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Addition of Electrophilic and Heterocyclic Carbon-Centered Radicals to Glyoxylic Oxime Ethers

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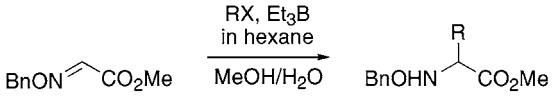
ABSTRACT



R = stabilized primary or secondary heterocyclic

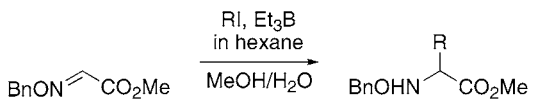
Stabilized primary radicals can be formed from alkyl halides in an atom transfer process with Et_3B. This process depends on the strength of the carbon–halogen bond and the stability of the resulting primary radical. Radicals formed from benzyl iodide and ethyl iodoacetate add to glyoxylic oxime ethers; however, more electrophilic radicals do not. Glyoxylic oxime ethers are also good radical acceptors for heterocyclic carbon-centered secondary radicals, giving novel α-amino acid derivatives.

The carbon−nitrogen double bonds of imine derivatives are of great interest as radical acceptors in synthetic organic chemistry.[1] The reductive radical addition to C=N bonds is important due to the prevalence of organic compounds in nature that contain the amine functional group. The use of environmentally benign conditions, especially aqueous media for radical reactions, is of increasing importance.[2−4] Triethylborane has proved to be a good reagent for radical reactions in water or aqueous media via an atom transfer process.[2,3] We have been interested in the intermolecular radical addition to glyoxylic oxime ethers using Et_3B in aqueous conditions.[2]

So far, the studies of reductive radical additions to glyoxylic oxime ethers have focused on the use of simple alkyl halides such as *i*-PrI, *s*-BuI, *c*-PenI, and *c*-HexI (**2**, Scheme 1).[5] A few alkyl halides containing ethers or a halogen have also been used.[6,7]

A number of factors are known to influence the addition of carbon radicals to glyoxylic imine derivatives.[7] These include the reactivity of the imine derivative, which can be increased through the addition of Lewis acids[7,8] and the nucleophilicity of the radical. Another factor governing the reaction is the efficiency of the atom transfer process between the ethyl radical formed from Et_3B and the alkyl halide. This same factor is also involved in the Et_2Zn-mediated radical additions to glyoxylic imines.[9] The efficiency of the atom transfer process is dependent on the stability of the radical formed from the alkyl halide. For this reason, secondary and tertiary alkyl halides are most commonly used.[9] It has also been noted that isopropyl bromide does not undergo the atom transfer process with Et_3B effectively.[7]

Scheme 1. Alkyl Radical Additions to Oxime Ethers



1

2 R = *i*-Pr, *s*-Bu, *c*-Pen and *c*-Hex

3 R = Et

(1) (a) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461. (b) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543.

(2) (a) Ueda, M.; Miyabe, H.; Nishimura, A.; Miyata, O.; Takemoto, Y.; Naito, T. *Org. Lett.* **2003**, *5*, 3835. (b) Miyabe, H.; Nishimura, A.; Fujishima, Y.; Naito, T. *Tetrahedron* **2003**, *59*, 1901. (c) Miyabe, H.; Ueda, M.; Naito, T. *J. Org. Chem.* **2000**, *65*, 5043.

(3) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **2002**, 674.

(4) Nambu, H.; Anilkumar, G.; Matsugi, M.; Kita, Y. *Tetrahedron* **2003**, *59*, 77.

(5) Miyabe, H.; Ueda, M.; Yoshioka, N.; Yamakawa, K.; Naito, T. *Tetrahedron* 2000, *56*, 2413.

