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Tetrahedron Letters 45 (2004) 113–115
Tetrahedron Letters

Liquid-phase synthesis of 2-substituted benzimidazoles, benzoxazoles and benzothiazoles ☆

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Received 19 September 2003; revised 17 October 2003; accepted 20 October 2003

Abstract—A novel acid fluoride for use in the liquid-phase synthesis of substituted benzimidazoles, benzoxazoles and benzothiazoles was developed. Its synthetic utility is exemplified by a structurally diverse set of aromatic heterocycles. Final cleavage is achieved by treatment with sodium methoxide in methanol for 12 h. The corresponding benzimidazoles, benzoxazoles and benzothiazoles were obtained in good isolated yields (22–62%, four steps).

The development of new methods for the synthesis of heterocyclic compound libraries, both in solution and in the solid-phase, represents an expanding area of combinatorial chemistry. The benzimidazole, benzoxazole and benzothiazole structural motifs may be found in numerous pharmaceutical agents with a diverse range of biological properties.[1] Although a wide range of methods are available for synthesizing benzimidazole,[2] benzoxazole[3] and benzothiazole,[4] a real need exists for new simple procedures that support many kinds of structural diversity and various substitution patterns in the target library.

Compounds that exhibit the functionality of benzimidazole, benzoxazole and benzothiazole have been extensively employed in the area of pharmaceuticals. These compounds are normally synthesized by condensing benzene-1,2-diamine, 2-aminophenol and 2-aminobenzenethiol with acyl chlorides or aldehydes,[2–4] but acyl chlorides and aldehydes are too reactive to load on PEG without further protection. The stability of acyl fluoride can even be worked up from ice water,[5] but has not been employed to functionalize the solid supports. The current literature presents an increasing number of examples of solid-phase syntheses of benzimidazoles, benzoxazoles and benzothiazoles, utilizing either linkers or coupling reagents. Furthermore, a number of solution-phase methods and reagents for converting aldehydes into benzimidazoles, benzoxazoles and benzothiazoles have recently been published.[2–4] In developing a new strategy for synthesizing 'benzimidazole, benzoxazole and benzothiazole'-based combinatorial libraries, the ability to synthesize a structurally distinct form of the benzimidazole, benzoxazole and benzothiazole precursor, which can easily be attached to a PEG support before synthesis, is considered here.

Common methods were used in a combinatorial synthesis of benzimidazoles, benzoxazoles and benzothiazoles, initially, the corresponding 4-fluoro-3-nitrobenzoic acid was loaded on solid support, and then the fluorine was substituted for the amino, hydroxyl and mercapto groups.[2c] The nitro group was reduced to an amino group, and then reacted with the aldehydes or acyl chlorides to generate the desired heterocyclic compounds. In the present work, the acyl fluoride was easily loaded on PEG, and the remaining acyl fluoride reacted with the benzene-1,2-diamine, 2-aminophenol and 2-aminothiophenol under mild conditions to form corresponding heterocyclic compounds.

In the present work (Scheme 1), terephthalic acid was converted to terephthaloyl fluoride by treating it with hydrogen fluoride–pyridine and dicyclohexylcarbodiimide (DCC).[5] it was then reacted with polyethylene glycol methyl ether (PEG, average molecular weight ca. 5000). One of the acyl fluorides on the terephthaloyl

Keywords: Benzimidazole; Benzoxazole; Benzothiazole.
☆ Supplementary data associated with this article can be found at doi:10.1016/j.tetlet.2003.10.095
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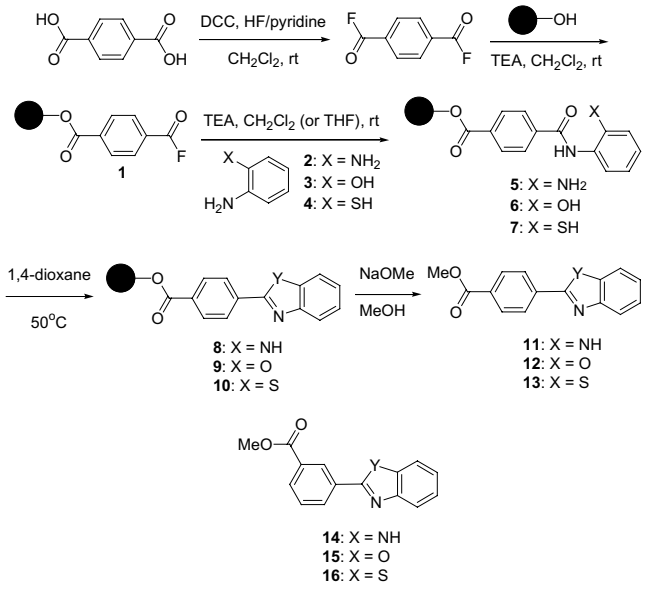
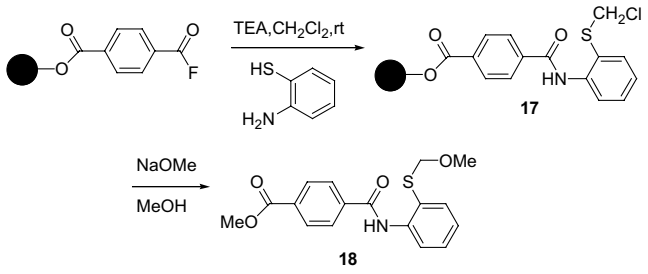
doi:10.1016/j.tetlet.2003.10.095



Scheme 1.

fluoride reacted with PEG to form an ester, and another acyl fluoride reacted with benzene-1,2-diamine, 2-aminophenol and 2-aminomercaptophenol to form the corresponding amides **5**, **6** and **7**. The amides thus obtained were refluxed in 1,4-dioxane with acetic acid to produce the corresponding benzimidazole **8**, benzoxazole **9** and benzothiazole **10**. Then, the PEG was cleaved by treatment with sodium methoxide to produce compounds **11**, **12** and **13**. Instead of the terephthalic acid with isophthalic acid, the corresponding benzimidazole **14**, benzoxazole **15** and benzothiazole **16** were obtained. Phthalic acid was treated in the same way, but the desired products were not then obtained. When acyl fluoride was reacted with 2-aminomercaptophenol in dichloromethane, the mercapto group reacted with dichloromethane to form a thioether **17**, after which the PEG was cleaved by sodium methoxide, yielding compound **18** (Scheme 2).

