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Investigación

Preparation of *N*-Acylbenzotriazole Derivatives of Dicarboxylic Acids

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Dedicated to the memory of Dr Raymundo Cruz Almanza†

Abstract. *N*-Acylbenzotriazole derivatives of dicarboxylic acids have been prepared by convenient methods.
Key words: *N*-acylbenzotriazole, dicarboxylic acids, synthesis.

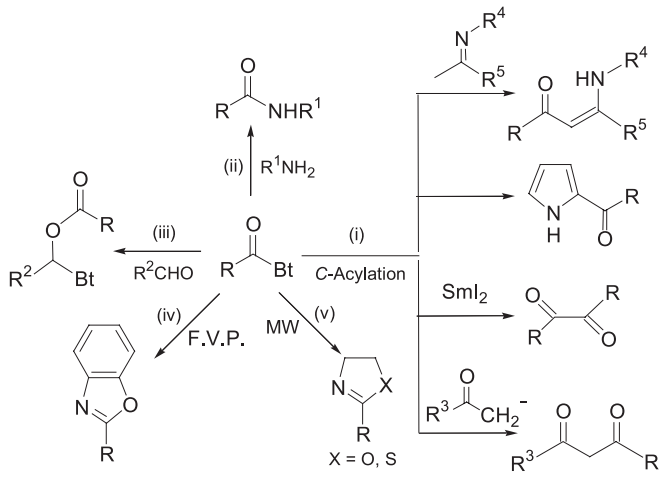
Resumen. Se describe la preparación de *N*-acilbenzotriazol derivado de ácidos carboxílicos.
Palabras clave: *N*-acilbenzotriazol, ácidos dicarboxílicos, síntesis.

Introduction

N-Acylbenzotriazoles are important: (i) as *C*-acylation reagents for the synthesis of 1,3- [1a] and 1,2-diketones, [1b] for the conversion of imines into enaminones, [1c] and for the regiospecific acylation of heterocycles; [1d,e] (ii) as neutral *N*-acylation reagents including formylation [2a] and trifluoroacylation; [2b] for the preparation of amides [3a-c] and peptides; [3d] (iii) as *O*-acylation reagents in additions to aldehydes to give esters; [4] (iv) in the preparation of benzoxazoles by flash vacuum pyrolysis (FVP); [5] and (v) in the syntheses of oxazolines and thiazolines under microwave irradiation (MW) [6] (Scheme 1).

Use of *N*-acylbenzotriazoles avoids racemization, [3b,d] assures regiospecificity [1d,e], and generally provides products in high yields. Unlike acid chlorides, *N*-acylbenzotriazoles are stable crystalline compounds that can be stored at room temperature without decomposition. Literature reports on the applications of *N*-acylbenzotriazoles in the last decade show a wide variety of organic transformations in which they have been used advantageously in place of acid chlorides. They are also the reagents of choice when the corresponding acid chlorides are unstable or difficult to isolate, for example RCOCl, with R = 4-diethylaminophenyl, 2-pyridyl, 2-indolyl or 2-pyrrolyl etc.

We reported a mild one-pot procedure for efficient conversion of carboxylic acids into the corresponding *N*-acylbenzotriazoles [7] that has several advantages over the previous methods [3a,8]. We recently found that these procedures require further modifications for the preparation of *N*-acylbenzotriazoles of important dicarboxylic acids which have low solubility; the present work involves the preparation of this class of derivatives.



