Efficient Conversion of Carboxylic Acids into N-Acylbenzotriazoles

Alan R. Katritzky,* Yuming Zhang, Sandeep K. Singh

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA
Fax +1(352)3929199; E-mail: Katritzky@chem.ufl.edu

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Abstract: An improved one-pot procedure for the preparation of N-acetylbenzotriazoles involves mild reaction conditions and allows the preparation of several derivatives not accessible by the previously reported methods.

Key words: N-acetylbenzotriazole, carboxylic acid, benzotriazole, thionyl chloride, acylation reagent

N-Acetylbenzotriazoles show great potential in organic synthesis as activated derivatives of carboxylic acids. N-Acetylbenzotriazoles have been used (i) as neutral N-acylation agents for the preparation of primary, secondary and tertiary amides1a–c and peptides;1d including N-formylation4a and N-trifluoroacetylation;2b (ii) for O-acylation in additions to aldehydes to give esters;3a (iii) for C-acylation reagents for the synthesis of 1,3- and 1,2-diketones,4b for the conversion of imines into enamines,4c and for the regiospecific acylation of pyrroles and indoles;4d and (iv) in the preparation of benzoxazoles by flash vacuum pyrolysis (Scheme 1).5

Scheme 1

N-Acetylbenzotriazoles have usually been prepared by two routes: (a) heating benzotriazole with an acid chloride;6 (b) reaction of 1-(methylsulfonyl)benzotriazole (1) with a carboxylic acid salt.1e The second method is advantageous in providing RCOBt in one step from acid and generally gives excellent yields; however, we have encountered problems with some base-sensitive, olefinic, acetylenic and dicarboxylic acids. Herein, we describe a mild and general procedure for access to N-acetylbenzotriazoles.

Our new procedure involves reaction of 1 equivalent of a carboxylic acid with 4 equivalents of benzotriazole and 1 equivalent of thionyl chloride in CH2Cl2 at room temperature for 2 hours. Success with a wide range of carboxylic acids demonstrates the general applicability of this procedure (Table 1). Aliphatic short chain propionic acid, long chain palmitic acid, and alicyclic 1-phenyl-cyclopropane carboxylic acid gave the corresponding N-acetylbenzotriazoles in 89–92% yields. Benzoic acid was converted into N-benzoylbenzotriazole 2d in 93% yield. 4-Hydroxybenzoic acid also gave p-hydroxybenzoylacetylbenzotriazole 2e. As heterocyclic examples, 2-thiophene-carboxylic acid and indole-2-carboxylic acid reacted with thionyl chloride and benzotriazole to give the desired product 2f and 2g (97% yield in each case).

Using the new procedure, methacrylic acid and crotonic acid were each successfully converted into the corresponding N-acetylbenzotriazoles 2h and 2i in 83% and 86% yields, respectively. Similarly, 1-(1H-1,2,3-benzotriazol-1-yl)-2-propyn-1-one (2k) was obtained in 83% yield. Phenylpropionic acid gave a 92% yield of 2l.

α-Halocarboxylic acids have now also been directly converted into N-acetylbenzotriazole derivatives 2m–o in excellent yields. Carboxylic acids substituted at α-position by methoxy, phenylthio or o xo groups also gave high yields of the corresponding N-acetylbenzotriazole derivatives 2p (96%), 2q (90%) and 2r (72%). Bis(N-acetylbenzotriazole) derivatives 2s–u with potential uses in the synthesis of polymers or macromolecules, were also prepared from the corresponding dicarboxylic acids in good yields. The unsymmetrical dicarboxylic acid monoester, mono benzotriazole derivative 2v was also prepared by this method; 2v can undergo regioselective functional group transformations.

Interestingly, furanones 3w and 3w’ were obtained in 53% and 19% yields, respectively from levulinic acid, presumably due to intramolecular O-acylation from intermediate N-acetylbenzotriazole 2w (Scheme 2). In conclusion, a mild one-pot general procedure has been devised for the efficient conversion of carboxylic acids into the corresponding N-acetylbenzotriazoles.
Preparation of N-Acylbenzotriazoles 2a–w; General Procedure

To a solution of benzotriazole (4.8 g, 40 mmol) in CH₂Cl₂ (50 mL) was added SOCl₂ (1.2 g, 10 mmol) at 25 °C with stirring. After 0.5 h, carboxylic acid (10 mmol) was added in one portion and stirring was continued for 2 h. The white precipitate was filtered off and washed with CH₂Cl₂ (2 × 50 mL). The combined organic solution was washed with aq 2 N NaOH (3 × 60 mL), dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel; hexanes–EtOAc, 4:1).

In the case of 2w, the organic layer was washed with 6 N HCl (3 × 60 mL), dried over Na₂SO₄ and the solvent was removed under reduced pressure to give crude unstable product 2w.

