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AN EFFICIENT FRIEDEL-CRAFTS SYNTHESIS OF 2-ACYLBENZOFURANS

MELVYN GILL

Department of Organic Chemistry, University of Melbourne,
Parkville, Victoria, Australia, 3052.

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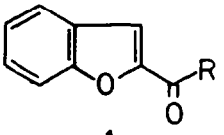
Abstract - 2-(Trimethylsilyl)benzofuran, available quantitatively from benzofuran itself, reacts rapidly with primary, secondary, and tertiary aliphatic carboxylic acid chlorides in the presence of titanium (IV) chloride at low temperature to afford the corresponding 2-acylbenzofurans in excellent yields. This approach offers significant synthetic advantage over existing routes to the title compounds.

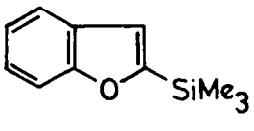
Various 2-acylbenzofurans of the type 1 have acquired practical importance as convenient intermediates in the preparation of more elaborate pharmacologically significant[1] and therapeutically valuable benzofurans.[1,2] Despite the pharmaceutical interest which these benzofurans have engendered[2] there exists to date no efficient and versatile method for the synthesis of 2-acylbenzofurans themselves.[3] In particular, the practicability of a general approach based on Friedel-Crafts acylation of benzofuran is seriously impaired by the predilection of this heterocycle towards polymerisation in the presence of even the mildest Lewis acids.[4,5] Benzofuran can however be acylated at high temperature using carboxylic acid anhydrides in the presence of phosphoric acid[6] but this method suffers in that yields are low (33-55%) and the reaction succeeds only when the carboxylic acid corresponding to the anhydride used is employed as solvent.[6] More recently the use of acetyl chloride with traces of anhydrous ferric chloride catalyst is reported[7] to afford 2-acetylbenzofuran in up to 60% yield but the scope of this reaction has not as yet been defined. We report here an alternative and eminently more versatile Friedel-Crafts approach to 2-acylbenzofurans which proceeds under extremely mild conditions, relying for its success on the highly efficient titanium (IV) chloride catalysed acylation of 2-(trimethylsilyl)benzofuran 2.

It was anticipated that the exposure of the trimethylsilylbenzofuran 2 rather than benzofuran itself to Friedel-Crafts conditions would afford two distinct synthetic advantages. Firstly, since benzofurans bearing (alkyl) substituents in the 2- position are considerably more stable than is benzofuran itself towards Friedel-Crafts catalysts, being acylated at C-3 in good yield,[4] polymerisation of 2 would be retarded. Secondly, and in accordance with the well established activating and ipso directing capacity of the trimethylsilyl group during electrophilic substitution,[8] the presence of this substituent α- to the heteroatom in 2 would facilitate the predominance of 2- over 3- acylated products.

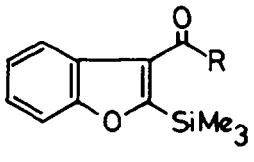
Consequently, 2-(trimethylsilyl)benzofuran 2[9] was readily prepared by metallation of benzofuran with butyl-lithium followed by addition



1



2



3

a) R=Me b) R=Et c) R=Pr^n d) R=Pr^i e) R=Bu^t f) R=CH_2Ph g) R=Ph

of chlorotrimethylsilane. The product, obtained in quantitative yield after isolation with pentane, was sufficiently pure for use directly in the subsequent Friedel-Crafts reactions. Treatment of 2-(trimethylsilyl)-benzofuran 2 and acetyl chloride (1.1 equiv.) in methylene dichloride at -78° with titanium (IV) chloride (1.3 equiv.) resulted within 3 minutes in the complete consumption of the substrate 2 as ascertained by thin layer chromatography. After 5 minutes, quenching the resulting deep red solution with water and isolation using ether afforded crystalline 2-acetylbenzofuran 1a in near quantitative yield. Although this product is probably pure enough for many purposes, chromatography removed impurities consisting of the 3-acetyl-2-silyl-benzofuran 3a and a quantity of polymeric material and afforded pure 1a in an overall yield of 88% from benzofuran. No further improvement in this yield could be attained by increasing the relative proportion either of acetyl chloride or of the catalyst employed and the consequence of decreasing the quantity of titanium (IV) chloride used was a corresponding decrease in the yield of 1a due to incomplete consumption of 2. The identity of the only relevent by-product of the reaction as the 3-acetyl-2-silylbenzofuran 3a follows from the ^1H NMR spectrum of the total reaction product which revealed in addition to resonances characteristic of 2-acetylbenzofuran, singlets at δ 0.37 and 2.70 due to the protons of the trimethylsilyl and acetyl groups, respectively, of 3a. The absence of an aromatic proton resonance near to δ 6.85 confirms the assignment of the acetyl group to C-3 in 3a and excludes the possibility that substitution had occurred in the benzenoid nucleus of 2.