Scheme 1

Results and Discussion

Preparation of *N*-Acylbenzotriazole Derivatives. Reaction of 1 equivalent of glutaric acid, 8 equivalents of benzotriazole and 2 equivalents of $SOCl_2$ in CH_2Cl_2 for 2 h according to the previous procedure [7] gave a very low yield of the corresponding *N*-acylbenzotriazole derivative **1a**. Increasing the reaction time to 48 h gave **1a** in 60% yield but a substantial amount of the diacid remained undissolved. Changing the solvent to THF gave **1a** in the same yield in 48 h but the diacid appeared to be more soluble in THF as compared to CH_2Cl_2. Interestingly, using THF as the solvent, the reaction of diglycolic acid, benzotriazole and $SOCl_2$ gave the corresponding *N*-acylbenzotriazole derivative **1b** in 98% yield in 24 h. Similar reactions with thiodiglycolic acid and *trans*-1,4-cyclohexanedicarboxylic acid gave *N*-acylbenzotriazoles **1c** and **1d** in 87% and 16% yields, respectively. Using this procedure, reactions of methylmalonic acid, phenylmalonic acid, diphenic acid and 3,3'-dithiodipropionic acid each gave the corresponding *N*-acylbenzotriazoles **1e** (80%), **1f** (82%), **1g** (94%) and **1h** (98%), respectively. However, derivative **1i** from 3,3-

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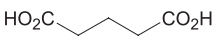
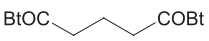
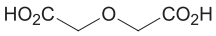
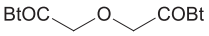
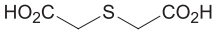
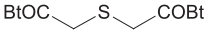
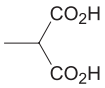
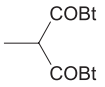
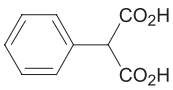
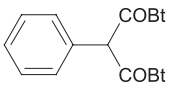
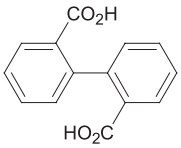
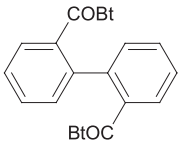
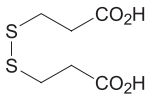
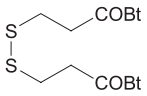
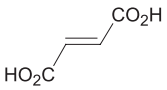
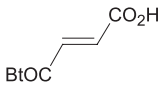
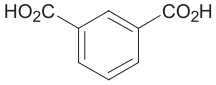
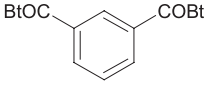
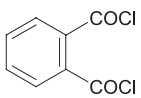
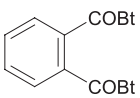
dimethylglutaric acid was obtained in a low yield (40%), and the reaction of fumaric acid resulted in mono-derivatization to give (2*E*)-4-1*H*-1,2,3-benzotriazol-1-yl)-4-oxobut-2-enoic acid (**1j**) in 65% yield (Table 1).

The above modification in the one pot procedure did not give satisfactory yields of *N*-acylbenzotriazole derivatives in the case of benzenedicarboxylic acids; these derivatives were prepared by the reaction of 1-(methylsulfonyl)benzotriazole [3a] with a salt of the carboxylic acid. Thus, reaction of 1 equivalent of 1,4-benzenedicarboxylic acid with 2 equivalents of 1-(methylsulfonyl)benzotriazole in presence of 2 equivalents of triethylamine in refluxing THF for 24 h gave the corresponding *N*-acylbenzotriazole derivative **1k** in 80% yield. Similarly, reaction of 1,3-benzenedicarboxylic acid gave **1l** in

Table 1. Preparation of *N*-acylbenzotriazole derivatives **1a**–**m**.

Entry	Dicarboxylic acid	Method [a]	Time (h)	Product (**1a–m**)		Yield (%) [b]
1		A	48		**1a**	60
2		A	24		**1b**	98
3		A	24		**1c**	87
4		A	24		**1d**	16
5		A	24		**1e**	80
6		A	24		**1f**	82
7		A	36		**1g**	94
8		A	24		**1h**	98
9		A	24		**1i**	40
10		A	48		**1j**	65
11		B	24		**1k**	80
12		B	24		**1l**	41
13		C	2		**1m**	59

[a]Method A: $SOCl_2$, BtH, THF, 25ºC; method B: $BtSO_2Me$, Et_3N, THF, 60ºC; method C: BtH, THF, 25ºC.
[b]Isolated yield.

41% yield. The *N*-acylbenzotriazole derivative of 1,2-benzenedicarboxylic acid, **1m** was prepared by the reaction of commercially available phthaloyl chloride with benzotriazole at 25 °C in 2 h. (Table 1). All of the *N*-acylbenzotriazole derivatives prepared except **1b** and **1k-l** are novel compounds and have been fully characterized by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis.

