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Domino Processes as a Tool for Recovering Substandard Reactions. Synthesis and Use of Nitroacetic Acid Esters and Amides

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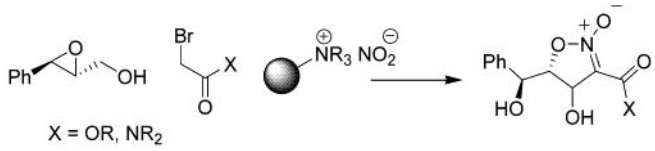
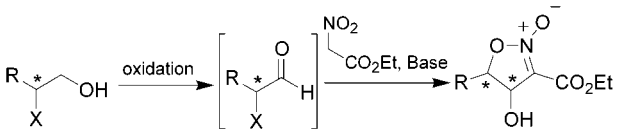
ABSTRACT



Elusive nitroacetic acid esters and amides were obtained through a halogen exchange reaction of the corresponding bromoacetic acid derivatives with polymer-supported nitrite anion. The process is flawed by a side product catalyzed degradation of the products. Domino processes turned out to be a powerful tool for overcoming such drawbacks, converting a substandard reaction into an efficient multicomponent preparation of 4-hydroxy-4,5-dihydroisoxazoles.

Multibond-forming reactions are especially effective in forming complex structures from relatively simple starting materials.[1] Over the last few years, we have developed new mild multibond-forming reactions for the preparation of valuable systems[2] such as 4-hydroxy-4,5-dihydroisoxazoles[3] (Scheme 1) and other interesting heterocycles.[4] A variety of electrophiles were used as starting materials for these processes,[5] while little variation was ever tried for the nitroacetic acid derivative.

Scheme 1. One-Pot Synthesis of 4-Hydroxy-4,5-dihydroisoxazoles



We became interested in adding an additional element of diversity to this process, by varying the nitroacetic acid derivative. These are simple yet elusive intermediates, useful in the preparation of biologically interesting compounds such as nitrogen-containing heterocycles[6] and unusual α-amino acids.[7] Despite this, very few general and convenient methods for their preparation are available.[6,8] The reaction between

[†] Tesi di Laurea, 2001. Università di Bologna.

(1) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(2) (a) Wade, P. A.; Shah, S. S.; Govindarajan, L. *J. Org. Chem.* **1994**, *59*, 7199. (b) Panek, J. S.; Beresis, R. T. *J. Am. Chem. Soc.* **1993**, *115*, 7898. (c) Schwab, W.; Jäger, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 603. Review: Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Osfrod, 1991; Vol. 4, p 1069.

(3) (a) Marotta, E.; Micheloni, L. M.; Scardovi, N.; Righi, P. *Org. Lett.* **2001**, *3*, 727. (b) Marotta, E.; Baravelli, M.; Maini, L.; Righi, P.; Rosini G. *J. Org. Chem.* **1998**, *63*, 8235, and references therein.

(4) (a) Righi, P.; Marotta, E.; Rosini, G. *Chem. Eur. J.* **1998**, *4*, 2501. (b) Righi, P.; Marotta, E.; Landuzzi, A.; Rosini, G. *J. Am. Chem. Soc.* **1996**, *118*, 9446, and references therein.

(5) α,*β*-Epoxy-, α-sulfonyloxy, *N*-tosyl α,*β*-aziridine-, α-bromo-aldehydes, and α-bromo enones were all successfully employed in these mild processes. For details, see refs 3 and 4.

(6) For a recent review, see: Kislyi, V. V.; Samet, A. V.; Semenov, V. V. *Curr. Org. Chem.* **2001**, *5*, 553.

(7) (a) Alvarez-Ibarra, C.; Csáky, A. G.; Gómez de la Oliva, C. *J. Org. Chem.* **2000**, *65*, 3544. (b) Tsukamoto, T.; Kitazume, T.; McGuire, J. J.; Coward, J. K. *J. Med. Chem.* **1996**, *39*, 66. (c) Hollinshead, S. P.; Trudell, M. L.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1990**, *33*, 1062.

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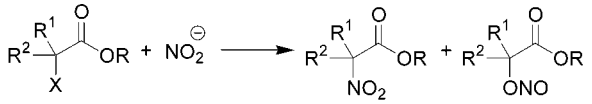
α-haloesters and nitrite anion is a general way of preparing α-nitroesters,[9] though varying amounts of the corresponding nitrite esters are obtained (Scheme 2).

