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SHORT COMMUNICATION

TITANIUM-INDUCED SYNTHESIS OF BENZOFURANS

N.D. Jumbam*, M.P.I. Yedwa# and W. Masamba

Department of Chemistry and Chemical Technology, Walter Sisulu University, Private Bag X1 WSU, 5117 Mthatha, Eastern Cape, South Africa

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ABSTRACT. Ketoesters derived from the acylation of *o*-hydroxyacetophenone with aliphatic as well as aromatic acid chlorides undergo intramolecular cyclization in the presence of low-valent titanium to afford benzofurans in good yields. The reduction of titanium trichloride with dry zinc powder in refluxing THF takes place in the presence of the ketoester which simultaneously cyclizes as the titanium catalyst is formed, rendering the pre-reduction of titanium trichloride in a separate step unnecessary.

KEY WORDS: Ketoesters, Low-valent titanium, Benzofurans

INTRODUCTION

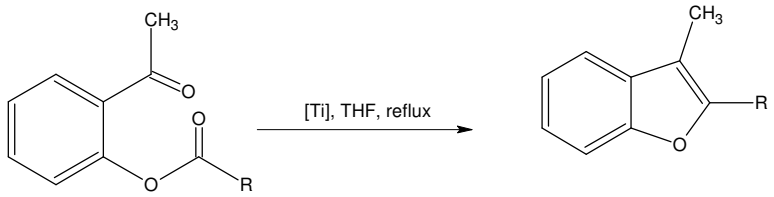
Low-valent titanium generated by the reduction of $TiCl_x$ (x = 3, 4) with various reducing agents is highly reactive and has proved to be a versatile tool for carbon-carbon bond forming reactions [1]. On account of its oxophilicity and electron transfer capability, it promotes the reductive deoxygenation of carbonyl compounds to olefins, generally referred to as "McMurry reaction" [2]. This reaction follows an intermolecular pathway on monocarbonyl compounds to yield acyclic alkenes and intramolecular pathway on dicarbonyl compounds to yield cycloalkenes [3]. For several years the McMurry reaction has been confined only to aldehydes and ketones as substrates, until the reaction was extended to the intramolecular coupling of keto esters whose intermediate enol ethers yield cycloalkanones on hydrolysis [4]. We established that the extension of the ketoester cyclization reaction to the closely related acyloxycarbonyl compounds could yield products with the enol ether being part of the heterocyclic ring system. This led to the synthesis of furans and benzofurans [5, 6]. While the titanium mediated synthesis of indoles has received extensive literature coverage [1, 5, 7], only scant attention has been paid to the synthesis of benzofurans and more particularly those from aromatic esters [8]. Since benzofuran ring systems are present in many natural and synthetic products that exhibit pharmacodynamic properties [9], we have embarked on expanding the scope of the reaction using both aliphatic and aromatic ester derivatives.

RESULTS AND DISCUSSION

Cyclization of acyloxyacetophenone derivatives. Compounds **1a-g** were prepared by the acylation of commercially available *o*-hydroxyacetophenone with different carboxylic acid chlorides in the presence of dimethylaminopyridine (DMAP) as catalyst. The reactions lasted on average for two days due to the difficulty in overcoming the strong intramolecular hydrogen bonding in *o*-hydroxyacetophenone. The resulting ketoesters were each treated with 3 equivalents of $TiCl_3$/Zn mixture in refluxing dry THF for four hours. As shown in Scheme 1 and Table 1, substituted benzofurans **2a-g** were obtained in good yield and in the same range. This

*Corresponding author. E-mail: njumbam@wsu.ac.za
#In memory of Mr M.P.I. Yedwa who has tragically passed away in the course of this work.

may be ascribed in part to balanced affinity of titanium for oxygen 'felt' by the intermediate titanium pinacolate generated in each case. Contrary to previous observations [5] compound **2a** was isolated, purified and characterized. On treatment with low-valent titanium, compound **1b** underwent a reduction of the chlorine atom with concomitant cyclization forming product **2a**. The reduction of the chlorine atom thus observed may not be totally unexpected given the report [5] on the low-valent titanium-induced reduction of an iodine atom from an aromatic nucleus.



1 **2**

Scheme 1

Table 1. Titanium-induced formation of substituted benzofurans.

Substrate	R	Product	Yield (%)
1a	CH_3	**2a**	**65**
1b	CH_2Cl	**2a**	**72**
1c	CH_2CH_3	**2c**	**71**
1d	$CH_2CH_2CH_2Ph$	**2d**	**77**
1e	Ph	**2e**	**76**
1f	$PhCH_3$-4	**2f**	**73**
1g	$PhOCH_3$-4	**2g**	**69**

EXPERIMENTAL

General. NMR spectra were recorded on a Varian instrument at 300 MHz (^{1}H) and 75 MHz (^{13}C) in $CDCl_3$ as solvent and TMS as internal standard. Chemical shifts (δ) are given in ppm, coupling constants (*J*) in Hertz. Multiplicity is assigned according to first order interpretation of the spectra. The melting points (Tottoli) are uncorrected. Column chromatography was performed on Merck silica gel (230-240 mesh), TLC on precoated sheets (Merck 5554) using mixtures of hexane/ethyl acetate in varied proportions as eluent. THF was distilled over sodium wire. $TiCl_3$ was purchased from Aldrich.

