Unsaturated Sulfoxides in Organic Synthesis: a New General Pyrrole Synthesis

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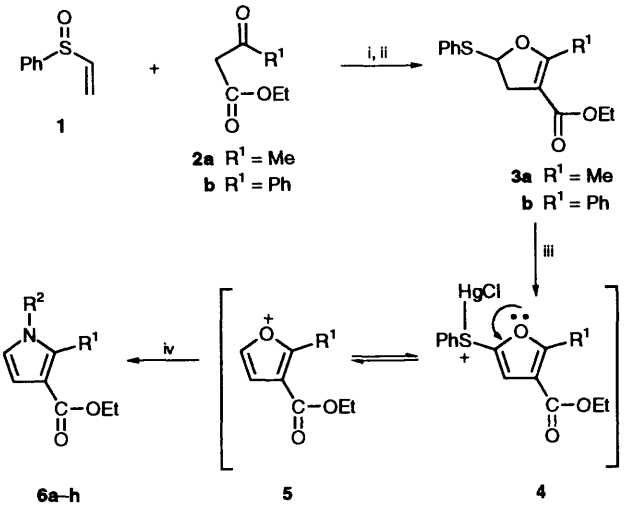
Pyrroles have been efficiently synthesised by a three-step reaction sequence. Michael addition of keto esters onto phenyl vinyl sulfoxide followed by Pummerer rearrangement gave the cyclic key intermediate **3**. Mercury(II) salt induced carbon–sulfur bond cleavage afforded a 1,4-dicarbonyl equivalent **5**. Treatment of the latter with an ammonium salt or a primary amine led to substituted pyrroles.

In continuation of our interest in using unsaturated sulfoxides in organic synthesis,[1a–d] we have recently described a general synthesis of furans starting from alkenyl sulfoxides.[2] In this communication, we report the extension of this synthetic strategy to a synthesis of substituted pyrroles, which may be inaccessable by traditional approaches.[3]

The new pyrrole synthesis began with the key intermediates **3a** and **3b** obtained previously from a two-step transformation sequence.[2] Michael addition of keto ester **2** onto phenyl vinyl sulfoxide **1** followed by acid induced Pummerer rearrangement afforded **4a** and **4b** in 75 and 64% yield over two steps, respectively (Scheme 1). In fact, dihydrofurans **3** can be viewed as a latent form of 1,4-dicarbonyl compounds. Mercury(II) salt induced carbon–sulfur bond cleavage generated the presumed intermediate **5**, a synthetic equivalent of a 1,4-dicarbonyl. Trapping of **5** with either an ammonium salt or a primary amine gave disubstituted or trisubstituted pyrroles (Table 1). Elaborate efforts have been made to optimize the yield of the reaction. When **3a** was heated in the presence of a large excess of amine with 2 equiv. of $HgCl_2$ in a sealed-tube at 150 °C for 2 h the pyrroles were obtained in good yields (Table 1, entries 1, 4 and 6). In order to tone down the drastic conditions, the reaction was carried out in an acetonitrile–water mixture (3:1) under reflux. Under these homogeneous conditions and with prolonged heating (24 h), only 24% yield of the product was formed (Table 1, entry 2). However, the reaction was much improved by breaking down the one-pot reaction into two stages. Compound **4a** was first refluxed with 2 equiv. of mercury(II) chloride in acetonitrile–water (3:1). Within 0.5 h, as indicated by TLC, **4a** was decomposed completely, presumably *via* mercury triggered carbon–sulfur bond cleavage. Then, after addition of an ammonium salt or a primary amine, the mixture was stirred overnight at room temperature. Fair to good yields of the pyrroles were obtained. The synthesis was proven to be general. Using this simple procedure, on treatment with different amines, compound **4b** also gave fair yield of the corresponding pyrroles.



Scheme 1 *Reagents and conditions:* i, NaOEt–EtOH; ii, CCl_3CO_2H, Ac_2O, toluene, reflux; iii, $HgCl_2$, MeCH–H_2O (3:1), reflux 1 h; iv, ammonium salt or primary amine