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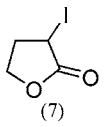
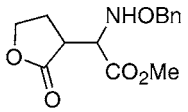
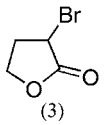
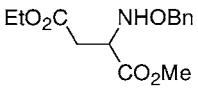
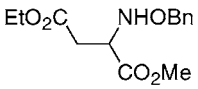
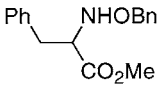
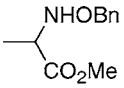
Table 1. Primary or Secondary Alkyl Radical Additions to Glyoxylic Oxime Ethers

entry	halide (equiv.)	product (diastereomeric ratio)[a]	yield (%)[b]
1	 (7)	 **4** (2:1)	49
2	 (3)	**3**	82
3	ICH_2CO_2Et (2)	 **5**	76
4	$BrCH_2CO_2Et$ (20)	 **5**	10
5	BnI (10)	 **6**	62[c]
6	BnBr (10)	**3**	50[c]
7	MeI (30)	 **7**	15
8	Allyl Iodide (10)	No reaction[d]	
9	CCl_3Br (10)	No reaction[d]	
10	$C_6F_5CH_2Br$ (10)	No reaction[d]	
11	$(CF_3)_2CFI$ (10)	No reaction[d]	

[a] Determined by ^1H NMR of the crude diastereomeric mixtures. [b] **3** was also formed in entries 1, 3, 4, and 7 in 8−49%. [c] Reaction carried out in dichloromethane. [d] Starting material was recovered.

We were interested in extending the range of alkyl halides used in the radical addition reaction to include primary and heterocyclic alkyl halides. The addition of heterocyclic carbon-centered radicals to **1** would provide a route for the synthesis of novel α-amino acid derivatives. The first heterocyclic alkyl halide that we chose to investigate was α-iodo-γ-butyrolactone.

α-Iodo-γ-butyrolactone is known to add to alkenes in aqueous conditions using Et_3B.[3] However, it was expected that this radical might be too electrophilic to add to **1**. This assumption was based on some unpublished work within our group that had shown that methyl 2-bromoacetate did not react under the same conditions. To our surprise, **4** was formed in 49% yield along with 5% of **3** (Table 1) under standard conditions.[2c] We carried out the reaction of α-bromo-γ-butyrolactone to see if this was a suitable radical precursor. However, only the ethyl adduct, **3**, was produced (82%). Clearly the atom transfer process does not take place. This result suggested to us that the carbon−halogen bond strength of methyl 2-bromoacetate might have prevented the atom transfer process from occurring. We decided to test this by carrying out the radical addition reaction with ethyl 2-bromoacetate and ethyl 2-iodoacetate. The results of these two reactions can be seen in entries 3 and 4 of Table 1. Ethyl 2-iodoacetate reacted to give the aspartic acid derivative **5** in 76% yield. In contrast, ethyl 2-bromoacetate only gave **5** in 10% yield, with 80% of **3** also being formed. This indicates that the atom transfer process is inefficient due to the strength of the carbon−halogen bond.

Table 2. Bond Strengths of Selected Alkyl Halides

entry	alkyl halide	bond strength[a] (kJ mol^{-1})	atom transfer process	radical addition yield (%)
1	*i*-Pr-I	234	++	99
2	*i*-Pr-Br	298	---	
3	$Br\text{-}CH_2CO_2H$	257[10]	+	10 (ethyl ester)
4	$I\text{-}CH_2CO_2H$	198[10]	++	76 (ethyl ester)
5	Bn-I	215	++	62
6	Bn-Br	256	---	
7	Me-I	239	++	15
8	allyl iodide	191[11]	++	
9	CCl_3-Br	231	++	
10	$C_6F_5CH_2$-Br	225	++	
11	$(CF_3)_2CF$-I	215	++	

[a] Unless indicated otherwise obtained from: *CRC Handbook of Chemistry and Physics*, 83rd ed.; Lide, D. R., Ed.; CRC Press Springer: Berlin, 2003.

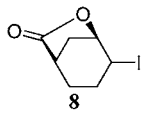
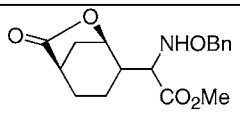
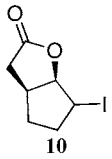
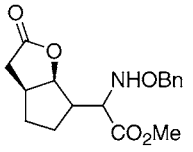
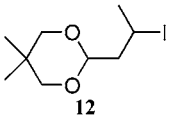
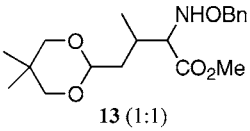
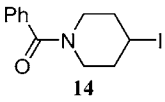
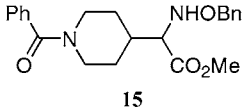
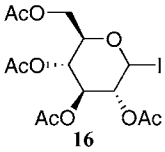
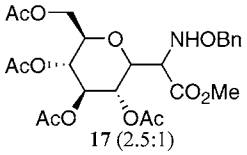
We also decided to investigate the reactions of benzyl iodide and benzyl bromide. As can be seen by entries 5 and 6 of Table 1, the iodide reacted to give the phenylalanine derivative **6** in 62% yield, while the benzyl bromide only gave **3** in 50% yield.

