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Diastereoselective Intermolecular Addition of the 1,3-Dioxolanyl Radical to *N*-Acyl Aldohydrazones. Asymmetric Synthesis of α-Amino Acid Derivatives

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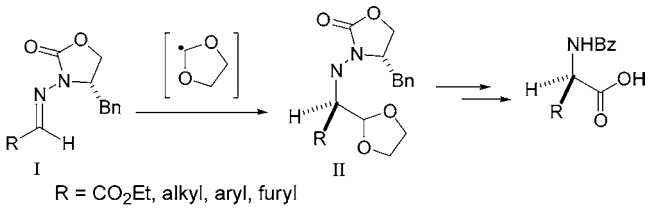
ABSTRACT



***N*-Acyl aldohydrazones I (R = CO_2Et, alkyl, aryl, and furyl) efficiently trap the 1,3-dioxolanyl radical intermolecularly without external activation at temperatures as low as −78 °C. For alkyl aldohydrazones, good diastereoselectivities are obtained in the presence of $InCl_3$ at low temperature. Elaboration of the adducts (II) allows for the asymmetric synthesis of α-amino acid derivatives.**

The intramolecular addition of a carbon-centered radical to a carbon−nitrogen π bond is sufficiently fast, for a variety of nitrogen functionalities and ring sizes, to efficiently sustain a radical chain.[1] These additions are in fact incorporated at present into a range of reliable and extraordinarily useful synthetic transformations.[2−4] The intermolecular radical addition to C=N π bonds, however, proved to be troublesome; e.g., plain aldoxime ethers, which behave as excellent intramolecular carbon radical traps, were found to be reluctant to perform intermolecularly.[5] With limitations, some solutions to this problem have been advanced in the last five years.[6] In particular, it was demonstrated that the intermolecular addition of carbon radicals is indeed synthetically useful for a variety of compounds where the C=N bond is activated by electron-withdrawing substituents.[7] Among them, glyoxylic imine derivatives have attracted the most attention because their adducts are α-amino acid derivatives, and their performance as radical traps has been studied for glyoxylate aldoxime **IIIa**[7e] and a variety of acyclic and cyclic related imines **IIIb**[7f] and **IIIc**[7f] (Figure 1, route A). While room still exists for improving yields and/or selectivity, the

(1) Even fully carbon-substituted C=N double bonds intramolecularly trap alkyl and vinyl radicals in the 1,5-exo ((a) Noya, B.; Alonso, R. *Tetrahedron Lett.* **1997**, *38*, 2745−2748. (b) Noya, B.; Paredes, M. D.; Ozores, L.; Alonso, R. *J. Org. Chem.* **2000**, *65*, 5960−5968.) and 1,6-exo modes (unpublished).

(2) For a review on *free radical cyclizations involving nitrogen*, including a compilation of cyclization and ring-opening rate constants for some representative cases, see: Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543−17594.

(3) For a review on the *addition of carbon-centered radicals to imines and related compounds*, see: Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461−5496.

(4) Although most examples apply to the addition at the C atom of the C=N bond, intramolecular addition at nitrogen is also known and synthetically useful; see: (a) Viswanathan, R.; Prabhakaran, E. N.; Plotkin, M. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 163−168. (b) Falzon, C. T.; Ryu, I.; Schiesser, C. H. *Chem. Commun.* **2002**, 2338−2339 and references therein. See also refs 2 and 3.

(5) Substitution at the radical trapping center, the sp^2 carbon atom of the aldoxime, is responsible for slowing and preventing the intermolecular addition of carbon radicals. In fact, the reaction takes place when the radical trapping center is unsubstituted, i.e., for formaldehyde-derived aldoxime ethers (H_2C=NOR): (a) Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631−1633. (b) Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.* **1991**, *32*, 3555−3556.

(6) For a detailed account, see ref 3, pp 5481−5492. See also ref 7.