1-(1H,1,2,3-Benzotriazol-1-yl)-1-propanone (2a)

Yield: 92%; mp 73–74 °C (Lit.⁶ mp 80–82 °C).

1H NMR: δ = 8.30 (d, J = 8.2 Hz, 1 H), 8.12 (d, J = 8.2 Hz, 1 H), 7.68–7.63 (m, 1 H), 7.51 (d, J = 8.1, 1.0 Hz, 1 H), 3.47 (q, J = 7.4 Hz, 2 H), 1.43 (t, J = 7.4 Hz, 3 H).

13C NMR: δ = 173.3, 146.1, 131.1, 130.3, 126.0, 120.1, 114.3, 29.1, 8.3.


1H,1,2,3-Benzotriazol-1-yl(1-phenylcyclopropyl)methanone (2b)

Yield: 92%; mp 73–74 °C.

1H NMR: δ = 8.21 (d, J = 8.2 Hz, 1 H), 8.00 (d, J = 8.2 Hz, 1 H), 7.59–7.50 (m, 1 H), 7.43–7.37 (m, 1 H), 7.30–7.17 (m, 3 H), 1.88–1.84 (m, 2 H), 1.55–1.51 (m, 2 H).

13C NMR: δ = 171.2, 145.4, 139.0, 131.5, 130.0, 129.1, 128.4, 127.3, 125.8, 119.8, 114.3, 32.7, 14.8.

Anal. Calcd for C₁₆H₁₃N₃O: C, 73.11; H, 4.89.

1H,1,2,3-Benzotriazol-1-yl(phenyl)methanone (2d)


1H NMR: δ = 8.39 (d, J = 8.4 Hz, 1 H), 8.23–8.20 (m, 2 H), 7.73–7.67 (m, 1 H), 7.50–7.47 (m, 1 H), 3.42 (t, J = 7.6 Hz, 2 H), 1.98–1.84 (m, 2 H), 1.51–1.26 (m, 24 H), 0.88 (t, J = 6.3 Hz, 3 H).

13C NMR: δ = 166.7, 145.8, 133.6, 132.3, 131.7, 131.5, 130.3, 128.4, 126.3, 120.2, 114.8.

1H,1,2,3-Benzotriazol-1-yl(4-hydroxylphenyl)methanone (2e)

Yield: 84%; mp 199–200 °C.

Materials were obtained from commercial suppliers and used without further purification. CH₂Cl₂ was distilled from CaH₂. 1H (300 MHz) and 13C NMR (75 MHz) spectra were recorded in CDCl₃ with TMS or CDCl₃, as internal reference. Elemental analyses were performed on a Carlo Erba-1106 instrument. HRMS were measured on a Kratos/AEI-MS 30 mass spectrometer.
Yield: 97%; mp 213–215 °C.

Yield: 96%; mp 151–152 °C (Lit. mp 158–159 °C).

3H NMR: δ = 156.2, 162.9, 145.0, 134.4, 131.9, 130.2, 126.2, 121.1, 119.8, 115.3, 114.3.


1-(1H,1,2,3-Benzotriazol-1-yl)-2-thienyl)methanone (2f)
Yield: 83%; mp 63–64 °C.

1-(1H,1,2,3-Benzotriazol-1-yl)-2-propyn-1-one (2k)
Yield: 92%; mp 124–125 °C.

1-(1H,1,2,3-Benzotriazol-1-yl)-2-propyn-1-one (2l)
Yield: 90%; mp 63–64 °C.

1-(1H,1,2,3-Benzotriazol-1-yl)-2-methyl-2-propen-1-one (2h)
Yield: 86%; mp 87–88 °C.

1-(1H,1,2,3-Benzotriazol-1-yl)-2,2-dichloro-1-ethanone (2o)
Yield: 86%; mp 103–104 °C.

1-(1H,1,2,3-Benzotriazol-1-yl)-2,2-dichloro-1-ethanone (2p)
Yield: 96%; mp 63–64 °C.

1-(1H,1,2,3-Benzotriazol-1-yl)-2-phenyl-1,2-ethanedione (2r)
Yield: 96%; mp 124–125 °C.

1-(1H,1,2,3-Benzotriazol-1-yl)-2-phenyl-1,2-ethanedione (2q)
Yield: 72%; mp 72–73 °C.
Yield: 75%; mp 170–171 °C.

Hz, 4 H), 2.00–1.80 (m, 4 H), 1.56–1.20 (m, 28 H).

Yield: 82%; mp 174–175 °C.

one (2s)

3.76 (s, 3 H), 2.94 (t, J = 6.3 Hz, 2 H), 2.73–2.61 (m, 2 H).

Yield: 87%; mp 51–52 °C.

Methyl 4-(1,2,3-benzotriazol-2-yl)-5-methylidihydro-2(3H)-furanone (3v)

Yield: 19%; mp 95–96 °C.

References


