Tetrahedron Letters 49 (2008) 4624–4625

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Di-*tert*-butyl dicarbonate as an efficient coupling reagent for the immobilization of carboxylic acid moieties

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ARTICLE INFO

Article history:
Received 17 April 2008
Revised 14 May 2008
Accepted 16 May 2008
Available online 24 May 2008

ABSTRACT

We describe an efficient methodology for anchoring diverse carboxylic acids to hydroxymethylated resins using di-*tert*-butyl dicarbonate as coupling reagent. The reaction is equally effective for aromatic and aliphatic acids, and Fmoc-protected amino acids.

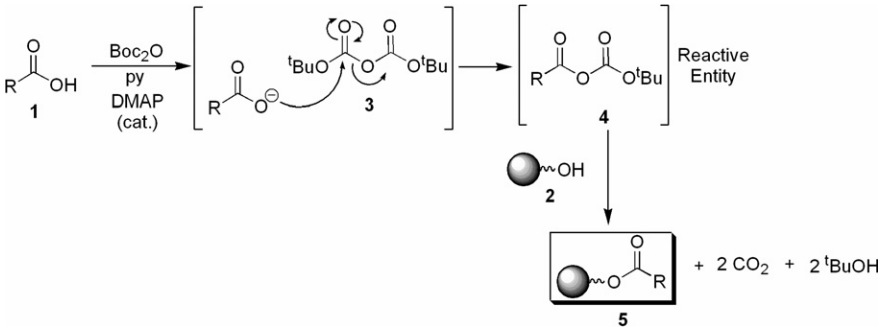
The combinatorial chemistry of small molecules together with high-throughput screening continue to be key technologies for accelerating drug discovery.[1] In order to achieve that goal, synthesis on a solid support[2] offers a number of indisputable advantages as compared to homogenous-phase chemistry. Purification of the crude reaction material is facilitated by filtration, which prevents time-consuming separation techniques and allows the addition of excess of building blocks and reagents in order to drive reactions to completion. Also, relative site isolation is achieved getting the 'pseudo-dilution effect',[3] while high dilution is generally required for efficient macrocyclization in solution.

The importance of solid-phase methodologies has been recognized not only in the area of drug discovery, but also in organic chemistry in general, and the concept has been extended to many different organic structures, particularly heterocycles and natural product scaffolds. Therefore, there is a growing need to expand the scope of synthetic transformations and organic structures that can be carried out through solid-phase methodologies.

The esterification of carboxylic acids is undoubtedly one of the most frequently employed transformations in organic chemistry and the methods of choice for the immobilization of carboxylic acids in solid-phase chemistry. Use of an ester linkage to attach carboxylic acids to solid supports is of general utility, beyond the application to amino acids in solid-phase peptide synthesis.

As part of our continuing research program on the development of new methodologies in solid-phase synthesis,[4] we found that di-*tert*-butyl dicarbonate (Boc anhydride) is an effective reagent for the activation of carboxylic acid toward nucleophilic addition by a hydroxymethylated resin. This activating agent has been already used in homogeneous-phase chemistry for the conversion of various carboxylic acids to symmetrical anhydrides, esters, and amino acid amides as well as for dipeptide synthesis.[5,6]

Herein, we report that carboxylic acids **1** react with hydroxymethylated resin **2** in the presence of di-*tert*-butyl dicarbonate (**3**) and pyridine as a base and catalytic amounts of DMAP to give the immobilized esters **5** (Scheme 1). Activation of the carboxylic



Scheme 1.

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doi:10.1016/j.tetlet.2008.05.095

Table 1
Immobilization of carboxylic acid moieties to different hydroxymethylated resins by di-*tert*-butyl dicarbonate (**3**)[a]