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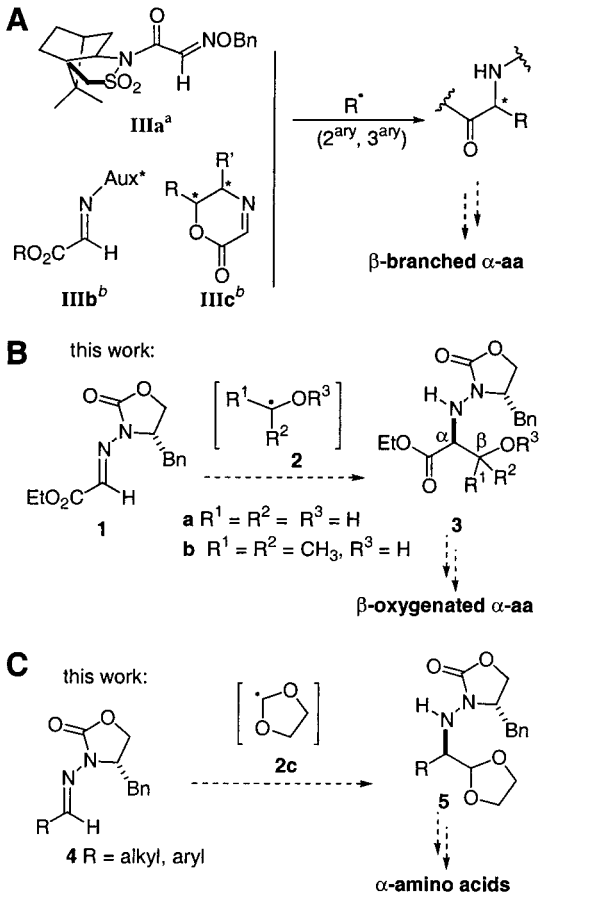


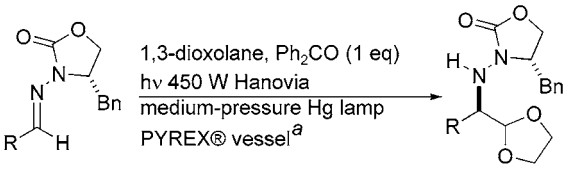
Figure 1. Route A: glyoxylic imine derivatives (**IIIa**−**c**) previously studied as radical traps for the preparation of α-amino acid derivatives. For **IIIa** see ref 7e. For details on the nature of Aux, R, and R′ in **IIIb** and **IIIc**, see ref 7f. Routes B and C: new synthetic pathways to α-amino acid derivatives now evaluated.

results obtained thus far point out a very important limitation inherent to the developed methodologies: they are inappropriate in their present form for the addition of primary carbon radicals, i.e., they are limited in practice to the preparation of *β*-branched α-amino acids.

We report herein further advances in this area after exploring: (a) the performance of the glyoxylic hydrazone **1** for the diastereoselective intermolecular trapping of α-oxygenated carbon radicals, i.e., the potential of **1** as a precursor of *β*-oxygenated α-amino acids (Figure 1, route B), and (b) the addition of the 1,3-dioxolanyl radical to alkyl and aryl *N*-acyl hydrazones **4** as a, presumably general, free-radical-based method for preparing enantiomerically pure α-amino acid derivatives (Figure 1, route C). The high stereoinduction reported for the 4-benzyl-2-oxazolidinone auxiliary[8] and the good behavior shown by α-oxygenated carbon-radicals, particularly the 1,3-dioxolanyl radical, when they add intermolecularly to C=N bonds[9] augured well for a successful endeavor.