The general procedure was demonstrated by preparing 4-(1*H*-benzoimidazol-2-yl)-benzoic acid methyl ester **11**. To a solution of DCC (2.26 g, 10.1 mmol) in dichloromethane (20 mL) was added HF-pyridine (308 μL, ~70% HF); followed a solution of terephthalic acid (1.66 g, 10 mmol) and pyridine (2 mL) in dichloromethane (80 mL) was added by cannula. After the reaction mixture was stirred at room temperature for 2 h, it



Scheme 2.

was filtered, and the filtrate was added to a solution of poly(ethylene glycol)methyl ether (10 g, 2 mmol, PEG) and triethylamine (1.38 mL) in dichloromethane (20 mL) by cannula. The reaction solution was stirred at room temperature for 12 h, and the solution was concentrated to a volume of about 30 mL. The solid was removed by filtration, and the filtrate was added to diethyl ether (400 mL) to precipitate the PEG-R **1**. After the mixture had been left to stand for 15 min, PEG-R **1** was obtained by filtration (Fig. 1). To a solution of PEG-R **1** in dichloromethane (100 mL) was added a solution of benzene-1,2-diamine (0.65 g, 6 mmol) and triethylamine (1.39 mL) in dichloromethane (40 mL) by cannula. The reaction mixture was stirred at room temperature for 12 h, and potassium carbonate (1.5 g) was added. After 1 h, the solution was concentrated to a volume of about 30 mL. The solid was removed by filtration, and the filtrate was added to diethyl ether (400 mL) to precipitate out PEG-R **5**. After the mixture was left to stand for 15 min, PEG-R **5** was obtained by filtration. It was dissolved in 1,4-dioxane (65 mL) and glacial acetic acid (5 mL) was added; the resulting solution was refluxed for 12 h. After the solution was cooled to room temperature, it was concentrated to a volume of about 30 mL, and added to diethyl ether (400 mL) to precipitate out PEG-R **8**. After the solution had been left to stand for 15 min, PEG-R **8** was obtained by filtration. To a solution of PEG-R **8** (1 g, 0.2 mmol) in methanol (10 mL) was added sodium methoxide (1.39 mL, 0.7 M in methanol), which was stirred at room temperature for 12 h. The reaction was quenched by adding some ammonium chloride and stirred for 20 min. The reaction solution was added to diethyl ether (250 mL) to precipitate the PEG. After the solution had been left to stand for 15 min, PEG was removed by filtration, and the filtrate was concentrated, which was purified by flash chromatography on silica gel. The structures and yields of compound **11**–**16** are shown in Table 1.

In summary, a new acyl fluoride reagent was developed as a linker to load on PEG, and incorporated as a skeleton of a target compound. This compound is used to synthesize substituted benzimidazoles, benzoxazoles, and benzothiazoles has not been reported. The reaction conditions are amendable to synthesize large combinatorial libraries.

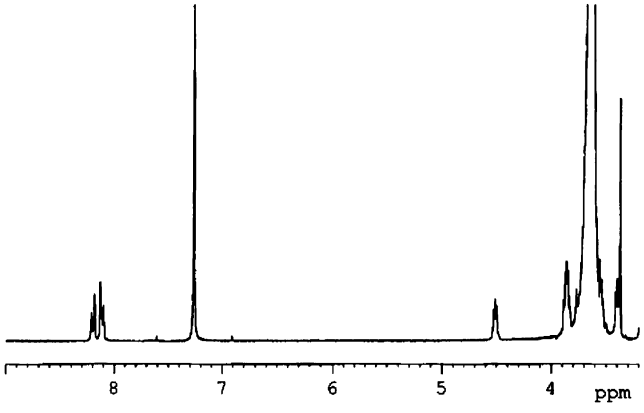
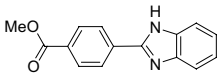
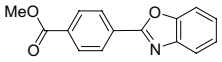
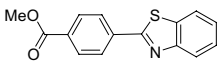
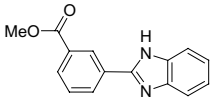
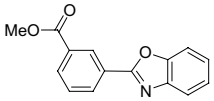
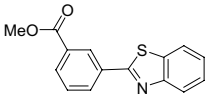


Figure 1. The H NMR spectrum of compound PEG-R **1**.

Table 1. The structures and yields of compound **11**–**16** via Scheme 1

Compound	Structure	% Yield[a]
11		44
12		56
13		22
14		27
15		62
16		37

[a] The yield was calculated based on the theoretical loading of the PEG, and the products were purified by flash chromatography on SiO_2.

Supplementary material

Supplementary material includes the ^1H NMR and ^{13}C NMR spectra and data of compounds **11**–**16** and **18**.

Acknowledgements

The authors would like to thank the National Science Council of the Republic of China for financially supporting this research under contract no. NSC 91-2113-M-259-006.

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