Importantly, 2-(trimethylsilyl)benzofuran 2 also reacted efficiently in the presence of titanium (IV) chloride with a range of other primary, secondary and tertiary aliphatic carboxylic acid chlorides. The range of acyl chlorides used and the products of these reactions are summarised in Table 1. In each case the appropriate 2-acylbenzofuran 1b-1f was obtained rapidly and in consistently high yield without significant contamination by the corresponding 3-acyl-2-silylbenzofuran 3b-3f. During the acylation of 2 with pivalyl chloride it proved necessary to warm the reaction mixture from -78° to -15° to ensure complete reaction since at temperatures below -20° the yellow crystalline complex formed between pivalyl chloride and titanium (IV) chloride[10] proved insufficiently soluble in methylene dichloride to maintain a reasonable rate of acylation. At -15° dissolution of the complex and its subsequent acylation of 2 were rapid, affording the t-butyl ketone 1e apparently free from any 2-t-butylbenzofuran.[11]

In summary, this new approach provides superior access in terms of efficiency and convenience both to known and to new benzofuranyl ketones. In addition, it is potentially applicable to the synthesis of a wide variety of 2-acylated benzofurans which would be inaccessible by the previous routes.[3-7]

Finally we have studied the benzoylation of 2-(trimethylsilyl)benzofuran 2. In contrast to the excellent yields and high ipso selectivity observed in reactions with aliphatic carboxylic acid chlorides the reaction between the silylbenzofuran 2 and benzoyl chloride in the presence of titanium (IV) chloride afforded an appreciable amount (15%) of 3-benzoyl-2-

Table 1. Products of Acylation of 2-(Trimethylsilyl)benzofuran 2 in the Presence of Titanium (IV) Chloride

Acid Chloride RCOCl	Temperature °C	Time minutes	Products (% yield) 2-Acylbenzofuran[a]	3-Acyl-2-(trimethylsilyl)benzofuran[b]
MeCOCl	-78	5	1a (88)	3a (< 4)
EtCOCl	-78	5	1b (89)	3b (trace)
Pr^nCOCl	-78	5	1c (92)	3c (-)
Pr^iCOCl	-78	5	1d (87)	3d (-)
Bu^tCOCl	-78 to -15	60 at -15	1e (75)	3e (< 3)
$PhCH_2COCl$	-78	15	1f (74)	3f (5)

a - Refers to yield of purified material.

b - Yields are estimated from ^1H NMR spectra of the total reaction products except for 3f which refers to purified, isolated material (see Experimental and Table 2). A dash indicates that the compound was not detected in the ^1H NMR spectra.

(trimethylsilyl)benzofuran 3g in addition to the expected 2-benzoylbenzofuran 1g (50%). This reaction takes place rapidly at -15° but is prohibitively slow below -20° due to the insolubility of the benzoyl chloride - titanium (IV) chloride complex.[10] That the observed decrease in regioselectivity is not entirely attributable to the increased temperature[12] is attested to by the more favourable result obtained above with pivalyl chloride under similar conditions.

The ability to control site-selectivity during electrophilic aromatic substitution reactions by the strategic placement of a trimethylsilyl group has been recognised for some time[13] although its synthetic exploitation to date has been limited and has rested mainly with benzenoid compounds.[8,13] The report here that the trimethylsilyl group upon introduction into the benzofuran nucleus permits highly efficient and remarkably facile acylation under conditions which, moderate as they are, cause rapid and total resinification of benzofuran itself, suggests further potential for this strategy in the often problematical area of heteroaromatic electrophilic substitution.

EXPERIMENTAL

I.R. spectra were measured as KBr discs (solids) or between NaCl plates (oils) on a Perkin-Elmer 537 spectrometer. ^{1}H NMR spectra were recorded on a Jeol JNM-PMX 60 spectrometer at 60 MHz for solutions in $CDCl_3$ with TMS as internal standard. Mass spectra were run on a VG Micromass 7070 instrument operating at 70 eV. Melting points are uncorrected.

Petrol refers to light petroleum (b.p. 60-80°). Merck Kieselgel 60 F_{254} was used for PLC. THF was distilled from Na-benzophenone ketyl immediately prior to use. Reactions were routinely performed under an Ar atmosphere.

2-(Trimethylsilyl)benzofuran, 2

To benzofuran (1.08 ml, 10 mmol) in THF (15 ml) at -78° was added n-BuLi (7.5 ml, 1.7 M in hexane, 12.75 mmol). After 1 h at -78° chlorotrimethylsilane (1.9 ml, 15 mmol) was added to the colourless suspension and the mixture was stirred at -78° for 1 h and then at room temperature overnight. Dilution with pentane, filtration, and removal of the solvent from the filtrate gave 2 (1.98 g) as a colourless liquid, NMR δ 0.32 (9H, s, $SiMe_3$), 6.85 (1H, s, C-3H), and 7.06-7.60 (4H, m, ArH). Silylbenzofuran 2 was used without further purification.

