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Original Scientific Paper

C-Acylation of 2-Methylfuran and Thiophene using *N*-Acylbenzotriazoles*

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Reactions of 2-methylfuran and thiophene with readily available *N*-acylbenzotriazoles (RCOBt, where R = 4-tolyl, 4-methoxyphenyl, benzyl, 4-nitrophenyl, 4-diethylaminophenyl, 2-pyridyl and 1-naphthyl) in the presence of $TiCl_4$ or $ZnBr_2$ produced 2-methyl-4-acylfurans **2a-e** and 2-acylthiophenes **3a-f** in average yields of 54 % and 75 %, respectively. Literature yields for the preparation of the same compounds are significantly lower.

INTRODUCTION

We recently described the C-acylation of pyrroles and indoles using *N*-acylbenzotriazoles in the presence of $TiCl_4$ under mild conditions to give high yields of isomerically pure 2- and 3-acylated pyrroles and 3-acylated indoles.[1] As part of our continuing interest in the chemistry of *N*-acylbenzotriazoles, we describe here analogous C-acylations of 2-methylfuran and thiophene. Some Friedel-Crafts reactions of furans and thiophenes are complicated by the high reactivity of these heterocyclic rings under strong Lewis acid conditions.[2] Syntheses of acylthiophenes have been reported using carboxylic acid chlorides and catalysis with $AlCl_3$[3] and $SnCl_4$.[4] Other reported methods for C-acylation of furans and thiophenes require special reagents and/or give low to moderate yields.[5–9] We now apply readily available *N*-acylbenzotriazoles for C-acylations of 2-methylfuran and thiophene in good to excellent yields in the presence of the relatively mild Lewis acids, $TiCl_4$ or $ZnBr_2$. Our method is particularly useful in cases where the corresponding acyl chlorides are unstable or difficult to prepare, for example, the 4-diethylaminobenzoyl or pyridyl-2-carboxyl derivatives. Yields obtained by our method are compared in Tables I and II with literature yields.

RESULTS AND DISCUSSION

Preparation of N-*Acylbenzotriazoles*

N-Acylbenzotriazoles **1a–f** with aryl or heterocyclic groups (R = 4-tolyl, 4-methoxyphenyl, benzyl, 4-diethylaminophenyl, 2-pyridyl, and 1-naphthyl) were readily prepared in 70–90 % yields from the corresponding carboxylic acids following the earlier reported one-step procedure.[10]

Synthesis of 2-Acyl-5-methylfurans

The C-acylation proceeds with $TiCl_4$ catalysis at 25–35 °C or by heating up to 90 °C in dichloroethane with $ZnBr_2$. As shown in Table I, when 4-methylphenyl- (**1a**), benzyl- (**1c**), or 4-diethylaminophenylacylbenzotriazole (**1d**) were

* Dedicated to Professor Nenad Trinajstić on the occasion of his 65th birthday.
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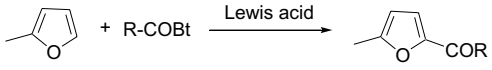
TABLE I. C-Acylation of 2-Methylfuran

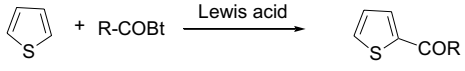


1a-e **2a-e**

Compnd.	R	Lewis acid	temp. °C	time h	yield[a] %	previous work reagent	previous work yield / %
1a	4-$CH_3C_6H_4$	$ZnBr_2$	90	3.5	**2a** (94)[b]	4-$CH_3C_6H_4COCl/AlCl_3$[c]	59
1b	4-$MeOC_6H_4$	$TiCl_4$	22	3.5	**2b** (81)[d]	4-$MeOC_6H_4COCl/AlCl_3$[c]	40
1c	$C_6H_5CH_2$	$ZnBr_2$	90	12	**2c** (68)	$C_6H_5CH_2Br/Pd(PPh_3)_2Cl_2$[e]	81
1d	4-$Et_2NC_6H_4$	$ZnBr_2$	90	3.5	**2d** (98)[f][g]	–	–
1e	2-pyridyl	$TiCl_4$	35	12	**2e** (54)[h][i]	2-Cyanopyridine/n-BuLi[j]	–

[a] Isolated yield; [b] Yield with $TiCl_4$ was 63 %; [c] Ref. 2; [d] Yield with $ZnBr_2$ was 75 %; [e] Coupling with 4-methyl-2-furanyl acid chloride[7]; [f] Yield with $TiCl_4$ was 49 %; [g] m.p. 66–67 °C; [h] Yield with $ZnBr_2$ was 20 %; [i] m.p. 52–53 (lit.[11] m.p. 52–53 °C); [j] Ref. 11.

