A Side Reaction Encountered in Using the Peptide Coupling Reagent *N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ)

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An unusual side reaction has been found during an attempt to form an amide link between 2-aminothiazole and thiophene-2-carboxylic acid in the presence of EEDQ. Ethyl *N*-(2-thiazolyl)-carbamate (**3**) was isolated in significant amounts indicating that 2-aminothiazole, and perhaps other heterocyclic amines, can react directly with EEDQ to form carbamates.

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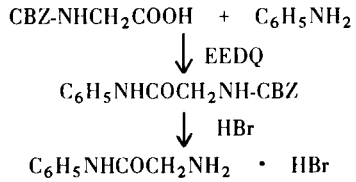
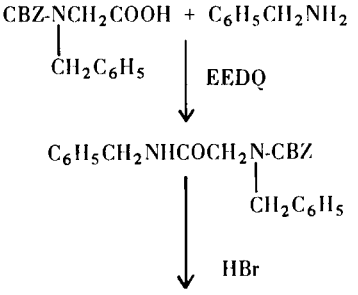
N-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) is a convenient reagent for the synthesis of amides and peptides (1). It has been used to couple amines with carboxylic acids under mild conditions and, with optically active acids, without significant racemization (2-11). Apparently, only one side reaction has been previously reported (6) from an experiment employing EEDQ. Thus, an attempt to prepare an amide from 2-aminopyrimidine and lithocholic acid-3-formate in tetrahydrofuran (THF) solution using EEDQ produced an unspecified (6) yield of an anhydride derived from the carboxylic acid.

In connection with another study, we were interested in preparing amides from various carboxylic acids and amines. EEDQ in THF functioned well to couple protected amino acids (*e.g.*, *N*-CBZ-glycine or *N*-CBZ-*N*-benzylglycine) with aliphatic or aromatic amines (*e.g.*, benzylamine or aniline) (see Experimental).

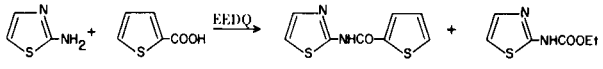


(1)



(2)

However, the reaction of thiophene-2-carboxylic acid with 2-aminothiazole unexpectedly produced significant amounts of ethyl *N*-(2-thiazolyl)carbamate (3) as well as a small amount of the desired amide.



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Compound **3** is also formed from combination of 2-aminothiazole with EEDQ in the absence of any carboxylic acid if a small amount of *p*-toluenesulfonic acid is used as catalyst. In addition, 2-aminopyridine and thiophene-2-carboxylic acid, while producing some desired amide in the presence of EEDQ, also gave small amounts (high resolution mass spectral evidence) of the carbamate derived from 2-aminopyridine.

These observations for the first time show that despite Belleau's (1) statement that "EEDQ fails to react with amines under conditions of ready peptide synthesis", certain heterocyclic amines, at least, will react with EEDQ. Therefore, one should be aware that whenever EEDQ is used in reactions with heterocyclic amines carbamate side products may be formed in the reaction mixture.

EXPERIMENTAL

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. A Varian A-60 spectrometer (TMS standard) was used to measure nmr spectra and mass spectra were determined on a Hitachi Perkin-Elmer Model RMU-6E or on an AEI-MS-30 mass spectrometer. Ir spectra were determined in potassium bromide pellets. Analyses were carried out by the Physical Measurements Laboratory of Pfizer Inc.

N-Phenyl-2-aminoacetamide Hydrobromide (**1**).

To 5.0 g. (0.024 mole) of carbobenzyloxyglycine (Aldrich Chemical Co.) in 40 ml. of THF was added 2.5 g. (0.027 mole) of aniline and 7.48 g. (0.03 mole) of EEDQ (Aldrich Chemical Co.) in 40 ml. of THF. The reaction was stirred 1 hour at room temperature and then heated to reflux. After 3 hours, the reaction was complete (tlc). Concentration of the solvent to 1/2 volume produced a precipitate which was filtered, washed with THF and then triturated thoroughly with 250 ml. of ether to remove any adherent quinoline, weight 5.98 g. (88%), m.p. 145-149°. Without further characterization, the CBZ group was removed from this compound as follows: 60 ml. of 30% hydrogen bromide in acetic acid was added slowly to 5.9 g. of the intermediate and the reaction stirred at room temperature overnight. After the reaction was poured slowly into 400 ml. of ether, 4.3 g. (77%) of white solid **1** was collected, m.p. 203-207° dec.; ir: 3.4 μ (broad, NH_3^+), 5.94 (C=O); ms: (Calcd. 150) m^+ 150, 93.

