# A New Synthesis of α-Amino Acid Derivatives Employing Methyl Nitroacetate as a Versatile Glycine Template

Richard S. Fornicola, Eric Oblinger, and John Montgomery*

*Department of Chemistry, Wayne State University, Detroit, Michigan 48202-3489*

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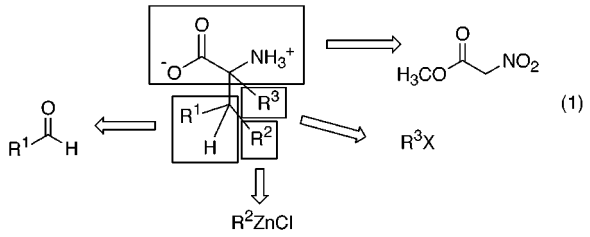
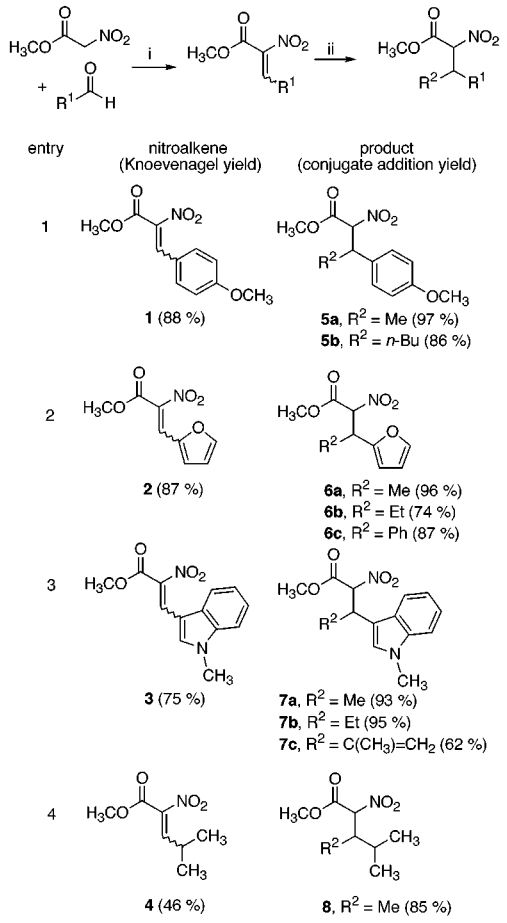
Non-natural α-amino acids are highly versatile building blocks in the preparation of a variety of pharmaceutically significant molecules.[1,2] Applications include small molecule drug discovery[3] and the preparation of peptides constructed of nonproteinogenic amino acids.[4] For these applications, considerable effort has been directed toward the development of multicomponent syntheses of amino acids.[5] Most methods, such as the elegant solid-phase Ugi condensation recently reported by Armstrong, involve diversity introduction largely at the carboxyl and amino termini of the amino acid, with the α-carbon substituent itself being derived from a single component.[5a,b] The recently reported method of Petasis, involving Mannich condensations with organoboronic acids, is an efficient example in which the α-carbon substituent of an α-amino acid is derived from two components.[5c] To provide rapid access to an increasingly diverse range of unnatural amino acids, we have developed a direct linear sequence in which the amino acid framework is derived from a nitroacetate, and the α-carbon diversity is derived from three widely available components: an aldehyde, an organozinc, and a reactive electrophile (eq 1). The method provides very simple access to a broad spectrum of highly functionalized nonnatural α-amino acids.




(1)

Highly electrophilic α,β-unsaturated nitroacetates are readily assembled by the Lehnert modification of the Knoevenagel condensation employing $TiCl_4$ in the presence of *N*-methylmorpholine in THF (Table 1).[6] Aromatic and aliphatic aldehydes were tolerated in the sequence in moderate to good yield. The unsaturated nitroacetates were then directly functionalized with transmetalation-derived organozincs in THF (prepared in situ from a 1.5:1 ratio of organolithiums or Grignard reagents and zinc chloride). No catalysis is required in organozinc conjugate additions to the highly electrophilic unsaturated nitroacetates (Table 1).[7] In all cases examined, the uncatalyzed conjugate additions proceeded in good to excellent yield at 0 °C in THF to give a 1:1 mixture of diastereomers. To our knowledge, this report constitutes the first examples of conjugate additions of unstabilized carbon nucleophiles with unsaturated nitroacetates.[8]

**Table 1. Knoevenagel Condensations/Conjugate Additions**[a]




[a] Reagents and Conditions: (i) $TiCl_4$, *N*-methylmorpholine, THF, 0−25 °C; (ii) $R^2Li$ or $R^2MgBr$, $ZnCl_2$, THF, 0−25 °C.

A variety of methods for quaternization of the α-position of the functionalized nitroacetates are possible. In an important early study by Bergbreiter and Wong, a number of procedures for alkylation of α-methyl nitroacetates were developed;[9] however, functionally elaborate α-alkyl nitroacetates were not available at the time of their study. Representative alkylation procedures that we examined include palladium-catalyzed allylic alkylations (eq 2),[10] phosphine-promoted Michael additions to acrylates and

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(4) See refs 1 and 2 of the following manuscript: Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656.