The carbon−halogen bond dissociation energies for a number of different alkyl halides are shown in Table 2. It was decided to attempt the radical addition reactions of the alkyl halides shown in entries 8−11 of Table 1 which are all commercially available. The bond strengths of these compounds were expected to be low enough to allow the radicals to form when reacted with Et_3B (entries 8−11 of Table 2).

As can be seen in entry 7 (Table 1) the reaction of methyl iodide only gave 15% yield of the alanine derivative **7** and 49% of the ethyl adduct **3**. The lower stability of the resulting methyl radical compared to the ethyl radical is likely to be the reason for the low yield. Allyl iodide did not react with **1** in the presence of Et_3B. This is probably due to polym-

(6) Miyabe, H.; Yoshioka, N.; Ueda, M.; Naito, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3659.
(7) Jorgensen, K. A.; Halland, N. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1290.
(8) Miyabe, H.; Shibata, R.; Sangawa, M.; Ushiro, C.; Naito, T. *Tetrahedron* **1998**, *54*, 11431.
(9) (a) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *Synlett* **1999**, 1148. (b) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *J. Org. Chem.* **1999**, *64*, 9189.

Table 3. Synthesis of Heterocyclic α-amino Acids

entry	alkyl halide	RI (equiv.)	Et_3B (equiv.)	product (diastereomeric ratio)[a]	yield (%) product	yield (%) 3
1	 **8**	2	3 (6 X 0.5)	 **9** (2:1)	75	20
2	 **10**	2	3 (6 X 0.5)	 **11** (1:1)	63	33
3	 **12**	12	3 (6 X 0.5)	 **13** (1:1)	72	5
4	 **14**	3	2 (4 X 0.5)	 **15**	43	49
5	 **16**	3	3 (6 X 0.5)	 **17** (2.5:1)	16	63

[a] Determined by ^1H NMR of the crude diastereomeric mixtures.

erization, and starting material was recovered (entry 8, Table 1). Bromo trichloromethane is known to undergo the atom transfer reaction with Et_3B and react with alkenes.[3] In our case, no reaction occurred (entry 9, Table 1). The absence of any ethyl adduct may indicate that the bromine atom transfer process occurs efficiently reducing the amount of ethyl radical present in the reaction. The radical is presumably too electrophilic to react. Pentafluorobenzyl bromide and 2-iodoperfluoro propane have not been reacted with Et_3B, to the best of our knowledge. Again no product was formed from the resulting radicals (entries 10 and 11, Table 1). Starting material was again recovered indicating that the atom transfer reaction with Et_3B had occurred. We believe that the radicals formed from these halides are too electrophilic to react.

Having investigated the addition of electrophilic radicals, we turned to the reaction of heterocyclic radicals. The addition of heterocyclic carbon-centered radicals to **1** would provide a route for the synthesis of novel α-amino acids derivatives. Several alkyl halides containing heterocycles were synthesized using literature procedures.[12] The radical addition reactions were carried out following the standard procedure.[2c] A minor modification was made in that a smaller number of equivalents of the alkyl halide were used. A large excess of alkyl halide has been generally used to minimize the amount of **3** produced. As the excess alkyl halide is generally not recovered after the reaction this is not efficient for alkyl halides that have to be synthesized in several steps. In an attempt to keep the amount of ethyl adduct **3** to a minimum, the Et_3B was added in portions of 0.5 equiv over the course of the reaction to maintain a high ratio of alkyl halide to ethyl radical.