Anal. Calcd. for $C_8H_{10}N_2O \cdot HBr$: C, 41.56; H, 4.98; N, 12.12. Found: C, 41.46; H, 4.69; N, 12.24.

N-Benzyl-2-(benzylamino)acetamide Hydrobromide (**2**).

By essentially the same two-step procedure described above for compound **1**, 1.5 g. (0.005 mole) of *N*-CBZ-*N*-benzylglycine, 1.5 g. (0.0063 mole) of EEDQ and 0.61 g. (0.0057 mole) of benzylamine in 40 ml. of THF was converted to 1.52 g. (89%) of compound **2**, m.p. 220° dec.; ir: 3.46 μ (broad, NH_2^+), 5.95 (C=O); ms: (Calcd. 254) m^+ 254, 149, 120, 106. An analytically pure sample was prepared by recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{18}N_2O \cdot 0.75$ HBr: C, 60.99; H, 6.00; N, 8.89. Found: C, 60.67; H, 6.12; N, 8.82.

Reaction of 2-Aminothiazole and Thiophene-2-carboxylic Acid in the Presence of EEDQ.

A combination of 2.05 g. (0.016 mole) of 2-thiophenecarboxylic acid (Aldrich Chemical Co.), 1.89 g. (0.019 mole) of 2-aminothiazole and 4.95 g. (0.020 mole) of EEDQ in 70 ml. of THF was refluxed for 18 hours. All solvent was removed under vacuum and 50 ml. of ether added to produce, in two crops, 1.62 g. of a crude solid which by mass spectrum contained a small amount of desired amide (m^+ 210) but a major ion at m^+ 172. After recrystallization from 2-propanol, there was obtained 1.07 g. (34%) of **3**, m.p. 153-154.5°; ir: 5.77 μ (C=O); ms: (Calcd. 172) m^+ 172, 127, 113, 100.

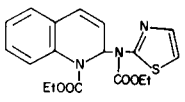
Anal. Calcd. for $C_6H_8N_2O_2S$: C, 41.84; H, 4.68; N, 16.27. Found: C, 41.81; H, 4.68; N, 16.17.

Reaction of 2-Aminothiazole with EEDQ.

A solution of 0.10 g. (0.001 mole) of 2-aminothiazole, 0.247 g. (0.001 mole) of EEDQ and a few crystals of *p*-toluenesulfonic acid in 2 ml. of THF was refluxed for 18 hours. Cooling produced a solid (**4**) which was filtered, weight 42 mg., m.p. 210-255° which was raised to m.p. 242-244° on recrystallization (THF); ms: m^+ 373, 344, 328, 300, 282; ir: 3.37, 5.79, 5.85 μ; uv λ max (methanol): 232 (ϵ, 31,164); 266 (ϵ, 16,865); (note that EEDQ shows λ max (methanol): 230 (ϵ, 34,137); 263 (ϵ, 7,967). High resolution ms: ($C_{18}H_{19}N_3O_4S$ Calcd. 373.1096): Found: 373.0665, 300.0797, 254.0101, 228.0589.

Anal. Calcd. for $C_{18}H_{19}N_3O_4S$: C, 57.89; H, 5.13; N, 11.25. Found: C, 57.86; H, 5.06; N, 11.06.

Based on the above data, the structure of **4** is tentatively assigned as:



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The THF filtrate was evaporated to dryness and the residue recrystallized from 2-propanol to yield compound **3**, m.p. 148-152°; mixture m.p. with authentic **3** gave m.p. 151-155°; ms: (Calcd. 172) m^+ 172, 129, 127, 113, 100, 99; ir spectrum was identical to authentic **3**.

Preparation of Authentic Ethyl *N*-(2-Thiazolyl)carbamate (**3**).

To 10.0 g. (0.100 mole) of 2-aminothiazole in 200 ml. of ether at -10° was slowly and simultaneously added a solution of 11.9 g. (0.110 mole) of ethyl chloroformate and a solution of 4.5 g. of sodium hydroxide in 50 ml. of water. After complete addition the reaction was stirred for 1 hour. The ether layer was then separated, and the sodium hydroxide layer washed twice more with ether. The combined ether layers were stirred with anhydrous potassium carbonate, filtered and evaporated to dryness to yield a white solid, 14.2 g. (83%), m.p. 150-153°; identical in ir and ms spectrum to compound **3** isolated above.

Anal. Calcd. for $C_6H_8N_2O_2S$: C, 41.84; H, 4.68; N, 16.27. Found: C, 42.06; H, 4.69; N, 16.10.

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