TABLE II. C-Acylation of Thiophene



1a-f **3a-f**

Compnd.	R	Lewis acid	temp. °C	time h	yield[a] %	previous work reagent	previous work yield / %
1a	4-$CH_3C_6H_4$	$ZnBr_2$	90	3.5	**3a** (89)[b][c]	4-$CH_3C_6H_4COCl$/Stannic chloride[d]	93
1b	4-$MeOC_6H_4$	$TiCl_4$	22	3.5	**3b** (78)[e]	4-$MeOC_6H_4COCl/AlCl_3$[f]	67
1c	$C_6H_5CH_2$	$ZnBr_2$	90	12	**3c** (80)	$C_6H_5CH_2Br/KF$[g]	50
1d	4-$Et_2NC_6H_4$	$ZnBr_2$	90	3.5	**3d** (58)[h]	–	–
1f	1-naphthyl	$ZnBr_2$	90	24	**3f** (97)[i]	α-Naphthoyloxytrichlorosilane/$AlCl_3$[j]	69

[a] Isolated yield; [b] Yield with $TiCl_4$ was 65 %; [c] m.p. 72–74 (lit.[4] m.p. 75–76); [d] Ref. 4; [e] m.p. 73–74 (lit.[12] m.p. 73.5–74.0); [f] Ref. 12; [g] Coupled with 2-thenoyl acid chloride[9]; [h] Yield with $TiCl_4$ was 10 %; [i] Lit.[13] m.p. 69.5–70.0; [j] Ref. 13.

used with $ZnBr_2$, higher yields of the corresponding acylfurans **2a** (84 %), **2c** (68 %) and **2d** (98 %) were obtained as compared to using $TiCl_4$. On the other hand, 4-methoxybenzoyl- (**1b**), or 2-pyridylacylbenzotriazole (**1e**) gave higher yields of **2b** (81 %) and **2e** (54 %) with $TiCl_4$ as compared to using $ZnBr_2$. 2-Acylfurans **2a–e** were characterized by ^1H and ^{13}C NMR spectroscopy and also by elemental analysis for novel **2d**.

Synthesis of 2-Acylthiophenes

Using the method developed for the preparation of 2-acylfurans, the preparation of 2-acylthiophenes was carried out. As shown in Table II, 4-methylphenyl- (**1a**), benzyl- (**1c**), 4-diethylaminophenyl- (**1d**) or 1-naphthyl-acylbenzotriazole (**1f**) in the presence of $ZnBr_2$ gave the acylthiophenes **3a**, **3c**, **3d**, and **3f** in 89, 80, 58, and 97 % yields, respectively. In the presence of $TiCl_4$, (4-methoxyphenyl)(2-thienyl)methanone (**3b**) was obtained in 78 % yield (Table II).

CONCLUSION

We have shown that *N*-acylbenzotriazoles offer a convenient route for direct access to 2-acyl-5-methylfurans and 2-acylthiophenes.

EXPERIMENTAL

General

Dichloromethane was freshly distilled from calcium hydride. $ZnBr_2$ was dried in the oven for 24 hours prior to use. Column chromatography was performed on silica gel (200–425 mesh). Melting points are uncorrected. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ (with TMS for ^1H and chloroform-*d* for ^{13}C as the internal reference) unless specified otherwise.

General Procedure for the Preparation of N*-Acylbenzotriazoles (**1a–f**)*

A mixture of aromatic or heteroaromatic acid (20 mmol), 1-(methylsulfonyl) benzotriazole[10] (20 mmol) and triethyl-

amine (4.0 mL, 28 mmol) were dissolved in THF (120 mL) and the solution was refluxed overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in chloroform. Aqueous work-up gave the crude product that was recrystallized to give pure *N*-acylbenzotriazoles **1a–f.**

*1*H-*1,2,3-Benzotriazol-1-yl(4-methylphenyl)methanone (**1a**)*

Colorless prisms (from ethanol). Yield: 91 %; m.p. 123–124 °C (Lit.[6] m.p. 123–124 °C).

*1*H-*1,2,3-Benzotriazol-1-yl(4-methoxyphenyl)methanone (**1b**)*

Colorless flakes (from ethanol); Yield: 72 %; m.p. 96–97 °C (Lit.[6] m.p. 96–97 °C).

*1-(1*H-*1,2,3-Benzotriazol-1-yl)-2-phenyl-1-ethanone (**1c**)*

White crystals (from CH_2Cl_2/hexanes); Yield: 84 %; m.p. 65–66 °C (Lit.[6] m.p. 66–67 °C).