The reactions of **8**, **10**, **12**, **14**, and **16** all took place although the yields ranged from poor to good (Table 3). The radical addition reaction of **8** gave the amino acid derivative **9** in 75% yield along with 20% of the ethyl adduct **3**. The related iodide **10** also reacted well to give **11** in 63% and **3** in 33% yield. Although compound **12** does not have the iodide directly attached to the heterocyclic ring it was of interest as it opens up the possibility of utilizing the masked aldehyde functionality for further functionalization. When **12** was used in the radical addition reaction, **13** was isolated in 72% yield with only 5% of **3** isolated. Piperidine-based amino acid derivatives have been shown to be inhibitors of matrix metalloproteinases.[13] Compound **14** was synthesized

(10) Lagoa, A. L. C.; Diogo, H. P.; Dias, M. P.; Minas da Piedade, M. E.; Amaral, L. M. P. F.; Ribeiro da Silva, M. A. V.; Martino Simoes, J. A.; Guedes, R. C.; Costa Cabral, B. J.; Schwarz, K.; Epple, M. *Chem. Eur. J.* **2001**, *7*, 483.

(11) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255.

(12) **4** according to: Perrier, M. *J. Am. Chem. Soc.* **1947**, *69*, 3148. **8** according to: Bartlett, P. A.; McQuaid, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 7854. **10** according to: Clive, D. L. J.; Kale, V. N. *J. Org. Chem.* **1981**, *46*, 231. **12** according to: Weyerstahl, P.; Brendel, J. *Liebigs Ann. Chem.* **1992**, 669. **14** from the tosylate using NaI. **16** according to: Gervay, J.; Nguyen, T. N.; Hadd, M. J. *Carbohydr. Res.* **1997**, *300*, 119.

from the tosylate and used without purification. The piperidine containing amino acid **15** was isolated in 43% yield along with **3** in 49%. The reasons for the moderate yield of **15** are not clear at this stage. Finally the sugar iodide **16** was used to synthesize the glycopyranosyl glycine derivative **17** in 16% yield. The conditions for the reaction had to be changed from a 1:1 mixture of methanol/water to a 1:1 mixture of acetonitrile/water. This change was needed to prevent the iodide **16** reacting with methanol to give the 1-methoxy derivatives, which were inseparable from any product. The low yield of **17** compared to the high yield of **3** (63%) may be due to steric hindrance preventing the approach of the radical to the oxime ether. The stability of the alkyl halide in the aqueous conditions is also a problem, with hydrolysis to the glucopyranose derivative likely.

In conclusion, there are two factors to be considered when thinking about the use of alkyl halides for the addition to oxime ethers. The first is the efficiency of the atom transfer process. This is related to the stability of the radical formed compared to the ethyl radical from Et_3B, as well as the strength of the carbon−halogen bond. The second factor is the electrophilicity or nucleophilicity of the radical and whether this is compatible with the oxime ether. Thus, the methyl radical formed from methyl iodide reacts too slowly and therefore the reaction is inefficient even though the bond strength is low (entry 7, Table 2). This is also the case with the pentafluorobenzyl, trichloromethyl and perfluoropropane radicals, which are all too electrophilic to react. On the other hand, radicals formed from benzyl iodide and ethyl iodoacetate reacted well.

We have established that complex and interesting alkyl halides can be used in the radical addition reaction to glyoxylic oxime ethers. The success of the reactions depends on the wise choice of the alkyl halide. This is to maximize the atom transfer process and match the nucleophilicity of the resulting radical to the oxime ether.

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Supporting Information Available: Experimental procedures and characterization data for compounds **4**, **5**, **9**, **11**, **13**, **15**, and **17**. ^{1}H NMR spectra of compounds **4**−**7**, **9**, **11**, **13**, **15**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (a) Shieh, W.-C.; Xue, S.; Reel, N.; Wu, R.; Fitt, J.; Repic. O. *Tetrahedron: Asymmetry* **2001**, *12*, 2421. (b) Pikul, S.; Ohler, N. E.; Ciszewski, G.; Laufersweiler, M. C.; Almstead, N. G.; De, B.; Natchus, M. G.; Hsieh, L. C.; Janusz, M. J.; Peng, S. X.; Branch, T. M.; King, S. L.; Taiwo, Y. O.; Mieling, G. E. *J. Med. Chem.* **2001**, *44*, 2499.