Scheme 2. Synthesis of Nitroalkanes



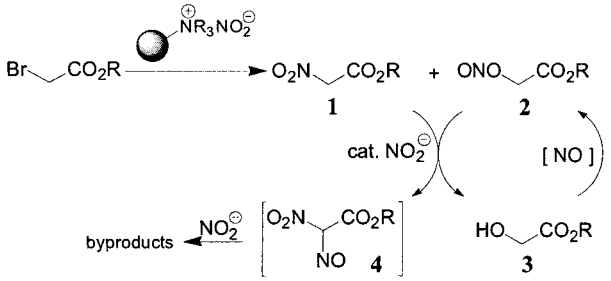
Although iodoacetates and silver nitrite can sometimes be used,[10] the readily available bromoacetates and sodium nitrite would represent a more convenient alternative.[11] Unfortunately, nitroacetates cannot be prepared by this method.[6,12]

In this Letter, we report a general method for the preparation of nitroacetic acid esters and amides from the corresponding α-bromoacetic acid derivatives and a convenient reusable polymer-supported nitrite anion source. This method turned out to be much more effective when inserted into a one-pot multibond-forming process for the preparation of 4-hydroxy-4,5-dihydroisoxazoles from α,*β*-epoxy alcohols, α-bromo acetates, or acetamides.

We were attracted by the method developed by Gelbard and Colonna,[13] where branched α-bromoesters are treated with polymer-supported nitrite anion (Amberlite IRA 900, NO_2^- form), in anhydrous benzene, at room temperature, to form the corresponding α-nitroesters.[14] Again, the preparation of no nitroacetic acid ester was reported.

When we applied these reaction conditions[15] to ethyl bromoacetate, an almost instantaneous reaction took place, leaving ethyl hydroxyacetate as the only detectable product instead of the expected nitro/nitrite mixture of products. A coarse screening of solvents and temperatures allowed us to identify that when the same reaction is performed in acetonitrile at −15 °C, a mixture of ethyl nitroacetate (**1**, R = Et) and the corresponding hydroxyl acetate (**3**, R = Et) is obtained (Scheme 3). Prolonged exposure of the reaction

Scheme 3. Polymer-Supported Nitrite Anion Substitution Reaction of Bromoacetates



mixture to the resin, after the starting material is consumed, leads to the complete decomposition of the nitro derivative, leaving only hydroxyacetate.

In the course of our study, we made the following observations. (i) A reaction mixture, where degradation is half complete, survives unchanged for several days at room temperature after the resin is filtered. (ii) Pure ethyl nitroacetate in acetonitrile (**1**, R = Et) undergoes no decomposition when exposed to the polymer-supported nitrite at room temperature. (iii) When a catalytic amount (5%) of ethyl bromoacetate is added to the latter solution, cooled at −15 °C, a comparably small amount of **3** is readily formed and a slow degradation of the nitroacetate is observed; warming to room temperature completes the degradation in a few hours, and during this period, no increase in the level of hydroxyacetate **3** is observed. From these experiments, it follows that (i) the nitrite anion and (ii) the byproducts are both necessary for the degradation to proceed; (iii) only a catalytic amount of byproducts is sufficient to complete the degradation, and at −15 °C, the catalytic cycle has a slow turnover. These observations are summarized in Scheme 3.

Product **1**, deprotonated by the nitrite anion, undergoes a fast nitrosation by the nitrite ester[16] to form byproduct **4** and hydroxyacetate **3**. Nitroso derivative **4** can be further deprotonated to collapse into a series of byproducts,[17] some of which have nitrosating properties, thus closing the catalytic cycle by slowing the regeneration of the nitrite ester **2** from **3**. It is important to stress that this catalytic degradation can be observed only for activated primary nitroalkanes, since it requires easy double deprotonation of the carbon bearing the nitro group.