To check route B, we irradiated solutions of hydrazone **1** and benzophenone in methanol, 2-propanol, and 1,3-dioxolane at room temperature. According to our expectations, we indeed obtained adducts **3a**, **3b** (31%, 55%, unoptimized, Figure 1B), and **3c** (88%, Table 1, entry 1), respectively.[10]

Table 1. Photoinduced Radical Addition of the 1,3-Dioxolanyl Radical onto Activated (**1**) and Inactivated (**4a**) *N*-Acyl Aldohydrazones



entry		*T* (° C)	$InCl_3$	time (h)	product (yield)[b]	dr[c]
1	**1**	rt			**3c** 88%	1.5:1
2	**1**	−78		0.25	**3c** ∼quant	4.1:1
3	**1**	−78	2 equiv	0.5	**3c** 63−72%	4.1:1
4	**4a**	rt		0.5	**5a** ∼quant	1.8:1
5	**4a**	−78		4.5	**5a** 68%	4.6:1
6	**4a**	−78	2 equiv	1.25	**5a** 87%	10.1:1[d]

[a] For details see Supporting Information. [b] Isolated yields. [c] Diastereoselectivities were determined by ^1H NMR analysis. [d] Dr = 99:1 for the one-pot procedure: see text, Scheme 1, and Table 2, entry 1.

The reaction proceeded quickly (<2 h) in the absence of external activators, clearly reflecting the combined beneficial effect of the activating ethoxycarbonyl group in **1** and the comparatively higher nucleophilicity of radicals **2a**−**c**.[11] Such an effect was particularly notable for the last case, where the addition of the 1,3-dioxolanyl radical took place even at −78 °C to efficiently give **3c** in only 15 min (Table 1, entry 2).

The stereoselectivity of the addition, studied for **3c**, was, however, low: the small diastereomeric ratio of 1.5:1

(7) Compounds where a C=N bond activated by electron-withdrawing substituents successfully traps carbon radicals intermolecularly include the following. α-Sulfonyl oxime ethers: (a) Kim, S.; Song, H.-J.; Choi, T.-L.; Yoon, J.-Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2524−2526. (b) Kim, S.; Yoon, J.-Y. *J. Am. Chem. Soc.* **1997**, *119*, 5982−5983. (c) Kim, S.; Lee, I. Y.; Yoon, J.-Y.; Oh, D. H. *J. Am. Chem. Soc.* **1996**, *118*, 5138−5139. Glyoxylic aldoxime ethers: (d) Miyabe, H.; Nishimura, A.; Ueda, M.; Naito, T. *Chem. Commun.* **2002**, 1454−1455. (e) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176−185. Glyoxylic aldimines: (f) Bertrand, M. P.; Coantic, S.; Feray, L.; Nouguier, R.; Perfetti, P. *Tetrahedron* **2000**, *56*, 3951−3961 and references therein. Glyoxylic aldonitrones: (g) Ueda, M.; Miyabe, H.; Teramachi, M.; Miyata, O.; Naito, T. *Chem. Commun.* **2003**, 426−427. *N*-Sulfonylimines: (h) Miyabe, H.; Ueda, M.; Naito, T. *Chem. Commun.* **2000**, 2059−2060.

(8) Friestad recently introduced 2-oxazolidinones as auxiliaries for the asymmetric synthesis of amines: (a) Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2001**, *123*, 9922−9923. (b) Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2000**, *122*, 8329−8330.

(9) We have recently demonstrated that the use of α-oxygenated carbon radicals in intermolecular radical addition is particularly convenient, so that even fully carbon-substituted ketoxime ethers efficiently trap them: Torrente, S.; Alonso, R. *Org. Lett.* **2001**, *3*, 1985−1987. In these cases, and as an additional synthetic advantage, the addition results in higher functionalized adducts. See also: (a) Yamada, K.; Fujihara, H.; Yamamoto, Y.; Miwa, Y.; Taga, T.; Tomioka, K. *Org. Lett.* **2002**, *4*, 3509−3511. (b) Kim, S.; Kim, N.; Chung, W.; Cho, C. H. *Synlett* **2001**, 937−940.