Starting materials

Preparation of acyloxycarbonyl compounds. To a stirred solution of 2-hydroxyacetophenone (5 g, 36.8 mmol) in CH_2Cl_2 (30 mL) and pyridine (6 g, 75.9 mmol) was added a catalytic amount of dimethylaminopyridine (DMAP) followed by acetyl chloride (2.8 g, 36.0 mmol). The mixture was refluxed for 2 days. The reaction mixture was allowed to cool to ambient temperature and HCl (0.1 M, 30 mL) was added and the aqueous layer extracted twice with CH_2Cl_2 (20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (30 mL) and water (20 mL), then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography using hexane/ethyl acetate (6/1) as eluent giving the anticipated

product **1a** as colourless crystals (5.42 g, 83%). All products listed in Table 1 were obtained as described in this procedure.

Preparation of benzofurans via McMurry-type reactions. To a solution of substrate **1a** (5 g, 28.0 mmol) in dry THF (60 mL) were added $TiCl_3$ (13 g, 84.0 mmol) and zinc powder (5.5 g, 84.0 mmol) under argon. The reaction mixture was refluxed for four hours during which thin layer chromatography indicated complete conversion of the substrate. The mixture was allowed to cool to room temperature and filtered over a plug of silica gel. The filter cake was washed with ethyl acetate (50ml) and the filtrate evaporated *in vacuo* to afford that the crude product that was then purified by column chromatography on silica gel using hexane/ethyl acetate (10/1) as eluent giving pure **2a** as a colourless oil (2.66 g, 65%). All products listed in Table 1 were obtained according to this procedure.

*2,3-Dimethylbenzofuran (**2a**).* Yield 65%, oil; ^{1}H-NMR, δ ($CDCl_3$): 2.09 (s, 3H), 2.31 (s, 3H), 7.16 (s, 2H), 7.35 (m, 2H). ^{13}C-NMR, δ ($CDCl_3$): 7.8, 11.7, 109. 7, 110.4, 118.5, 121.9, 122.9, 130.5, 150.4, 153.8.

*2-(Ethyl)-3-methylbenzofuran (**2c**).* Yield 71%, oil; ^{1}H-NMR, δ ($CDCl_3$): 1.18 (t, 3H, *J* = 7.5 Hz), 2.04 (s, 3H), 2.63 (q, 2H, *J* = 7.5 Hz), 7.24 (m, 2H), 7.45 (m, 2H). ^{13}C-NMR, δ ($CDCl_3$): 8.2, 13.2, 20.1, 109.2, 110.9, 119.1, 122.4, 123.5, 130.9, 154.2, 155.9.

*3-Methyl-2-(3-phenylpropyl)benzofuran (**2d**).* Yield 77%, oil; ^{1}H-NMR, δ ($CDCl_3$): 2.06 (quintet, 2H, J = 7.56 Hz), 2.45 (s, 3H), 2.60 (t, 2H, J = 7.55 Hz), 2.71 (t, 2H, J = 7.42 Hz), 7.02 (dd, 1H, J = 8.24 Hz, 1.10 Hz), 7.22 (m, 6H), 7.43 (dt, 1H, J = 8.10 Hz, 1.66 Hz), 7.72 (dd, 1H, J = 7.83 Hz, 1.65 Hz). ^{13}C-NMR, δ ($CDCl_3$): 7.9, 25.7, 29.6, 35.2, 109.8, 110.5, 118.7, 121.9, 123.1, 125.8, 128.3, 128.4, 128.5, 130.4, 141.8, 153.8.

*2-Phenyl-3-methylbenzofuran (**2e**).* Yield 76 %, m.p.: 34 ^{o}C, ^{1}H-NMR, δ ($CDCl_3$): 2.47 (s, 3H), 7.30-7.50 (m, 7H), 7.81 (dm, 2H). ^{13}C-NMR, δ ($CDCl_3$): 9.9, 111.3, 111.7, 119.7, 122.7, 124.7, 127.1, 128.3, 129.0, 131.6, 131.8, 151.1, 154.2.

*2-(4-Methylphenyl)-3-methylbenzofuran (**2f**).* Yield 73%, m.p.: 108 ^{o}C; ^{1}H-NMR; δ ($CDCl_3$): 2.40 (s, 3H), 2.46 (s, 3H), 7.27 (m, 4H), 7.50 (m, 2H), 7.70 (d, 2H, J = 6.81 Hz). ^{13}C-NMR; δ ($CDCl_3$): 9.5, 21.4, 110.6, 110.9, 119.1, 122.3, 124.1, 126.6, 128.6, 129.3, 131.2, 137.8, 150.9, 153.7.

*2-(4-Methoxyphenyl)-3-methylbenzofuran (**2g**).* Yield 69%, m.p.: 112 ^{o}C; ^{1}H-NMR: δ ($CDCl_3$): 3.14 (s, 3H), 4.55 (s, 3H), 7.77 (d, 2H, J = 8.92 Hz), 8.01 (m, 2H), 8.25 (m, 2H), 8.50 (d, 2H, J = 8.93 Hz). ^{13}C-NMR; δ ($CDCl_3$): 9.28, 55.1, 109.6, 110.7, 114.0, 118.9, 122.2, 123.8, 124.0, 128.0, 131.3, 150.7, 153.5, 159.3.

CONCLUSIONS

The titanium-induced synthesis of benzofurans has proved to be the method of choice for differently substituted ketoesters. The ease of workup by simple filtration of the reaction mixture is a substantial advantage for the process. The only drawback however, is the need for stoichiometric amounts of the titanium reagent. The stable titanium dioxide formed in the process does not allow for *in situ* reduction and regeneration of the low-valent titanium reagent.

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