**) and 1 mmol of 1,2-diarylsulfonyl-ethene (**10**) in Et_2O/DMSO (2:1) is added dropwise to a stirred mixture of NaH (50 mg) in dry Et_2O (10 ml) at lab temperature. Stirring is continued for 8 h at which time the mixture is diluted with water followed by extracted with ether. The ethereal layer is dried over anhydrous Na_2SO_4. Concentration of the solvent gave crude product, which is purified by filtration through a column of silica gel (60-120) mesh, BDH with hexane / EtOAc, 4:1 as eluent.

REFERENCES AND NOTES

* To whom correspondence should be addressed: Email: vkpuram2001@yahoo.com

[1] G. Dannhard, W. Kiefer, G. Kramer, S. Maehrlein and U. Nowe, *Eur. J. Med. Chem*., **35**, 499 **(**2000).

[2] C. F. Lee, L. M. Yang, T. Y. Hwu, A. S. Feng, J. C. Tseng and T. Y. Luh, *J. Am. Chem. Soc*., **122**, 4992 (2000) and references therein.

[3] A. Gossauer, Pyrrole. In *Houben- Weyl*. Thieme: Stuttgart, **E6a / 1**, 556 (1994).

[4] O. A. Tarasova, N. A. Nedolya, V. Yu. Vvedensky, L. Brandsma and B. A. Trofimov, *Tetrahedron Lett.*, **38**, 7241 (1997).

[5] T. L. Glichrist, *J. Chem. Soc., Perkin Trans. 1*, 2849 (1999).

[6] D. H. R. Barton and S. Z. Zard, *J. Chem. Soc, Chem. Commun*., 1098 (1985).

[7] D. H. R. Barton, J. Kervagoret and S. Z. Zard, *Tetrahedron*, **46**, 7587 (1990).

[8] T. D. Lash, J. R. Bellettini, J. A. Bastian and K. B. Couch, *Synthesis*, 170 (1994).

[9] N. Ono, H. Katayama, S. Nishiyama and T. Ogawa, *J. Heterocyclic Chem*., **31**, 707 (1994).

[10] M. Adamczyk and R. E. Reddy, *Tetrahedron Lett.*, **36**, 7983 (1995).

[11] E. T. Pelkey, L. Chang and G. W. Gribble, *J. Chem. Soc, Chem. Commun*., 1909 (1996).

[12] B. Quiclet-Sire, I. Thevenot and S. Z. Zard, *Tetrahedron Lett*., **36**, 9469 (1995).

[13] O. H. Oldenziel and A. M. Van Leusen, *Synth. Commun*., 281 (1972).

[14] A. M. Van Leusen, H. Siderius, B. E. Hoogenboom and D. Van Leusen, *Tetrahedron Lett.*, 5337 (1972).

[15] W. G. Davies, E. W. Hardisty, T. P. Nevell and R. H. Peters, *J. Chem. Soc. (B)*, 998 (1970).

[16] V. Padmavathi, B. Jagan Mohan Reddy, M. Rajagopala Sarma, P. Thriveni, *J. Chem. Research (S)*, 79 (2004).

[17] D. Bhaskar Reddy, N. Chandrasekhar Babu, V. Padmavathi, and R. P. Sumathi, *Synthesis*, 491 (1999).

[18] V. Padmavathi, R. P. Sumathi, N. Chandrasekhar Babu, D. Bhaskar Reddy, *J. Chem. Research (S)*, 610 (1999).

[19] V. Padmavathi, R. P. Sumathi, K. Venugopal Reddy, A. Somasekhar Reddy and D. Bhaskar Reddy, *Synth. Commun.*, **30**, 4007 (2000).