Experimental

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, with tetramethylsilane (TMS) as an internal standard. Solvents were distilled by standard methods. Reagents obtained commercially were used without further purification.

General procedure:
Method A (for 1a-1j): To a solution of BtH (9.6 g, 80 mmol) in THF (100 ml), $SOCl_2$ (1.5 mL, 20 mmol) was added dropwise with stirring at room temperature. After 30 min, a solution of dicarboxylic acid (10 mmol) in THF (50 mL) was added. After 24-48 h (Table 1), the solid was filtered and washed with THF (50 mL). The solvent was removed under vacuum from the combined filtrate. To the residue, $CHCl_3$ (150 mL) was added; the mixture was washed with water (30 ml) and saturated Na_2CO_3 (3 × 30 mL). The organic layer was dried over anhydrous Na_2SO_4, then it was filtered and the solvent was evaporated under vacuum to obtain a solid, which was recrystallized from an appropriate solvent or solvent mixture to obtain the pure product.

1,5-Di(1*H*-1,2,3-benzotriazol-1-yl)-1,5-pentanedione (1a). Colorless prisms; mp 188-189 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.55 (quintet, *J* = 7.2 Hz, 2H), 3.70 (t, *J* = 7.2 Hz, 4H), 7.52 (dd, *J* = 8.1, 6.9 Hz, 2H), 7.67 (dd, *J* = 8.1 Hz, 6.9 Hz, 2H), 8.13 (d, *J* = 8.4 Hz, 2H), 8.29 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.8, 34.7, 114.6, 120.4, 126.5, 130.7, 131.3, 146.4, 171.8. Anal. Calcd for $C_{17}H_{14}N_6O_2$ requires C, 61.07; H, 4.22; N, 25.14. Found: C, 60.98; H, 4.05; N, 25.22 %.

1-(1*H*-1,2,3-Benzotriazol-1-yl)-2-[2-(1*H*-1,2,3-benzotriazol-1-yl)-2-oxoethoxy]-1-ethanone (1b).[9] Colorless plates; mp 142-144 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.56 (s, 4H), 7.54 (dd, *J* = 8.1, 6.9 Hz, 2H), 7.70 (dd, *J* = 8.1, 6.9 Hz, 2H), 8.13 (d, *J* = 8.1 Hz, 2H), 8.29 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.3, 114.2, 120.6, 126.8, 131.0, 131.1, 146.0, 168.2. Anal. Calcd for $C_{16}H_{12}N_6O_3$ requires C, 57.14; H, 3.60; N, 24.99. Found: C, 57.45; H, 3.49; N, 25.00 %.

1-(1*H*-1,2,3-Benzotriazol-1-yl)-2-{[2-(1*H*-1,2,3-benzotriazol-1-yl)-2-oxoethyl]sulfanyl}-1-ethanone (1c). Pale yellow prisms; mp 150-160 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.58 (s, 4H), 7.54 (dd, *J* = 8.1, 6.9 Hz, 2H), 7.68 (dd, *J* = 8.1, 6.9 Hz, 2H), 8.13 (d, *J* = 8.1 Hz, 2H), 8.23 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.8, 114.5, 120.6, 126.7, 131.0, 131.3, 146.5, 167.9. Anal. Calcd for $C_{16}H_{12}N_6O_2S$ requires C, 54.54; H, 3.43; N, 23.85. Found: C, 54.75; H, 3.30; N, 23.78 %.

***trans*-1*H*-1,2,3-Benzotriazol-1-yl[4-(1*H*-1,2,3-benzotriazol-1-ylcarbonyl)cyclohexyl]methanone (1d).** White flakes; mp 247 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.94-2.08 (m, 4H), 2.35-2.41 (m, 4H), 4.05 (m, 2H), 7.53 (ddd, *J* = 8.1, 6.9, 0.8 Hz, 2H), 7.69 (ddd, *J* = 8.4, 6.9, 0.8 Hz, 2H), 8.15 (d, *J* = 8.1 Hz, 2H), 8.33 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.3, 42.8, 114.8, 120.4, 126.5, 130.7, 131.4, 146.4, 174.9. Anal. Calcd for $C_{20}H_{18}N_6O_2$ requires C, 64.16; H, 4.85; N, 22.45. Found: C, 64.41; H, 4.75; N, 22.12 %.