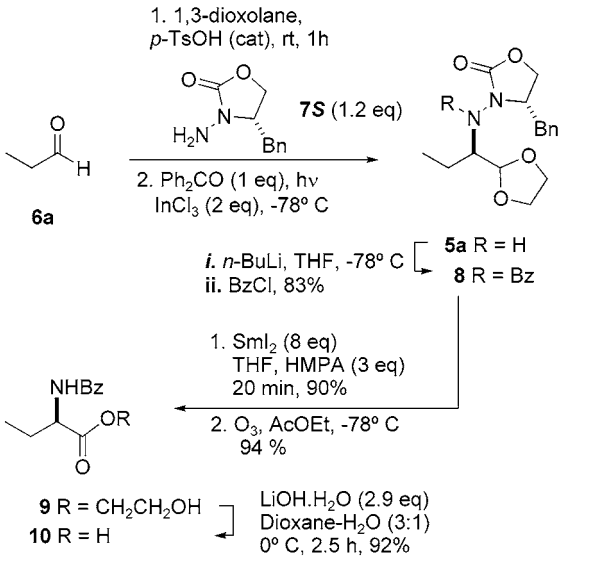
(10) For details see Supporting Information.

(11) Use of an external activating agent was found to be mandatory for the intermolecular addition of plain carbon radicals to inactivated *N*-acylhydrazones: see ref 8.

obtained at room temperature could only be moderately increased to 4.1:1 at low temperature, with no further improvement on adding chelating $InCl_3$ (Table 1, entries 1−3). While we were concerned with the stability of both the starting hydrazone and the final adduct under the H-abstracting photochemical conditions, we observed neither dimerization nor change of the diastereomeric ratio on prolonged irradiation under the reaction conditions. It thus appears that the solvent was adequately protecting these systems from hydrogen abstraction and subsequent side reactions, making meaningful the use of the same photochemical radical generation procedure for further studies on diastereoselectivity. For these, we selected hydrazone **4a**, which incorporates not an electron-withdrawing activating substituent but rather an ethyl group. Although, as expected, its reactivity against the 1,3-dioxolanyl radical diminished as compared to **1**, the addition still proceeded quickly at room temperature (0.5 h) and at a convenient rate even at low temperatures (4.5 h at −78 °C) (Table 1, entries 4 and 5). Regarding stereoselectivity, it was only slightly higher than that obtained for **1**, both at room temperature and at −78 °C, but now, for **4a**, the addition of $InCl_3$ (2 equiv) had a remarkable effect and the diastereomeric ratio reached a value of 10.1:1 in a considerably reduced reaction time (Table 1, compare entries 5 and 6).

The process could be done in one pot starting from propionaldehyde (**6a**).[12] Its treatment with (*S*)-3-amino-4-benzyl-1,3-oxazolan-2-one (**7*S***)[13] in 1,3-dioxolane in the presence of catalytic amounts of *p*-TsOH for 1 h, followed by UV irradiation (1−1.5 h) in the presence of Ph_2CO and $InCl_3$ at −78 °C, led to **5a** (241−681 mg scale) with improved yields (93−99% overall) and selectivities (dr = 99:1−98:2, Scheme 1). To demonstrate the usefulness of this

Scheme 1



addition as the key step for the asymmetric synthesis of α-amino acids, we transformed **5a** into **10** as indicated in Scheme 1.[14,15] Initial conversion of **5a** into its benzamide derivative **8** allowed for additional stereomeric enrichment by crystallization and the subsequent preparation of **10** with properties identical to those of an authentic sample prepared from pure (*R*)-2-aminobutyric acid.[10,16] It thus follows that the stereochemical outcome of the reaction results from the overwhelming preferential addition of the dioxolanyl radical on the In-chelated *N*-acyl hydrazone from the opposite face to the benzyl group.[8b,17] Noteworthy, the same face is the most exposed one for the nonchelated hydrazone, a factor that undoubtedly contributes to the high net stereochemical induction observed.

