A Novel Synthesis of 5-Acylaminooxazoles

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Received May 22, 1995

1,2-Diacylamino-1,2-di(benzotriazol-1-yl)ethanes **2**, easily prepared from the condensation of 1,2-di(benzotriazol-1-yl)ethane-1,2-diol (**1**) and primary amides, were converted to 5-acylaminooxazoles in good to moderate yields *via* intramolecular cyclization upon treatment with sodium hydride.

J. Heterocyclic Chem., **32**, 1651 (1995).

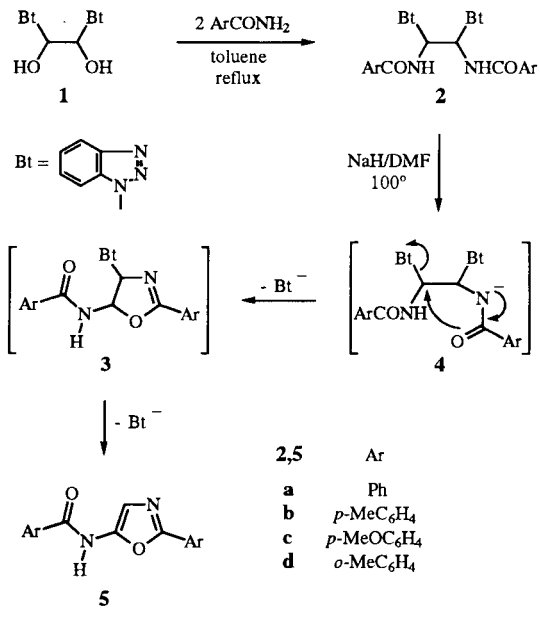
Oxazoles have attracted renewed attention owing to their usefulness as azadienes in the Diels-Alder reaction for the preparation of pyridine and furan derivatives [1,2], and their presence in natural occurring products such as alkaloids and macrocyclic antibiotics [3,4]. In particular, 5-acylaminooxazoles have recently shown their usefulness as masked dipeptide equivalents in the preparation of cyclopeptide alkaloids [5,6]. As a consequence, new methodology for the construction of the oxazole system is of considerable significance [7,8].

Few synthetic approaches to 5-acylaminooxazoles have been reported. The pioneering work of Fleury *et al* [9-11] demonstrated that the cyclization of α-acylamino amides to 5-(trifluoroacetamido)oxazoles occurs by treatment with neat trifluoroacetic anhydride in the presence of a strong acid. However, this procedure appears to be largely restricted to trifluoroacetamido-substituted oxazoles. Another important route to 5-acylaminooxazoles was developed by Lipshutz *et al* by treatment of α-amidonitriles with an acid halide in the presence of boron trifluoride [5].

Our previous work has demonstrated the versatility of benzotriazole as a synthetic auxiliary in many transformations [12-15]. *N*-(1-Benzotriazol-1-ylalkyl)amides have emerged as versatile α-amidoalkylating reagents. They react with CH acids [16] and aromatics [17] to give amidoalkylation products, with sodium alkoxides to give α-(alkoxyalkyl)amides [18] and with sodium alkylthiolates to form α-[(alkylthio)alkyl]amides [19]. However, the vicinal dibenzotriazole analogs **2** have not previously been reported. Herein, we report the preparation of 1,2-diacylamino-1,2-di(benzotriazol-1-yl)ethanes **2** and their easy transformation to 5-acylaminooxazoles **5**.

1,2-Di(benzotriazol-1-yl)ethane-1,2-diol (**1**) was prepared in almost quantitative yield by reacting glyoxal with two equivalents of benzotriazole in aqueous acetic acid based on the literature procedure [20]. As shown in Scheme 1, the reactions of **1** with primary amides in the presence of a catalytic amount of Amberlyst® 15 ion exchange resin in refluxing toluene with azeotropic removal of water gave 1,2-diacylamino-1,2-di(benzotriazol-1-yl)ethanes **2** in almost quantitative yield. As judged on the basis of their crude nmr spectra, derivatives **2a-d** were all reasonably pure mixtures of the two expected diastereoisomers and were advantageously used directly in the next step without further purification. Derivative **2d** thus obtained was purified by washing with hot ethyl acetate and was characterized by ^{1}H nmr and elemental analysis (see Experimental).

Scheme 1



Transformations of compounds **2a-d** to 5-acylaminooxazoles **5a-d** were accomplished in good to moderate yields by treatment of **2a-d** with sodium hydride in dry *N,N*-dimethylformamide at 100°. Compounds **5a-d** are all novel; their structures are fully supported by nmr data and CHN analyses (see Experimental). A 1H singlet at *ca* 7.3 ppm in the ^{1}H nmr spectra is characteristic of the 4-proton of the oxazole system. As illustrated in Scheme 1, the formation of oxazoles probably proceeds *via* the intramolecular displacement of one benzotriazolyl group, followed by the elimination of the second benzotriazolyl anion.