*1*H-*1,2,3-Benzotriazol-1-yl[4-(diethylamino)phenyl]-methanone (**1d**)*

Yellow crystals (from ethanol/hexanes); Yield: 85 %; m.p. 86–87 °C (Lit.[6] m.p. 86–87 °C).

*1*H-*1,2,3-Benzotriazol-1-yl(2-pyridyl)methanone (**1e**)*

Brown crystals (from $CHCl_3$/hexanes); Yield: 91 %; m.p. 98–100 °C (Lit.[6] m.p. 98–100 °C).

*1*H-*1,2,3-Benzotriazol-1-yl(1-naphthyl)methanone (**1f**)*

White microcrystals (from benzene); Yield: 88 %; m.p. 136–137 °C (Lit.[6] m.p. 136–137 °C).

General Procedure for C-Acylation of 2-Methylfuran and Thiophene Using N-*Acylbenzotriazoles **1a–f***

To the mixture of 2-methylfuran or thiophene (2.5 mmol) and *N*-acylbenzotriazole (2.0 mmol) in CH_2Cl_2 (15 mL), $TiCl_4$ (1.0 M in CH_2Cl_2, 4 mL, 4 mmol) or $ZnBr_2$ (4 mmol) was added and the mixture was stirred for a specified time and temperature (see Tables I–II for details). The reaction was quenched by adding MeOH (2 mL). The solvents were evaporated under reduced pressure and the residue was subjected to column chromatography on silica-gel using hexanes/ethyl acetate (2:1) as the eluent to give the C-acylated furan **2a–e** or thiophene **3a–f**.

*(5-Methyl-2-furyl)(4-methylphenyl)methanone (**2a**)*

Yellow oil; Yield: 94 %. ^{1}H NMR δ/ppm: 2.43 (s, 3H), 2.45 (s, 3H), 6.20 (d, J = 3.3 Hz, 1H), 7.10 (d, J = 3.3 Hz, 1H), 7.28 (d, J = 7.9 Hz, 2H), 7.84 (d, J = 7.9 Hz, 2H). ^{13}C NMR δ/ppm: 14.1, 21.6, 108.9, 122.4, 129.0, 129.2, 134.9, 142.9, 151.0, 158.4, 181.9.

*(4-Methoxyphenyl)(5-methyl-2-furyl)methanone (**2b**)*

Yellow oil; Yield: 81 %. ^{1}H NMR δ/ppm: 2.45 (s, 3H), 3.88 (s, 3H), 6.20 (dd, J = 0.8, 3.4 Hz, 1H), 6.95–6.99 (m, 2H), 7.10 (d, J = 3.4 Hz, 1H), 7.95–7.99 (m, 2H). ^{13}C NMR δ/ppm: 14.1, 55.4, 108.8, 113.6, 121.8, 130.2, 131.4, 151.2, 158.0, 163.0, 180.8.

*2-Phenyl-1-(5-methyl-2-furyl)-1-ethanone (**2c**)*

Yellow oil; Yield: 68 %. ^{1}H NMR δ/ppm: 2.39 (s, 3H), 4.05 (s, 2H), 6.14 (d, J = 3.5 Hz, 1H), 7.13 (d, J = 3.5 Hz, 1H), 7.20–7.32 (m, 5H). ^{13}C NMR δ/ppm 14.0, 45.1, 109.1, 120.0, 126.8, 128.6, 129.4, 134.5, 151.0, 158.0, 185.8.

*[4-(Diethylamino)phenyl](5-methyl-2-furyl)methanone (**2d**)*

Yellow needles; Yield: 98 %; m.p. 66–67 °C. ^{1}H NMR δ/ppm: 1.21 (t, J = 7.0 Hz, 6H), 2.44 (s, 3H), 3.43 (q, J = 7.0 Hz, 4H), 6.17 (d, J = 2.6 Hz, 1H), 6.67 (d, J = 9.1 Hz, 2H), 7.08 (d, J = 3.3 Hz, 1H), 7.96 (d, J = 9.1 Hz, 2H). ^{13}C NMR δ/ppm: 12.5, 14.1, 44.5, 108.4, 110.2, 120.3, 124.1, 131.9, 150.9, 151.8, 156.8, 180.2.

Anal. Calcd for $C_{16}H_{19}NO_2$ (M_r = 257.34): C 74.68, H 7.44, N 5.44 %; found: C 74.81, H 7.56, N 5.42 %.

*(5-Methyl-2-furyl)(2-pyridinyl)methanone (**2e**)*

Brown solid; Yield: 54 %; m.p. 52–53 °C (Lit.[11] m.p. 52–53 °C). ^{1}H NMR δ/ppm: 2.46 (s, 3H), 6.25 (d, J = 3.5 Hz, 1H), 7.44–7.48 (m, 1H), 7.83–7.89 (m, 1H), 7.97 (d, J = 3.5 Hz, 1H), 8.14 (d, J = 7.8 Hz, 1H), 8.70 (d, J = 4.2 Hz, 1H). ^{13}C NMR δ/ppm: 14.1, 109.4, 123.7, 126.3, 126.4, 136.8, 148.4, 150.0, 154.2, 159.2, 178.4.