1,3-Di(1*H*-1,2,3-benzotriazol-1-yl)-2-methyl-1,3-propanedione (1e). Colorless needles; mp 158.0-160.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.98 (d, *J* = 7.2 Hz, 3H), 6.25 (q, *J* = 7.2 Hz, 1H), 7.54 (dd, *J* = 8.1, 6.9 Hz, 2H), 7.70 (dd, *J* = 8.4, 6.9 Hz, 2H), 8.13 (d, *J* = 8.4 Hz, 2H), 8.28 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 48.1, 114.5, 120.6, 126.8, 131.1, 131.3, 146.6, 168.7. Anal. Calcd for $C_{16}H_{12}N_6O_2$ requires C, 60.00; H, 3.78; N, 26.44. Found: C, 59.95; H, 3.54; N, 26.28 %.

1,3-Di(1*H*-1,2,3-benzotriazol-1-yl)-2-phenyl-1,3-propanedione (1f). Colorless plates; mp 193-195 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40-7.47 (m, 3H), 7.52 (dd, *J* = 8.1, 6.9 Hz, 2H), 7.63 (s, 1H), 7.67 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.75 (d, *J* = 7.2 Hz, 2H), 8.11 (d, *J* = 8.1 Hz, 2H), 8.26 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 58.8, 114.5, 120.7, 126.9, 129.3, 129.5, 130.0, 130.7, 131.1, 131.4, 146.6, 166.3. Anal. Calcd for $C_{21}H_{14}N_6O_2$ requires C, 65.96; H, 3.69; N, 21.98. Found: C, 65.99; H, 3.57; N, 22.02 %.

1*H*-1,2,3-Benzotriazol-1-yl[2'-(1*H*-1,2,3-benzotriazol-1-ylcarbonyl)[1,1'-biphenyl]-2-yl]meth- anone (1g). Colorless prisms; mp 223-225 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41-7.50 (m, 4H), 7.54-7.60 (m, 4H), 7.63-7.67 (m, 4H), 7.99 (d, *J* = 7.8 Hz, 2H), 8.16 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 114.9, 120.0, 126.4, 127.6, 130.5, 130.6, 131.3, 131.6, 131.9, 132.2, 140.6, 145.9, 167.2. Anal. Calcd for $C_{26}H_{16}N_6O_2$ requires C, 70.26; H, 3.63; N, 18.91. Found: C, 70.18; H, 3.50; N, 18.93 %.

1-(1*H*-1,2,3-Benzotriazol-1-yl)-3-{[3-(1*H*-1,2,3-benzotriazol-1-yl)-3-oxopropyl]disulfanyl}-1-propanone (1h). Colorless prisms; mp 104-105 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.27 (t, *J* = 6.9 Hz, 4H), 3.90 (t, *J* = 6.9 Hz, 4H), 7.50 (dd, *J* = 8.1, 6.9 Hz, 2H), 7.64 (dd, *J* = 8.1, 7.2 Hz, 2H), 8.10 (d, *J* = 8.4 Hz, 2H), 8.25 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.2, 35.6, 114.5, 120.4, 126.4, 130.7, 131.1, 146.3, 170.6. Anal. Calcd for $C_{18}H_{16}N_6O_2S_2$ requires C, 52.41; H, 3.91; N, 20.37. Found: C, 52.46; H, 3.78; N, 20.28 %.

1,5-Di(1*H*-1,2,3-benzotriazol-1-yl)-3,3-dimethyl-1,5-pentanedione (1i). Colorless prisms; mp 98-100 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 6H), 3.84 (s, 4H), 7.50 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.64 (dd, *J* = 7.8, 7.5 Hz, 2H), 8.11 (d, *J* = 8.4 Hz, 2H), 8.27 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.6, 34.1, 44.4, 114.6, 120.2, 126.2, 130.4, 131.1, 146.3, 171.0. Anal. Calcd for $C_{19}H_{18}N_6O_2$ requires C, 62.97; H, 5.01; N, 23.19. Found: C, 63.01; H, 5.03; N, 23.37 %.