In summary, 5-acylaminooxazoles can be readily prepared from primary amides and easily available 1,2-di(benzotriazol-1-yl)ethane-1,2-diol.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. The ^1H, and ^{13}C nmr spectra were recorded on a Varian Gemini 300 MHz spectrometer. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer in this Department. *N,N*-Dimethylformamide was dried by distillation over calcium hydride. Flash column chromatography was carried out on silica gel (EM Merck 60, 230-400 mesh). 1,2-Di(benzotriazol-1-yl)ethane-1,2-diol (**1**) was prepared according to the literature procedure [20].

1,2-di(2-Methylphenacylamino)-1,2-di(benzotriazol-1-yl)ethane (**2d**).

1,2-Di(benzotriazol-1-yl)ethane-1,2-diol (4 g, 13.5 mmoles), 2-methylbenzamide (3.7 g, 27 mmoles) and Amberlyst® 15 ion exchange resin (0.1 g) were refluxed for 6 hours in toluene (100 ml) with azeotropic removal of water. The mixture was cooled to room temperature and the resulting solid was collected by filtration and washed with hot ethyl acetate, 6.5 g (90%), mp 223-225°; ^1H nmr (deuteriodimethyl sulfoxide): δ 2.09-2.52 (m, 6H), 7.05-8.36 (m, 18H), 10.11-10.62 (m, 2H).

Anal. Calcd. for $C_{30}H_{26}N_8O_2$: C, 67.91; H, 4.94; N, 21.12. Found: C, 67.89; H, 4.86; N, 21.19.

General Procedure for the Preparation of 5-Acylaminooxazoles **5a-d**.

To a solution of the appropriate 1,2-diacylamino-1,2-di(benzotriazol-1-yl)ethane **2** (in the cases of **5a-c** crude materials **2a-c** prepared by the same procedure as described above for **2d** were used) (5 mmoles) in dry *N,N*-dimethylformamide (50 ml) under argon, was added sodium hydride (95%, 0.25 g, 10 mmoles). The mixture was stirred at 100° for 3 hours and then poured into water (150 ml). The mixture was extracted with diethyl ether (3 x 100 ml), and the organic layers were combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave the crude product, which was purified by column chromatography (silica gel, hexane:ethyl acetate = 2:1).

2-Phenyl-5-(phenacylamino)oxazole (**5a**).

This compound was obtained in 62% yield as colorless needles (ethyl acetate/hexanes), mp 187-188°; ^1H nmr (deuteriochloroform): δ 7.31 (s, 1H), 7.44-7.57 (m, 6H), 7.95-7.99 (m, 2H), 8.05-8.08 (m, 2H), 11.31 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 112.9, 124.6, 126.4, 127.1, 127.5, 127.9, 128.9, 131.2, 132.1, 145.1, 153.9, 163.5 (C=O).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.63; H, 4.56; N, 10.59.

2-(4-Methylphenyl)-5-[(4-methylphenacyl)amino]oxazole (**5b**).

This compound was obtained in 61% yield as a colorless powder (ethyl acetate/hexanes), mp 105-107°; ^1H nmr (deuteriochloroform): δ 2.40 (s, 3H), 2.44 (s, 3H), 7.23-7.30 (m, 4H), 7.33 (s, 1H), 7.80-7.86 (m, 4H), 8.44 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 20.5, 20.6, 112.7, 123.8, 124.7, 127.2, 128.2, 128.6, 129.3, 139.1, 141.7, 144.9, 153.8, 163.5 (C=O).

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 74.23; H, 5.53; N, 9.55.

2-(4-Methoxyphenyl)-5-[(4-methoxyphenacyl)amino]oxazole (**5c**).

This compound was obtained in 44% yield as a colorless powder (ethyl acetate/hexanes), mp 98-99°; ^1H nmr (deuteriochloroform): δ 3.76 (s, 3H), 3.78 (s, 3H), 6.82 (d, 2H, J = 8.9 Hz), 6.88 (d, 2H, J = 8.9 Hz), 7.26 (s, 1H), 7.72 (d, 2H, J = 8.9 Hz), 7.95 (d, 2H, J = 8.9 Hz), 9.63 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 55.2, 55.3, 113.7, 113.9, 114.0, 119.8, 124.8, 127.3, 129.4, 144.5, 155.0, 160.9, 162.8, 163.7.

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.97; H, 5.06; N, 8.44.

2-(2-Methylphenyl)-5-[(2-methylphenacyl)amino]oxazole (**5d**).

This compound was obtained in 51% yield as colorless needles (ethyl acetate/hexanes), mp 97-98°; ^1H nmr (deuterochloroform): δ 2.53 (s, 3H), 2.67 (s, 3H), 7.22-7.42 (m, 7H), 7.51 (d, 1H, J = 7.3 Hz), 7.83 (d, 1H, J = 7.7 Hz), 8.39 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 19.6, 21.5, 113.0, 125.4, 125.6, 125.7, 126.9, 128.2, 129.5, 130.6, 131.0, 131.3, 133.8, 136.7, 136.8, 144.3, 155.0, 166.4 (C=O).

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 74.21; H, 5.55; N, 9.56.

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Submitted in honor of the 65th anniversary of Richard Neldein.

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