Pergamon

Tetrahedron Letters 40 (1999) 875–878

TETRAHEDRON
LETTERS

An Efficient Procedure for the Esterification of Nitroacetic acid : Application to the Preparation of Merrifield Resin-Bound Nitroacetate

Catherine Sylvain, Alain Wagner, Charles Mioskowski*

Laboratoire de Synthèse Bioorganique, Université Louis Pasteur de Strasbourg, Unité associée au CNRS,
Faculté de Pharmacie, 74 route du Rhin - 67401 Illkirch, France #.

Received 4 November 1998; accepted 24 November 1998

Abstract: Nitroacetic esters are prepared in good yield by reaction, at 0 °C, of nitroacetic acid with various alcohols in the presence of DCC. These reaction conditions were applied to the preparation of Merrifield resin-bound nitroacetate.

Keywords : esterifiction, nitro compounds, coupling reaction, solid-phase synthesis

Nitroacetic ester chemistry has been the subject of numerous investigations [1]. The presence of an active methylene group makes these esters remarkable intermediates for the formation of carbon-carbon bond. They readily undergo nucleophilic addition with a wide range of electrophiles such as alkyl halides, carbonyl compounds and also 1,4-addition with Michael acceptors. In addition, the nitro group can easily be reduced into an amine function or oxidized into the corresponding ketone (Nef reaction) [2]. The combination of these transformations allows the access to structural and functional diversity. Thus, nitroacetic ester is a suitable building block for the development of original combinatorial solid phase synthesis.

However, anchoring nitroacetic acid to the solid support (Merrifield resin) appears to be problematic. Nitroacetic acid is a very sensitive compound which, under basic conditions, readily undergoes decarboxylation and decomposes in the presence of oxophilic reagents because of the reactivity of the activated nitro group. Therefore, classical esterification procedures can not be used for the preparation of nitroacetic esters. In consequence, most of the studies concerning nitroacetic ester chemistry are confined to commercially available methyl and ethyl nitroacetates. These esters are prepared by refluxing nitroacetic acid in methanol or ethanol in the presence of sulfuric or hydrochloric acid [3].

Fax: (33) 3 88 67 88 91; E-mail : mioskow@aspirine.u-strasbg.fr

PII: S0040-4039(98)02544-1

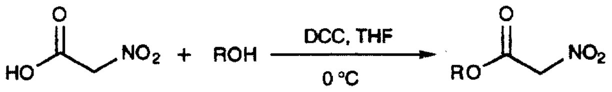
The prevalent reactions to prepare other alkyl nitroacetates are *trans*-esterification of the methyl or ethyl ester under acidic conditions [4], nitration of the corresponding alkylacetate, alkylbromoacetate or alkyliodoacetate [5], deacylation of the corresponding 2-nitroacetylacetonate [6]. However, these reactions proceed in poor yields *via* a multistep process and thus can hardly be considered to anchor nitroacetic acid to Merrifield resin.

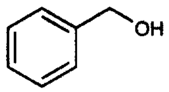
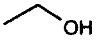
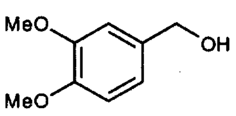
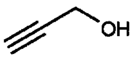
Being concerned by the development of nitroacetic ester chemistry on solid support, we reinvestigated the preparation of alkyl nitroacetate by esterification of nitroacetic acid [7]. To avoid decomposition of the acid, we attempted several reaction conditions that are known to proceed smoothly. We first tested the reaction of nitroacetic acid and benzyl chloride under basic conditions. The utilization of dicyclohexylamine, cesium carbonate or silver carbonate as bases resulted in the decarboxylation of nitroacetic acid. No ester formation was detected. We then tried the coupling reaction between nitroacetic acid and benzyl alcohol. The Mitsunobu conditions, DCC/DMAP, DCC/HOBt or mixed anhydride procedures were tested, but none of them resulted in the formation of the desired benzyl nitroacetate.

Finally we found that the slow addition, at 0 °C, of a solution of DCC in THF to an equimolar mixture of nitroacetic acid / benzyl alcohol in THF yielded the desired ester. Using this procedure, the benzylnitroacetate was obtained in 87 % yield after purification. If the reaction is carried out in methylene chloride instead of THF the ester is obtained in only 54 % yield, presumably because of the poor solubility of the nitroacetic acid in this solvent. It is noteworthy that the presence of DMAP, even in catalytic amounts, leads to the decarboxylation of the nitroacetic acid. Similarly, if the temperature rises up during the addition of DCC instantaneous loss of CO_2 is observed. We tested various alcohols for the synthesis of nitroacetate esters by conducting the reaction under the above mentioned conditions (Table 1).

This DCC coupling procedure allows a one step synthesis of various nitroacetic esters in yields ranging from 65 to 90 %. The indicated yields are based on nitroacetic acid conversion after silica gel chromatography of the nitroacetate ester.

Under these reaction conditions, acid sensitive alcohols (e.g. allyl-, propargyl-, *tert*-butyl-, 3,4-dimethoxybenzyl-) led to the corresponding nitroacetate ester in good yield. Also, substrates bearing acid sensitive protecting groups like acetonide and tetrahydropyranyl ethers undergo facile esterification without degradation. Sterically hindered esters such as menthyl and *tert*-butyl esters were obtained in 78 and 65 % yield, respectively. Thus, contrary to the previously reported methods that were limited to structurally simple alcohols, it appears that our conditions are compatible with numerous alcohols and afford the corresponding nitroacetate ester in good yield, in a one step procedure .