*(4-Methylphenyl)(2-thienyl)methanone (**3a**)*

White solid; Yield: 89 %; m.p. 72–74 °C (Lit.[4] m.p. 75–76 °C). ^{1}H NMR δ/ppm: 2.41 (s, 3H), 7.11–7.14 (m, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 3.7 Hz, 1H), 7.67 (d, J = 4.8 Hz, 1H), 7.77 (d, J = 8.0 Hz, 2H). ^{13}C NMR δ/ppm: 21.4, 127.7, 128.9, 129.2, 133.7, 134.3, 135.2, 142.9, 143.6, 187.7.

*(4-Methoxyphenyl)(2-thienyl)methanone (**3b**)*

Brown solid; Yield: 78 %; m.p. 73–74 °C (Lit.[12] m.p. 73.4–74.0 °C). ^{1}H NMR δ/ppm: 3.89 (s, 3H), 6.98 (d, J = 8.9 Hz, 2H), 7.15 (dd, J = 3.9, 4.8 Hz, 1H), 7.63–7.64 (m, 1H), 7.68 (dd, J = 0.8, 4.9 Hz, 1H), 7.91 (d, J = 8.9 Hz, 2H). ^{13}C NMR δ/ppm: 55.4, 113.6, 127.7, 130.6, 131.5, 133.4, 134.0, 143.7, 163.0, 186.8.

*2-Phenyl-1-(2-thienyl)-1-ethanone (**3c**)*

Gummy solid; Yield: 80 %. ^{1}H NMR δ/ppm: 4.16 (s, 2H), 7.08 (t, J = 4.4 Hz, 1H), 7.22–7.33 (m, 5H), 7.58 (d, J = 5.0 Hz, 1H), 7.74 (d, J = 3.7 Hz, 1H). ^{13}C NMR δ/ppm: 46.2, 126.9, 128.1, 128.6, 129.3, 132.6, 134.0, 134.2, 143.7, 190.3.

*[4-(Diethylamino)phenyl](2-thienyl)methanone (**3d**)*

Yellowish gummy solid; Yield: 58 %. ^{1}H NMR δ/ppm: 1.22 (t, J = 7.0 Hz, 6H), 3.44 (q, J = 7.0 Hz, 4H), 6.70 (d, J = 9.1 Hz, 2H), 7.13 (dd, J = 3.7, 4.8 Hz, 1H), 7.61 (dd, J = 0.9, 4.9 Hz, 1H), 7.65 (dd, J = 0.9, 3.7 Hz, 1H), 7.89 (d, J = 9.1 Hz, 2H). ^{13}C NMR δ/ppm: 12.5, 44.5, 110.1, 124.4, 127.4, 131.9, 132.2, 132.7, 144.5, 151.0, 185.8.

Anal. Calcd. For $C_{15}H_{17}NOS$ (M_r = 259.37): C 69.46, H 6.61, N 5.40 %; found: C 69.03, H 7.70, N 5.32 %.

*1-Naphthyl(2-thienyl)methanone (**3f**)*

Yellow oil[13]; Yield: 97 %. ^{1}H NMR δ/ppm: 7.10 (t, J = 3.8 Hz, 1H), 7.46–7.56 (m, 4H), 7.71–7.75 (m, 2H), 7.89–7.92 (m, 1H), 7.99 (d, J = 8.3 Hz, 1H), 8.15–8.18 (m, 1H). ^{13}C NMR δ/ppm: 124.2, 125.4, 126.5, 127.0, 127.2, 128.1, 128.3, 130.5, 131.2, 133.7, 135.0, 135.6, 136.1, 145.3, 189.6.

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SAŽETAK

C-acilacija 2-metilfurana i tiofena pomoću *N*-acilbenzotriazola

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Reakcije 2-metilfurana i tiofena s već pripravljenim *N*-acilbenzotriazolima (RCOBt, gdje je R = 4-tolil, 4-metoksiofenil, benzil, 4-nitrofenil, 4-dietilaminofenil, 2-piridil i 1-naftil) u prisutnosti $TiCl_4$ ili $ZnBr_2$ daju 2-metil-4-acilfurane **2a-e** i 2-aciltiofene **3a-f** u prosječnom iskorištenju od 54 % odnosno 75 %. Iskorištenja dana u literaturi za pripravu istih spojeva značajno su manja.