Acylation of 2-(trimethylsilyl)benzofuran, 2: General Procedure.

$TiCl_4$ (71 µl, 0.65 mmol) was added dropwise to a vigorously stirring mixture of 2 (95 mg, 0.5 mmol) and the appropriate acyl chloride (0.55 mmol) in CH_2Cl_2 (1 ml) at -78°. The consumption of 2 was monitored by TLC using petrol - CH_2Cl_2 (9:1) and when complete (Table 1) H_2O (2 ml) was added and the mixture was allowed to warm to room temperature. Dilution with H_2O (10 ml), extraction with ether (3 x 10 ml) and evaporation of the washed (H_2O) and dried ($MgSO_4$) ethereal solvent afforded the crude product which was further purified by PLC on silica gel using petrol - CH_2Cl_2 (2:3). 3-Acyl-2-silylbenzofurans of the type 3 ran with consistently higher R_f values than the corresponding 2-acylbenzofurans 1.

During acylation of 2 with pivalyl chloride addition of $TiCl_4$ at -78° produced a yellow suspension. This suspension was allowed to warm to -15° and the clear red solution which resulted was maintained at -15° for 1 h prior to the addition of H_2O (2 ml) and work up as described above.

Yields of compounds 1a-1f and 3a-3f are recorded in Table 1. Physical, analytical and spectroscopic data for new compounds are presented in Table 2.

The following have been described before: 2-acetylbenzofuran, 1a, m.p. 72-73° (lit.[6] 75-76°), 2-propionylbenzofuran, 1b, m.p. 50-53° (lit.[6] 56°), and 2-n-butyrylbenzofuran, 1c, m.p. 62-64° (lit.[6] 71°).

Benzoylation of 2-(trimethylsilyl)benzofuran, 2

$TiCl_4$ (71 µl, 0.65 mmol) was added dropwise to 2 (95 mg, 0.5 mmol) and benzoyl chloride (64 µl, 0.55 mmol) in CH_2Cl_2 (1 ml) at -78°. The resulting yellow suspension was allowed to warm to -15° and the red solution thus produced was

Table 2. Physical, Analytical and Spectroscopic Data for New Benzofurans 1d-1f and 3f, g.

Compound	m.p. or b.p.[a] °C	ANALYTICAL DATA Found % C	Found % H	Calculated % C	Calculated % H	$\nu_{c=o}$ cm^{-1}	MASS SPECTRUM m/z (rel. abund.)	^1H NMR SPECTRUM δ (number of protons, multiplicity, coupling constant)
1d	95/0.3 mmHg	76.55	6.2	76.55	6.45	1680	188 (M^+, 22), 145 (100), 89 (23)	1.25 (6H, d, J 7Hz), 3.46 (1H, heptet, J 7Hz), 7.10-7.73 (5H, m)
1e	65/0.3 mmHg	77.15	7.3	77.2	7.0	1670	202 (M^+, 26), 145 (100), 89 (20), 57 (83), 41 (24), 39 (10), 29 (24)	1.42 (9H, s), 7.16-7.70 (5H, m)
1f	79-81[b]	81.35	5.0	81.35	5.1	1680	236 (M^+, 17), 145 (100), 91 (11), 89 (26), 43 (32), 41 (26), 39 (15), 29 (13)	4.17 (2H, s), 7.09-7.66 (10H, m)
3f	93-95[c]	74.05	6.4	74.0	6.55	1670	308 (M^+, 1), 293 (8), 217 (100), 175 (15), 43 (13)	0.38 (9H, s), 4.30 (2H, s), 7.09-7.80 (9H, m)
3g	93-95.5[d]	73.15	6.35	73.45	6.15	1645	294 (M^+, 8), 279 (100), 105 (25), 77 (30)	0.37 (9H, s), 7.08-7.90 (9H, m)

a - Refers to Kugelrohr air bath temperature

b - prisms from petrol

c - plates from H_2O-MeOH

d - fronds from H_2O-MeOH.

stirred at this temperature for 5 min. Addition of H_2O (2 ml), isolation with ether as described above and PLC using petrol-CH_2Cl_2 (1:1) gave the more polar 2-benzoylbenzofuran, 1g (55 mg, 50%), m.p. 87-89° (lit.[14] 90-91°) and the less polar *3-benzoyl-2-(trimethylsilyl)-benzofuran*, 3g (22 mg, 15%) for which physical, analytical and spectroscopic data are presented in Table 2.

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