ROH	Yield
	87 %
	90 %
	75 %
	68 %
	65 %

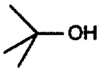
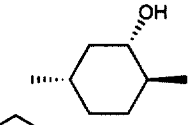
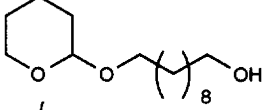
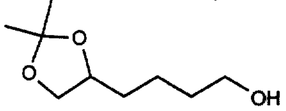
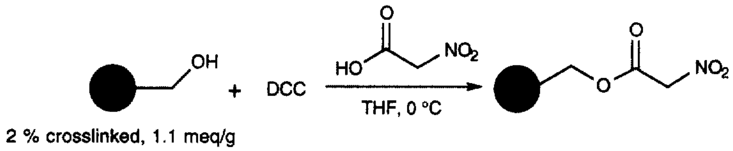
ROH	Yield
	65 %
	78 %
	73 %
	85 %

Table 1

We then applied an analogous procedure to anchor nitroacetic acid to hydroxylated Merrifield resin. A solution of DCC in THF was added, at 0 °C, to a mixture of hydroxylated Merrifield resin and nitroacetic acid. However, even if the reaction was conducted carefully, a slight loss of CO_2 was observed and the derivatization never went to completion. In consequence, we inverted the order of addition (*i.e.* nitroacetic acid to a mixture of hydroxylated Merrifield resin and DCC). This modification resulted in an efficient derivatization of the resin [8] (scheme 2).



Scheme 2

A solution of nitroacetic acid in THF was slowly added to a mixture of hydroxylated Merrifield resin and DCC at 0 °C. The heterogeneous reaction mixture was sonicated overnight at room temperature. The resin was then thoroughly washed. After drying under vacuum, IR analysis of the resin showed characteristic nitro and ester absorption at 1563 and 1752 cm^{-1} respectively and microanalysis showed a loading of 0.95 meq/g that is close to that of the starting resin.

In summary we report a convenient procedure for the preparation of various alkyl nitroacetates. This simple process represents an improvement for the synthesis of acid sensitive alkyl nitroacetates. The latter are usually prepared *via* a multistep synthesis and are obtained in poor yields. The above reported procedure also allows the preparation of nitroacetate-functionalized resin, which is currently used to develop original chemistry on solid support.

Acknowledgment: We thank the "Laboratoires Fournier" of Dijon for the financial support of this work through a grant to Catherine Sylvain.

References and Notes.

1. For reviews, see: Schipchandler MT, Synthesis, 1979;666-686. Shvekhgeimer MGA. Russ. Chem. Rev. 1998;67:35-68. Seebach D, Colvin EW, Lehr F, Weller T. Chimia, 1979;33:1-18. Rosini G, Ballini R. Synthesis 1988;833-847.
2. Nef JU. Annalusis 1894;280:264-268. Pinnick HW. Org. React. 1990;38:655-792. McMurry JE, Melton J, Padgett H. J. Org. Chem. 1974;39:259-260. McMurry JE, Melton J. J. Org. Chem. 1973;38:4367-4373. Olah GA, Gupta BGB. Synthesis 1980:44-45. Crosslay MJ, Crumbie RL, Fung YM, Potter JJ, Pegler MA. Tetrahedron Lett. 1987;28:2883-2886.
3. Mori H, Okubo M, Oke YO, Noguchi N, Miho F. Chem. Pharm. Bull. 1984;32:2200-2204. Steinkopf W Justus Liebigs Ann. Chem. 1923;434:28-32.
4. Seebach D, Hungerbühler E, Naef R, Schnurrenberger P, Weidmann B, Zuger M. Synthesis;1982:138-140. Hellmann H, Hallmann G, Linsens F. Chem. Ber. 1953;86:1346-1361.
5. Feuer H, Monter RP. J. Org. Chem. 1969;34:991-995.
6. Sifniades S. J. Org. Chem. 1975;40:3562-3566. Cohen JB. J. Chem. Soc. 1911;99:1058-1066.
7. Armarego W F. J. Chem. Soc. © ;1969:986-990. Zen S, Koyama M, Koto S. Org. Synth. 1976;55:77-79.
8. *Typical procedure for the preparation Merrifield resin-bound nitroacetic ester :* A solution of DCC (6.3 g, 30 mmol) in THF (10 mL) is added to a suspension of hydroxylated Merrifield resin (6.1 g, 1.1 meq/g) in THF (25 mL). The mixture is shaken and cooled to 0 °C. Nitroacetic acid (3.2 g, 30 mmol) in THF (10 mL) is then added over a period of 3 hours. The reaction is warmed up to room temperature and sonicated overnight. The resin is then thoroughly washed with a mixture of methanol/DMF 1/1 (200 mL) followed by dichloromethane (200 mL). After drying under vacuum IR spectrum of the resin exhibited the typical ester and nitro signals at 1752 and 1560 cm^{-1}. Combustion analysis indicates a loading of approximately 1 meq/g.