Entry	Substrate	Hydroxymethylated resin	Pyridine (equiv)	Temperature (°C)	Time (h)	Yield[b] (%)
1	Benzoic acid	Wang resin	5	60	12	87
2	4-Iodobenzoic acid	Wang resin	5	60	18	81
3	4-Fluorobenzoic acid	Wang resin	5	60	24	98
4	5-Phenylvaleric acid	Wang resin	5	60	24	100
5	2-Nitrobenzoic acid	Wang resin	5	60	24	100
6	3-Acetoxybenzoic acid	Wang resin	5	60	24	82
7	Phenoxyacetic acid	Wang resin	5	60	24	100
8	2-Formyl-phenoxyacetic acid	Wang resin	8	60	24	85
9	6,6-Dibromopenicillanic acid	Wang resin	8	rt	24	85
10	Fmoc-Met-OH	Wang resin	5	rt	8	61
11	Fmoc-Gly-OH	Wang resin	5	rt	5	70
12	Fmoc-Leu-OH	Wang resin	5	rt	5	85
13	Benzoic acid	JandaJel Wang Resin	5	60	24	70
14	4-Iodobenzoic acid	JandaJel Wang Resin	5	60	24	54
15	4-Fluorobenzoic acid	JandaJel Wang Resin	5	60	24	79
16	Fmoc-Gly-OH	JandaJel Wang Resin	5	rt	8	75
17	Fmoc-Leu-OH	JandaJel Wang Resin	5	rt	5	64
18	4-Fluorobenzoic acid	Sasrin Resin	5	60	24	80
19	5-Phenylvaleric acid	Sasrin Resin	5	60	24	100

[a] Conditions: Boc_2O (5 equiv), pyridine (5–8 equiv), DMAP (cat.) in DMF/DCM.
[b] Determined by cleavage of the resulting resin with 10% TFA in DCM.

acid presumably proceeds through a mixed carbonic carboxylic anhydride **4**. Upon reaction with the hydroxymethylated resin **2** the corresponding ester **5** is obtained with the concomitant release of carbon dioxide.[6]

In order to establish the scope and limitations of this reaction, a series of acids and supports has been tested. The results obtained in this study are summarized in Table 1.

For the immobilization of aromatic acids to Wang resin (entries 1–6), the best result was obtained when the hydroxymethylated resin was treated with 5 equiv of di-*tert*-butyl dicarbonate (**3**), 5 equiv of pyridine, and catalytic DMAP at 60 °C for 12–24 h. The resin-bound products were obtained in very high yield (81–100%).[7] In the case of 2-formyl-phenoxyacetic acid (entry 8), the amount of the base was increased from 5 to 8 equiv in order to improve yield from 54% to 85%. Interestingly, similar coupling using standard DIC/DMAP reaction gave only 55% yield.[2d]

Immobilization of Fmoc-protected amino acids under the optimized conditions gave deprotection in some extent. Careful investigation has demonstrated that performing the reaction at room temperature prevents deprotection leading to the coupling products in good yield (entries 10–12).[8]

Other hydroxymethylated resins such as the Wang resin version of JandaJel® support[9] and the acid-labile SASRIN resin[10] have also been studied. Couplings were fairly similar to that achieved with standard Wang resin (entries 13–19).

In conclusion, we have demonstrated that di-*tert*-butyl dicarbonate (**3**) is a very efficient coupling reagent for immobilizing carboxylic acids to diverse hydroxymethylated resins. Aromatic and aliphatic acids, and Fmoc-protected amino acids were equally effective for the coupling. This approach provides an alternative method of anchoring organic molecules to different solid supports, acting as a valuable tool for the development of building blocks for solid-phase libraries.

Acknowledgments

Financial support from Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Agencia Nacional de Promoción Científica y Tecnológica, and Universidad Nacional de Rosario from Argentina is gratefully acknowledged.

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7. *Representative procedure:* Wang resin (82.8 mg, 1.1 mmol/g) was swollen in a 1:1 mixture of DCM/DMF (4 mL). 4-Fluorobenzoic acid (63.8 mg, 0.46 mmol, 5 equiv), $(Boc)_2O$ (99.4 mg, 0.46 mmol, 5 equiv), pyridine (36.5 μL, 0.46 mmol, 5 equiv) and catalytic DMAP were dissolved in DCM/DMF (1:1) (4 mL) and added to the mixture. The reaction was then warmed at 60 °C for 24 h. After that time, the mixture was filtered, washed with DCM (3 × 5 mL), AcOEt (3 × 5 mL), and MeOH (3 × 5 mL), and dried under vacuum. Finally, 88.3 mg (0.086 mmol) of the resulting resin was treated with 10% TFA in DCM to give 11.8 mg of 4-fluorobenzoic acid (98% yield).
8. For recent examples of the immobilization of Fmoc-protected amino acids to solid support, see: (a) Sandhya, K.; Ravindranath, B. *Tetrahedron Lett.* **2008**, *49*, 2435; (b) Topping, R. J.; Nuiry, I.; Mastriona, J.; Moss, J. A. *Tetrahedron Lett.* **2008**, *49*, 2907.
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