A New Method for Generation of 4- and 6-Aryl Thieno[2,3-*c*]furans, and 3-Aryl Furo[3,4-*b*]pyridine

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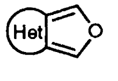
6-Aryl thieno[2,3-*c*]furans **2a–c**, 4-(3,4-dimethoxyphenyl)thieno[2,3-*c*]furan **3a**, and 3-(3,4-dimethoxyphenyl)furo[3,4-*b*]pyridine **4a**, which were intercepted *in situ* by dimethyl acetylenedicarboxylate to give the corresponding Diels–Alder adducts in good yields, were generated under acidic conditions from 2-(α-acetoxybenzyl)thiophene-3-carbaldehydes **5a–c**, 3-(α-acetoxy-3,4-dimethoxybenzyl)thiophene-2-carbaldehyde **10a** and 2-(α-acetoxy-3,4-dimethoxybenzyl)pyridine-3-carbaldehyde **12a**, respectively.

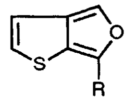
Recently, the heteroaromatic analogues of isobenzofurans **1** are of increasing interest as reactive intermediates for the synthesis of polycyclic heteroaromatics.[1–4] The methods so far reported for generation of **1** include those based on the Grignard reagent-promoted cyclization of thienyl-2-oxazolinium derivatives leading to thieno[2,3-*c*]furans,[1] thermal retro Diels–Alder reaction of 1,4-epoxides leading to furo[3,4-*c*]pyridines[2] and thermal treatment of (alkynylfuryl)oxiranes leading to furo[2,3-*c*]furans.[3] However, these methods need a number of steps for generation of these reactive intermediates. In connection with our synthetic studies in search of new compounds having antihyperlipidemic activity,[5] we now report a new method for generation of 6-aryl thieno[2,3-c]furans **2a–c**, 4-(3,4-dimethoxyphenyl)thieno[2,3-*c*]furan **3a** and 3-(3,4-dimethoxyphenyl)furo[3,4-*b*]pyridine **4a** from 2-(α-acetoxybenzyl)thiophene-3-carbaldehydes **5a–c**, 3-(α-acetoxy-3,4-dimethoxybenzyl)thiophene-2-carbaldehyde **10a** and 2-(α-acetoxy-3,4-dimethoxybenzyl)pyridine-3-carbaldehyde **12a**, respectively.

Our working hypothesis for generation of 6-aryl thieno-[2,3-*c*]furans **2** is as follows. The carbonium ion **6** generated from the acetoxy-aldehyde **5** would be attacked by the carbonyl group to form the oxonium ion **7** leading to the formation of **2** (Scheme 1).

Our study began with experiments to generate 6-(3,4-dimethoxyphenyl)thieno[2,3-*c*]furan **2a** which would be intercepted by dimethyl acetylenedicarboxylate (DMAD) to furnish the benzo[*b*]thiophene **9a**. Thus, the requisite acetoxyaldehyde **5a**† was prepared according to Scheme 2 in good overall yield (83%).[6] The reaction of **5a** with DMAD and



1



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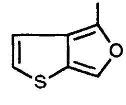

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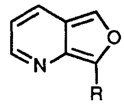

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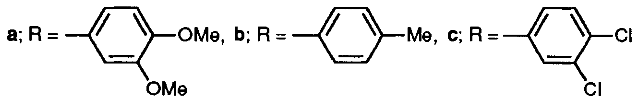

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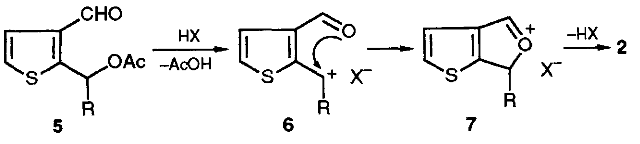
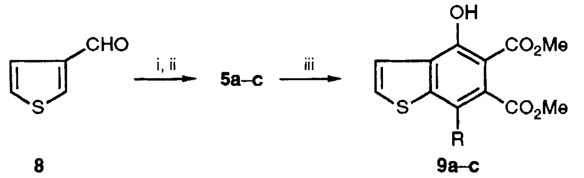
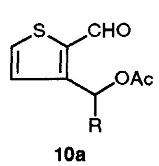
† *Selected data* for **5a**: m.p. 91–92 °C; ¹H NMR ($CDCl_3$) δ 2.14 (s, 3H), 3.85 (s, 6H), 6.73–7.07 (m, 3H), 7.20 (d, *J* 5.0 Hz, 1H), 7.37 (d, *J* 5.0 Hz, 1H), 7.56 (s, 1H), 9.99 (s, 1H). Satisfactory elemental analysis was obtained.