We finally made a preliminary survey on the scope and limitations of the method applying the one-pot protocol to relevant aldehydes **6b**−**e**. Aldehydes **6b** and **6c** were selected to study the influence of α-branching, either with alkyl or with oxygenated substituents, and also because of the significance of the corresponding amino acids derived from them. The process worked well for **6b**, which afforded adduct **5b** with good diastereoselection (dr = 97:3), thus opening a new pathway for the asymmetric synthesis of cyclopropyl-substituted amino acids.[18] For the special case of **6c**, carrying a dimethyl acetal function, the overall yield and the stereoselectivity were lower than those for **6b** but still sufficient (75%, 95:5) to be of practical synthetic value; thus, good prospects exist for the application of this methodology to the preparation of α-acetal α-amino acids.[19,20]

As for the aromatic aldehydes **6d** and **6e**, the reaction was quick and efficient to render the corresponding adducts in good yields.[21] Chiral induction at the α center was, however, either nonexistent for 4-methoxy-benzaldehyde or of the

(12) For the nonasymmetric one-pot intermolecular radical addition to aldimines derived from aromatic aldehydes, see: Yamada, K.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2003**, *5*, 1797−1799.

(13) *S*)-3-Amino-4-benzyl-1,3-oxazolan-2-one (**7*S***) was prepared from commercial (*S*)-4-benzyl-1,3-oxazolan-2-one (Supporting Information). For a recent work on the comparison of electrophilic amination reagents for N-amination of 2-oxazolidinones, see: Shen, Y.; Friestad, G. K. *J. Org. Chem.* **2002**, *67*, 6236−6239.

(14) Numerous methods have been reported for the reductive cleavage of N−N bonds; see: Enders, D.; Lochtman, R.; Meiers, M.; Müller, S.; Lazny, R. *Synlett* **1998**, 1182−1184 and references therein.

(15) Deslongchamps and Moreau first reported that aldehyde acetals reacted with ozone to give esters in high yield: Deslongchamps, P.; Moreau, C. *Can. J. Chem.* **1971**, *49*, 2465−2467. For additional methods, see: Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Synlett* **1999**, 777−779 and references therein.

(16) Commercially available (*R*)-2-aminobutanoic acid was converted to **10** according to: Nosho, Y.; Seki, T.; Kondo, M.; Ohfuji, T.; Tamura, M.; Okai, H. *J. Agric. Food Chem.* **1990**, *38*, 1368−1373.

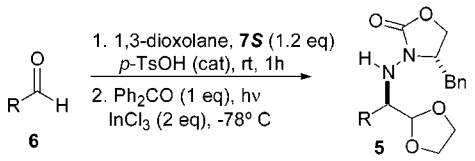
(17) Access to the enantiomer of **10** would be possible starting with **7*R***, accessible in turn from (*R*)-4-benzyl-1,3-oxazolan-2-one (see ref 13), which is also commercially available at approximately the same price as its enantiomer.

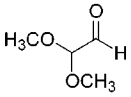
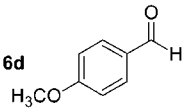
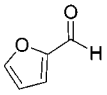
(18) First stereocontrolled synthesis of (*S*)-cleonin and related cyclopropyl-substituted amino acids has been recently published: Esposito, A.; Piras, P. P.; Ramazzotti, D.; Taddei, M. *Org. Lett.* **2001**, *3*, 3273−3275.

(19) For the first asymmetric synthesis of (*R*)- and (*S*)-2-amino-3,3-dimethoxypropanoic acid (α-formylglycine dimethylacetal), including references for its previous use in synthesis, see: DeMong, D. E.; Williams, R. M. *Tetrahedron Lett.* **2002**, *43*, 2355−2357.

(20) Although still not tested, controlled oxidation of **5c** should only affect the dioxolane ring, as acyclic dialkoxy acetals react much more slowly than cyclic ones due to stereoelectronic control: (a) Deslongchamps, P.; Atlani, P.; Frehel, D.; Malaval, A.; Moreau, C. *Can. J. Chem.* **1974**, *52*, 3651−3664. See also: (b) Li, S.; Deslongchamps, P. *Tetrahedron Lett.* **1993**, *34*, 7759−7762, (c) Sueda, T.; Fukuda, S.; Ochiai, M. *Org. Lett.* **2001**, *3*, 2387−2390. (d) Plesničar, B.; Cerkovnik, J.; Tuttle, T.; Kraka, E.; Cremer, D. *J. Am. Chem. Soc.* **2002**, *124*, 11260−11261 and references therein. See also ref 15.