(5) (a) Armstrong, R. W. *Acc. Chem. Res.* **1996**, *29*, 123. (b) Tempest, P. A.; Brown, S. D.; Armstrong, R. W. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 640. (c) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445.

(6) (a) Lehnert, W. *Tetrahedron* **1972**, *28*, 663. (b) Dauzonne, D.; Royer, R. *Synthesis* **1987**, 399.

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(8) For additions of stabilized nucleophiles to unsaturated nitroacetates, see: (a) Rodriguez, R.; Diez, A.; Rubiralta, M. *Heterocycles* **1996**, *43*, 513. (b) Dornow, V. A.; Menzel, H. *Liebigs Ann. Chem.* **1954**, *588*, 40. (c) Somei, M.; Tokutake, S.; Kaneko, C. *Chem. Pharm. Bull.* **1983**, *31*, 2153.

(9) Lalonde, J. J.; Bergbreiter, D. E.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 2323.

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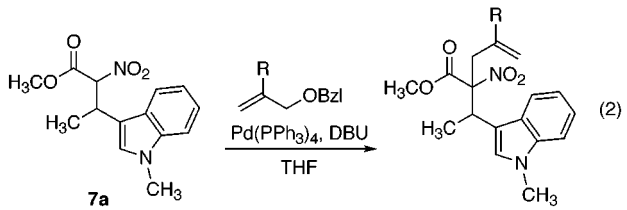
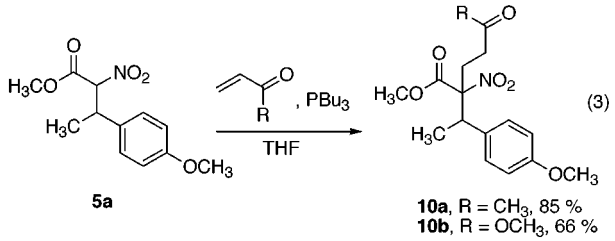
enones (eq 3),[11] and arylations employing triphenylbismuth dichloride (eq 4).[12] Generally, diastereomeric ratios in the




(2)

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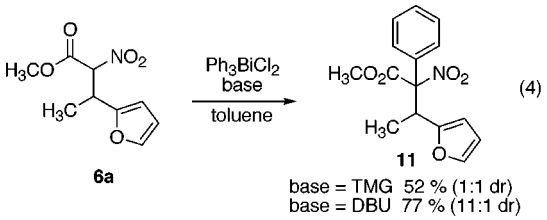
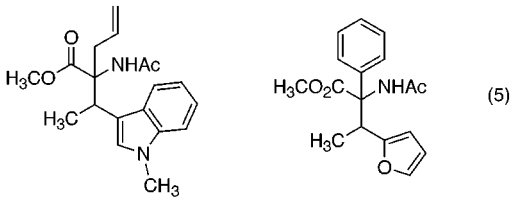



(4)

range of 1:1 or 1:2 were observed. However, we did observe in the case of the arylation procedure that base structure displayed a dramatic effect on the diastereoselectivity of the process. Tetramethylguanidine (TMG), which was originally employed by Bergbreiter and Wong,[9] afforded quite low diastereoselectivities in arylations of nitroacetates bearing chirality at the $\beta$-position. However, beginning with a 1:1 ratio of diastereomers of compound **6a**, arylation with diazabicycloundecene (DBU) as the base afforded compound **11** with a diastereomeric ratio of 11:1,[13] suggesting that a more extensive examination of base structure may improve diastereoselectivities in other variants.

The nitro functionality of nitroacetates may be effectively reduced to the primary amine by a variety of catalytic hydrogenation methods. However, yields were low with substrates **9a** and **11** due to overreduction and product decomposition. In these cases, reduction with $Sn^0$ or $Zn^0$ in AcOH was particularly effective with more desirable chemoselectivities than with catalytic hydrogenation.[14] For instance, the alkene of **12** and benzylic amine of **13** are unaffected in the tin or zinc-based reductions (eq 5). The nitro reduction products were directly derivatized with acetyl chloride and pyridine in dichloromethane prior to isolation.




(5)

In summary, a concise method for the preparation of structurally diverse $\alpha$-amino acids has been developed by a linear sequence involving Knoevenagel condensation, organozinc conjugate addition, and nitroacetate $\alpha$-alkylation.[15] The method offers significant advantages over most alternative procedures in terms of efficiency, simplicity, and potential for diversity generation. Future efforts will focus on further refinements of the scope and diastereoselectivity of the methodology, enantioselective applications, and solid- and solution-phase combinatorial applications in the preparation of various heterocyclic structures.

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**Supporting Information Available:** Experimental procedures and $^1$H NMR spectra for all reported compounds (34 pages).

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