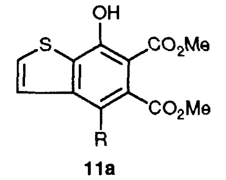
Scheme 1



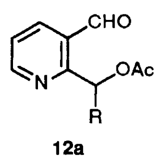
Scheme 2 *Reagents and conditions*: i, LTMDA (1.0 equiv.), LDA (1.1 equiv.), $\mathrm{Bu^nLi}$ (0.9 equiv), RCHO–THF, −78 °C; ii, $\mathrm{Ac_2O}$, $\mathrm{Et_3N}$–THF, 0 °C; iii, DMAD, TFA–PhH reflux; LTMDA = lithiated *N,N,N'*-trimethylethylenediamine, LDA = lithium diisopropylamide, THF = tetrahydrofuran



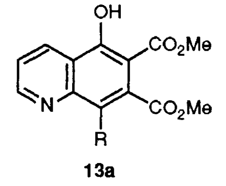
10a



11a



12a



13a

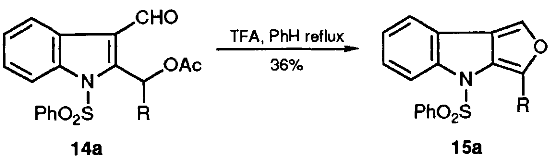


Table 1 Reactions of acetoxy aldehydes with DMAD[a]

Entry	Acetoxy-aldehyde	Reaction time/h	Product[b]	Yield (%)[c]
1	**5a**	1	**9a**	88
2	**5b**	5	**9b**	73
3	**5c**	10	**9c**	80
4	**10a**	3	**11a**	83
5	**12a**	0.5	**13a**	66

[a] The reaction was carried out on a 10 mmol scale under the same reaction conditions as those described in the typical procedure. [b] All products were characterized based on ^{1}H NMR, IR, and mass spectra and elemental analyses. [c] Isolated yield.

trifluoroacetic acid TFA‡ in refluxing benzene gave **9a** in 88% yield.

A typical procedure is as follows. A mixture of **5a** (3.20 g, 10 mmol) and DMAD (1.56 g, 11 mmol) was refluxed in benzene (15 ml) in the presence of TFA (0.02 ml). After one hour, the solvent was removed under reduced pressure. To the mixture was added methanol (50 ml) and the resulting crystals were collected by filtration to afford 3.54 g of **9a**.§

In Table 1 the results are shown of the reactions using the acetoxyaldehydes **5b,c** in which the R group is replaced by aryl groups other than 3,4-dimethoxyphenyl group. In any case, the adduct was obtained in a satisfactory yield. It is noteworthy that in the case of **5c**, which has electron-withdrawing substituents on the benzene ring, the reaction proceeded more slowly than those in the case of the other acetoxyaldehydes which have electron-donating substituents on the benzene ring. This is probably due to the decreased leaving ability of the acetoxy group of **5c**.

The method is also effective for generation of 4-aryl thieno[2,3-*c*]furans **3**. Thus, the reaction of **3a**, which was generated from **10a**¶ under the same reaction conditions as described above, with DMAD furnished **11a** in 83% yield (entry 4, Table 1).

Furthermore, we succeeded in the generation of 3-(3,4-dimethoxyphenyl)furo[3,4-*b*]pyridine **4a**, a hitherto unknown ring system; the reaction of acetoxyaldehyde **12a**, which is readily obtained from 2-bromopyridine in a good overall yield, with DMAD afforded the corresponding adduct **13a** in a satisfactory yield (entry 5, Table 1).

Various attempts were made to isolate **2**, **3** and **4**. However, these compounds are too unstable to be isolated. In order to confirm our working hypothesis, we tried to isolate 3-aryl furo[3,4-*b*]indole **15a** which would be more stable.[8] Treatment of the acetoxyaldehyde **14a** with a catalytic amount of TFA in refluxing benzene for 30 minutes afforded **15a** [m.p. 171–2 °C (decomp.)] in 36% yield (Scheme 3).

This new method should find application in the generation of the other heteroaromatic analogues of isobenzofurans which are useful reactive intermediates for syntheses of biologically active heteroaromatics.

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‡ The reaction of **5a** with DMAD in $\mathrm{H_2SO_4}$–benzene and *p*-TsOH–benzene under optimized conditions gave **9a** in 56% and 42% yields, respectively. In the use of $\mathrm{BF_3 \cdot OEt_2}$ as a catalyst, **9a** was not obtained at all.

§ *Selected data* for **9a**: m.p. 147–8 °C; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 3.62 (s, 3H), 3.86 (s, 3H), 3.93 (s, 6H), 6.90–7.00 (m, 3H), 7.38 (d. *J* 6.0 Hz, 1H), 7.65 (d, *J* 6.0 Hz, 1H), 11.73 (s, 1H). Satisfactory elemental analysis was obtained.

¶ The acetoxy aldehyde **10a** was prepared in a good overall yield from 3-bromothiophene based on directed lithiation methodology.[7]