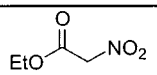
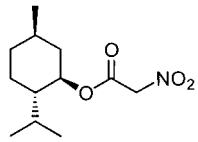
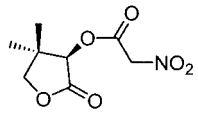
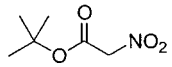
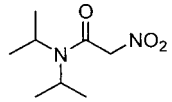
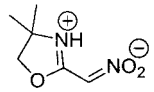
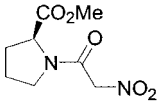
Attempts to intercept the initially formed nitrite ester by the use of known scavengers such as phloroglucinol[11] and 1,1′-(1,3-phenylen)dipyrrolidine[14] only resulted in the reduction of reaction rates to unacceptable levels. The effect of the halogen was also investigated, revealing, as expected, that chloroacetates react very slowly (28% conversion after 48 h at room temperature) and iodoacetates react slightly faster but with no selectivity (1:1 ratio of nitroacetate and hydroxyacetate).

The following procedure was then adopted. The dried resin (2 equiv) was suspended in acetonitrile. The mixture was cooled to −15 °C, and the bromoacetic acid derivative (1 equiv) was added. After the starting material was consumed, the resin was quickly filtered. A series of bromoacetic acid derivatives were tested under these conditions, and the results are reported in Table 1.

The spent resin can be regenerated by washing it with 1 N $NaNO_2$ until a negative AgCl test of the eluate is achieved. As an example, in the preparation of ethyl nitroacetate, the same resin was reused three times with no detectable adverse effects on reaction times, yields, and selectivity.

(8) Shipchandler, M. T. *Synthesis* **1979**, 666.
(9) Other general methods require the preparation of nitroacetic acid from its salts by heating nitromethane under strong alkaline conditions.
(10) Kornblum, N.; Chalmers, M. E.; Daniels, R. *J. Am. Chem. Soc.* **1955**, *77*, 6654.
(11) Kornblum, N.; Blackwood, R. K.; Powers, J. W. *J. Am. Chem. Soc.* **1957**, *79*, 2507.
(12) Kornblum, N.; Eicher, J. H. *J. Am. Chem. Soc.* **1956**, *78*, 1494.
(13) Gelbard, G.; Colonna, S. *Synthesis* **1977**, 113.
(14) Use of tetralkylammonium nitrites has also been reported: Munz, R.; Simchen, G. *Liebigs Ann. Chem.* **1979**, 628.
(15) Polymer-supported nitrite (4 mequiv/g), commercially available from Fluka Co., was used throughout this work.
(16) Kornblum, N.; Weaver, W. M. *J. Am. Chem. Soc.* **1958**, *80*, 4333.
(17) Jovitschitsch, M. Z. *Ber.* **1895**, *28*, 1213; **1906**, *39*, 785.

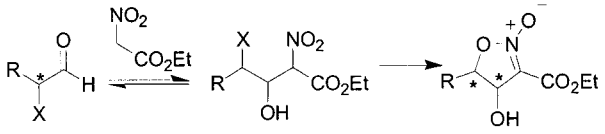
Table 1. Formation of α-Nitroacetic Acid Derivatives

entry	product	yield (%) of **1**	yield (%) of **3**
a		65	28
b		57	19
c		31[a]	48
d		74[b]	10
e		68[b]	18
f		53	27
g		60[a]	17

[a] Determined by GC. [b] Determined by NMR of the crude product.

Although this new preparation of nitroacetic acid esters and amides by halogen exchange reaction of the corresponding bromoacetic acid derivatives can be regarded as a very good achievement in relative terms (in the literature this reaction is considered as not viable),[18] this is a substandard process in absolute terms. However, in view of our needs, i.e., the preparation of diversely substituted 4,5-dihydroisoxazoles according to Scheme 1, the formation of byproducts of type **3** should not be detrimental since they are inert under those reaction conditions. So, we tried to overcome this problem by generating the nitroacetic acid derivatives in the presence of the aldehyde. In fact, we knew that in that reaction medium, nitroacetates are rapidly engaged in a nitroaldol equilibrium.

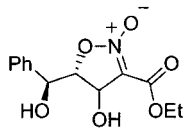
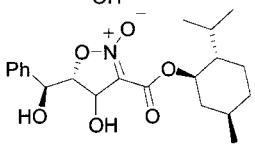
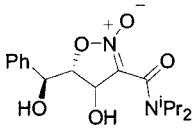
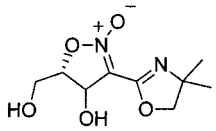
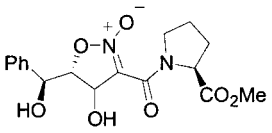
Scheme 4. Formation of 4-Hydroxy-4,5-dihydroisoxazoles