Table 2. One-Pot Conversion of Aldehydes into Chiral α-1,3-Dioxolanyl Amines **5**



entry	RCHO	product (yield %,[a] dr[b])
1	**6a** 	**5a** (93-99%, 98:2)
2	**6b** 	**5b** (85%, 97:3)
3[c]	**6c** 	**5c** (75%, 95:5)
4	**6d** 	**5d** (88%, 1:1)
5	**6e** 	**5e** (93%, 4:1)

[a] Isolated overall yields after two steps from the aldehyde (except for **5c**; see note *c*). [b] Diastereoselectivities were determined by ^{1}H NMR analysis; for details, see Supporting Information. [c] For **6c**, the aldohydrazone (**4c**, not shown) was first prepared in refluxing methanol in the presence of 3 Å molecular sieves; then, the radical addition was performed on chromatographed **4c** (96% yield), containing about 5% **4** (R = CHO).

same order as that for activated hydrazone **1** when starting from furfural.

In summary, the tendencies of photochemically generated 1,3-dioxolanyl radicals and acyl-, alkyl-, aryl-, and furyl-substituted *N*-acyl aldohydrazones adequately match to render the intermolecular addition quick and efficient, even at low temperature without requiring external activators. While further work is needed to reach adequate levels of diastereoselection for acyl-substituted and aromatic systems, the addition to alkyl aldohydrazones derived from 3-amino-4-benzyl-1,3-oxazolan-2-one performs adequately to be the basis for a new method for preparing enantiomerically pure α-amino acids. The radical addition procedure is convenient in terms of (a) simplicity, i.e., it is a one-pot operation from aldehydes, (b) reaction times, between 0.25 and 4 h for the cases tested, and (c) efficiency, yields from 75 to 99% and high stereoselectivities. The uses of light and cheap and benign 1,3-dioxolane[22] as both the solvent and the primary source for the carboxy group are also of environmental relevance.

While we have illustrated the conversion of the radical adducts into α-amino acids, the 1,3-dioxolane unit is amenable to a rich array of transformations, rendering compounds **5** useful precursors of a variety of 1,2-amino-oxygenated compounds. The addition of the 1,3-dioxolanyl and related radicals is thus expected to keep receiving increased attention in organic synthesis.[23]

Acknowledgment. We thank the DGES/FEDER (Grants PB98-0606 and BQU2002-01176) and the Xunta de Galicia (Grants XUGA20905B97 and PGIDT00PXI20901PR, and a fellowship to M.F.) for funding this work.

Supporting Information Available: Preparation procedures for all intermediates and adducts and characterization data, including NMR spectra (^{1}H, ^{13}C, DEPT), for adducts **3a**−**c** and **5a**−**e** and compounds **8**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Aldehydes **6d** and **6e** were selected as potential precursors of aromatic and heteroaromatic α-amino acids, preparation of which in enantiomerically pure form is complicated because of their comparatively easier base-catalyzed epimerization of the acidic α-methine proton. For a recent contribution, see: Saaby, S.; Bayón, P.; Aburel, P. S.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4352−4361.

(22) For a report on the properties of 1,3-dioxolane, including toxicological and environmental issues, see: http://www.epa.gov/chemrtk/dioxlne/c12846.pdf.

(23) For a treatise, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon*−*Carbon Bonds*; Pergamon Press: Oxford, 1986; pp 69−77. Recent work in this field includes: (b) Yoshimitsu, T.; Arano, Y.; Nagaoka, H. *J. Org. Chem.* **2003**, *68*, 625−627. (c) Mosca, R.; Fagnoni, M.; Mella, M.; Albini, A. *Tetrahedron* **2001**, *57*, 10319−10328. (d) Hirano, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2000**, 2457−2458. (e) Manfrotto, C.; Mella, M.; Freccero, M.; Fagnoni, M.; Albini, A. *J. Org. Chem.* **1999**, *64*, 5024−5028.