(*E*)-4-(1*H*-1,2,3-Benzotriazol-1-yl)-4-oxo-2-butenoic acid (1j). Colorless needles; mp 183 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.05 (d, *J* = 15.6 Hz, 1H), 7.63 (dd, *J* = 8.2, 6.9 Hz, 1H), 7.80 (dd, *J* = 8.2, 6.9 Hz, 1H), 8.12 (d, *J* = 15.6 Hz, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 8.26 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 114.2, 120.3, 127.0, 130.6, 131.1, 131.2, 136.4, 145.7, 162.3, 165.6. Anal. Calcd for $C_{10}H_7N_3O_3$ requires C, 55.30; H, 3.25; N, 19.35. Found: C, 55.30; H, 3.11; N, 19.38 %.

Method B (for 1k-1l):
A mixture of 1-(methylsulfonyl)-1*H*-benzotriazole (3.94 g, 20 mmol), dicarboxylic acid (10 mmol) and triethylamine (3.0 g, 30 mmol) in THF (40 ml) was heated to reflux for 24 h. Then the solvent was evaporated under vacuum and the residue was dissolved in chloroform. The organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent under vacuum gave the crude product, which was purified by column chromatography (silica gel) to obtain the pure product.

1*H*-1,2,3-Benzotriazol-1-yl[4-(1*H*-1,2,3-benzotriazol-1-ylcarbonyl)phenyl]methanone (1k).
White micro crystals; mp 232-234 ºC [lit. [10] mp 238-242 ºC]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (dd, *J* = 8.1, 6.9 Hz, 2H), 7.77 (dd, *J* = 8.2, 6.9 Hz, 2H), 8.21 (d, *J* = 8.2 Hz, 2H), 8.42 (s, 4H), 8.45 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 114.8, 120.4, 126.7, 130.8, 131.4, 132.1, 135.6, 145.9, 165.8.

1*H*-1,2,3-Benzotriazol-1-yl[3-(1*H*-1,2,3-benzotriazol-1-ylcarbonyl)phenyl]methanone (1l). White micro crystals; mp189-191 ºC [lit. [10] mp 199-201 ºC]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59 (dd, *J* = 8.2, 6.9 Hz, 2H), 7.76 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.84 (t, *J* = 7.8 Hz, 1H), 8.19 (d, *J* = 8.2 Hz, 2H), 8.44 (d, *J* = 8.3 Hz, 2H), 8.56 (dd, *J* = 7.8, 1.7 Hz, 2H), 9.07 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 114.8, 120.3, 126.6, 128.7, 130.7, 132.0, 132.2, 135.0, 136.2, 145.8, 165.5.

Method C (for 1m):
To a solution of benzotriazole (4.88 g, 41 mmol) in dry THF (20 mL), phthaloyl chloride (2.03 g, 10 mmol) was added dropwise with stirring. After 2 h, the precipitate was filtered. The solvent was evaporated under vacuum to obtain the crude product, which was recrystallized from chloroform/hexane to obtain 1*H*-1,2,3-benzotriazol-1-yl[2-(1*H*-1,2,3-benzotriazol-1-ylcarbonyl)phenyl]methanone (2.17 g, 59%).

1*H*-1,2,3-Benzotriazol-1-yl[2-(1*H*-1,2,3-benzotriazol-1-ylcarbonyl)phenyl]methanone (1m). [11] White micro crystals; mp 167-169 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49 (ddd, *J* = 8.4, 6.9, 0.9 Hz, 2H), 7.63 (ddd, *J* = 8.2, 6.9, 0.9 Hz, 2H), 7.82-7.88 (m, 2H), 8.07 (d, *J* = 8.2 Hz, 2H), 8.12-8.17 (m, 2H), 8.22 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 114.5, 120.3, 126.5, 130.6, 131.5, 131.6, 132.1, 133.9, 145.9, 166.4.

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