However, the irreversible intramolecular cyclization only takes place at temperatures close to the ambient values, where the catalytic degradation of nitroacetates (Scheme 3) is faster. So, as a compromise, we chose to run these new domino processes at 0 °C (Scheme 5). According to our standard procedure,[3a] *trans*-3-phenylglycidaldehyde was generated in situ by oxidation[19] of the corresponding alcohol (1 equiv) at room temperature. The mixture was cooled to 0 °C, and the domino reaction was started by adding the bromoacetic acid derivative (1 equiv), the polymer-supported nitrite (2 equiv), and diisopropylethylamine (3.3 equiv) to the aldehyde. After the mixture was stirred for 24 h at 0 °C, the corresponding 4,5-dihydroisoxazoles **5** were isolated as a ca. 6:4 mixture of 4,5-cis and 4,5-trans isomers.[3a]

This one-pot multibond-forming process employs a glycidol, polymer-supported nitrite anion, and a bromoacetic acid or amide as starting materials. After the initial in situ oxidation, three steps occur in a domino fashion: a halogen exchange, a nitroaldol C−C bond formation, and an intramolecular ring closure, allowing a substantial increase in structural complexity on going from reactants to products.

Table 2. Overall Yields of the Reactions Depicted in Scheme 5

entry	product	domino (%)	two-step (%)
a		84	45
b		81	48
e		74	20
f[a]		89	33
g		80	45

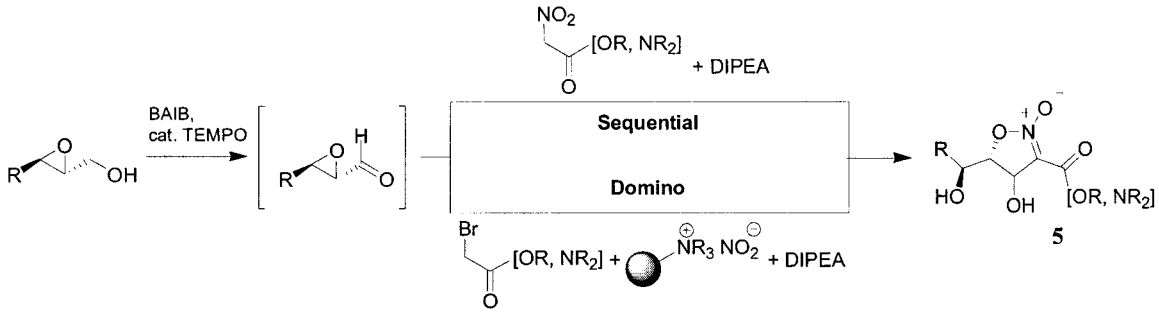
[a] Glycidol was used as the starting epoxy alcohol.

As a control, the same reactions were also performed in the usual two-step sequential way (Scheme 5): first the halogen exchange reaction was performed according to Scheme 3, and then the crude product obtained was used as the nitroacetic component in the following 4,5-dihydroisoxazole preparation. The overall yields of the two processes are reported in Table 2.

(18) "The halogen exchange reaction cannot be used for the synthesis of nitroacetic acid derivatives." This is the opening sentence of a very recent review on the preparation and use of these substrates. See ref 6.

(19) Piancatelli, G.; Margherita, R.; De Mico, A.; Parlanti, L.; Vescovi, A. *J. Org. Chem.* **1997**, *62*, 6974.

Scheme 5. One-Pot Sequential and Domino Preparations of 4-Hydroxy-4,5-dihydroisoxazoles



These results clearly show that this new domino process not only benefits from the reduction of waste, solvents, reagents, adsorbents, energy, and labor[1] that is characteristic of every efficient domino process when compared to stepwise processes, it also allows the products to be obtained in significantly higher yields than those that could be expected from the combination of the yields of each single step.

Therefore, this process demonstrates a concept that will find wider applicability: the domino methodology can be a powerful tool for getting the most out of reactions that are to be considered substandard if run in a stepwise manner. Further extensions of this concept are currently under investigation in our laboratories.

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Supporting Information Available: Descriptions of experimental procedures, selected characterization data, actual NMR spectra of 4,5-*trans*- and 4,5-*cis*-4-hydroxy-4,5-dihydroisoxazoles 2-oxides **5b**, **5e**, and **5f** or their derivatives, and actual IR spectra of **5b** and **5e** or their derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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