Experimental

Formation of Pyrrole **6a** *by a Sealed Tube Experiment.*—A mixture of dihydrofuran **3a** (396 mg, 1.5 mmol), mercury(II) chloride (814 mg, 3 mmol) and propylamine (1.23 dm^3, 15 mmol) in DMAC (2 cm^3) was transferred to a thick walled glass tube (OD = 1 cm). After flushing with nitrogen, the glass tube was sealed carefully with an oxygen/acetylene flame. The sealed tube was then immersed in a preheated oil bath (150 °C) for 2 h. After cooling to room temperature, the sealed tube was broken with a sharp cutter and its contents were poured into 20 cm^3 of water. The organic materials were extracted with diethyl ether (3 × 30 cm^3). The combined organic layers were washed once with 20% aqueous EDTA solution (20 cm^3). The organic solution was collected, dried, filtered and then evaporated to dryness. Chromatography of the organic residue (silica gel column; ethyl acetate–light petroleum, 2:98) gave pyrrole **6a** as a yellowish liquid (193 mg, 66%); ν_{max}(neat)/cm^{-1} 1700 (ester); δ_H(270 MHz; $CDCl_3$; *J*/Hz) 0.91 (3 H, t, *J* 7.3), 1.33 (3 H, t, *J* 7.0), 1.70–1.73 (2 H, m), 2.51 (3 H, s), 3.76 (2 H, t, *J* 7.3), 4.25 (2 H, q, *J* 7.0), 6.48 (1 H, d, *J* 3.0) and 6.52 (1 H, d, *J* 3.0); δ_C(67.8 MHz; $CDCl_3$) 10.8, 11.0, 14.4, 24.0, 48.2, 59.1, 109.1, 111.9, 119.8, 135.2 and 165.6; *m/z* 195 (M^+, 4.7%) and 166 ($M^+ - C_2H_5$, 6.3).

Formation of Pyrrole **6f** *by a One-pot Two-step Reaction.*—A mixture of dihydrofuran **4b** (123 mg, 0.38 mmol) and mercury(II) chloride (126 mg, 0.46 mmol) in acetonitrile–water (3:1, 8 cm^3) was refluxed for 1 h. The mixture was cooled to room temperature and then 40 wt.% aqueous methylamine (0.1 dm^3, 1.16 mmol) was introduced by syringe. The mixture was then stirred overnight at room temperature. The solution was filtered and the precipitate was washed with small amount of acetonitrile. The combined filtrates were dried and evaporated to dryness. Chromatography of the residue (silica gel column; ethyl acetate–light petroleum, 2:98) afforded pyrrole **6f** as a yellowish liquid (54 mg, 63%); ν_{max}(neat)/cm^{-1} 1700 (ester); δ_H(270 MHz; $CDCl_3$; *J*/Hz) 1.12 (2 H, t, *J* 7.0), 3.44 (3 H, s), 4.10 (2 H, q, *J* 7.0), 6.63 (1 H, d, *J* 3.0), 6.68 (1 H, d, *J* 3.0) and 7.32–7.43 (5 H, m); δ_C(67.8 MHz; $CDCl_3$) 14.1, 34.7, 59.2, 110.1, 113.5, 121.9, 127.8, 128.2, 130.6, 131.8, 138.5 and 164.7; *m/z* 229 (M^+, 56%) and 184 ($M^+ - OC_2H_5$, 100).

Table 1 Pyrrole synthesis

Entry	Dihydrofuran	Nitrogen source (equiv.)	Solvent[a,b]	Conditions	Product	R^1	R^2	Yield (%) pyrrole
1	**4a**	propylamine (10)	DMAC	*c*	**6a**	Me	Pr	66
2	**4a**	propylamine (4)	MeCN–H_2O	*d*	**6a**	Me	Pr	24
3	**4a**	propylamine (4)	MeCN–H_2O	*e*	**6a**	Me	Pr	62
4	**4a**	methylamine (10)	DMAC	*c*	**6b**[4]	Me	Me	64
5	**4a**	methylamine (4)	MeCN–H_2O	*e*	**6b**	Me	Me	60
6	**4a**	benzylamine (10)	DMAC	*c*	**6c**[5]	Me	$PhCH_2$	60
7	**4a**	benzylamine (4)	MeCN–H_2O	*e*	**6c**	Me	$PhCH_2$	56
8	**4a**	NH_4OH (10)	DMAC	*c*	**6d**[6]	Me	H	40
9	**4a**	NH_4OAc (4)	MeCN–H_2O	*e*	**6d**	Me	H	72
10	**4b**	propylamine (4)	MeCN–H_2O	*e*	**6e**	Ph	Pr	52
11	**4b**	methylamine (4)	MeCN–H_2O	*e*	**6f**	Ph	Me	63
12	**4b**	benzylamine (4)	MeCN–H_2O	*e*	**6g**	Ph	$PhCH_2$	40
13	**4b**	NH_4OAc (4)	MeCN–H_2O	*e*	**6h**	Ph	H	73

[a] DMAC = *N*,*N*-dimethylacetamide. [b] MeCN–H_2O in 3:1 v/v. [c] Sealed-tube 150 °C for 2 h. [d] Reflux 24 h. [e] Reflux 1 h with $HgCl_2$ (2 equiv.), then stirred overnight with an excess of the nitrogen-containing compounds.

Acknowledgements

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