Communication

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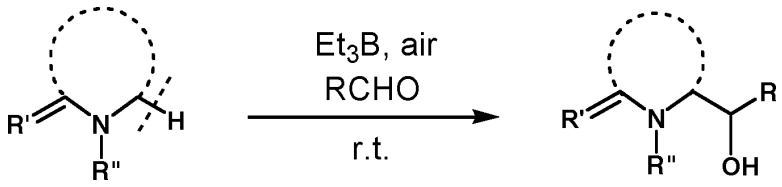

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Radical Hydroxyalkylation of C−H Bond Adjacent to Nitrogen of Tertiary Amides, Ureas, and Amines

Takehiko Yoshimitsu,* Yoshimasa Arano, and Hiroto Nagaoka*

Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose, Tokyo 204-8588, Japan

Received June 12, 2005; E-mail: takey@my-pharm.ac.jp

α-Hydroxyalkylated nitrogen compounds often serve as a rich source of biologically and synthetically important substances.[1] Therefore, novel chemical transformations that provide rapid access to these functional motifs are of great significance in pharmaceutical and fine chemical research.

We have recently reported the radical hydroxyalkylation of ethers and an acetal with aldehydes, which proceeded via hydrogen abstraction from the C−H bond α to oxygen by using Et_3B/air[2a,d] or Et_3B/TBHP.[2b,c] In this context, we became interested in the possibility of the direct α-amino sp^3 C−H hydroxyalkylation that would serve as a new mode for obtaining α-hydroxyalkylated nitrogen compounds.[3,4] Our idea stemmed from the following insights. First, the relatively small dissociation energy of the C−H bond adjacent to the nitrogen atom[5] would enable the selective abstraction of the α-hydrogen with radical species generated from Et_3B/air.[6] Second, the resultant nucleophilic α-aminoalkyl radicals[7] would undergo irreversible addition to aldehydes with the aid of the oxophilic and Lewis acidic Et_3B as an oxyradical scavenger.

In this communication, we show that several tertiary amides, ureas, and amines undergo direct intermolecular addition to aldehydes under the Et_3B/air conditions, thereby providing a unique and simple means for the radical sp^3 C−H transformation of nitrogen-containing molecules (Scheme 1).[8]

In our initial investigation of the feasibility of α-amino C−H hydroxyalkylation, 1-methyl-2-pyrrolidinone (**1**) was selected as the substrate. When γ-lactam **1** was subjected to the hydroxyalkylation under the Et_3B/air conditions, *N*-CH_2 alkylation products **3**/**4** and *N*-CH_3 alkylation product **5** were produced (Table 1). The regioselectivity of the reaction favoring *N*-CH_2 alkylation rather than *N*-CH_3 alkylation indicates that hydrogen abstraction occurs predominantly from the weaker C−H bond; compared to the less-substituted carbon center, the more highly substituted carbon center is susceptible to hydrogen abstraction due to the release of steric strain as well as the hyperconjugative stabilization of the incipient α-aminoalkyl radical. The amounts of C−H substrate and Et_3B influenced the efficiency of the reaction (entries 6 and 7); when the reaction was carried out with a relatively small amount of **1**, the amounts of ethyl adduct **6** and reduction byproduct **7** were increased, and the reaction time was prolonged (entry 6). The prolonged reaction time (42 h) was also necessary for obtaining a reasonable yield when 3 equiv of Et_3B was used (entry 7). Although the reaction proceeded under the open-air condition without air admission, it was significantly decelerated (entry 8); 41 h was required for completing the reaction under the open-air condition, in contrast to 14 h for the continuous air-admission condition (ca. 30 mL/h·mmol aldehyde).

These results prompted us to apply this radical C−H transformation to various nitrogen compounds. Table 2 shows that, under the Et_3B/air conditions, tertiary ureas and amines were also hydroxyalkylated with 4-methoxybenzaldehyde (**2a**) to afford alkylation products in good yields. Thus, the hydroxyalkylation of such urea

Scheme 1. Radical α-C−H Hydroxyalkylation of Nitrogen Compounds

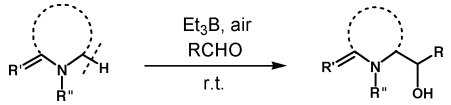
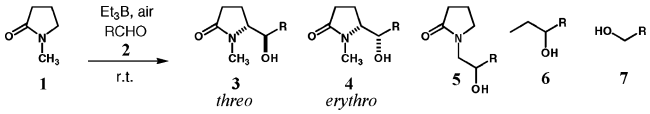


Table 1. Hydroxyalkylation of 1-Methyl-2-pyrrolidinone (**1**)



entry	R	time (h)	yield (%)[a,b] 3/4 (dr 3:4)	5	6	7
1	4-$MeOC_6H_4$ **2a**	14	68 (68:32)	7	6	trace
2	Ph **2b**	16	62 (67:33)	9	no[g]	4
3	3,4-methylenedioxyphenyl **2c**	14	62 (77:23)	6	8	no
4	2-BrC_6H_4 **2d**	12[c]	54 (42:58)	9	13	3
5	$C_{12}H_{25}$ **2e**	22[c]	50 (50:50)	no	no	no
6	4-$MeOC_6H_4$ **2a**	42[d]	54 (69:31)	6	11	6
7	4-$MeOC_6H_4$ **2a**	42[e]	65 (69:31)	7	1	no
8	4-$MeOC_6H_4$ **2a**	41[f]	68 (69:31)	7	5	no

[a] The reaction was carried out using 1-methyl-2-pyrrolidinone (**1**) (35 equiv relative to aldehyde) and Et_3B (6 equiv) with continuous air admission (ca. 30 mL/h·mmol aldehyde). [b] Isolated yield based on aldehyde. [c] 70 equiv of **1** was used. [d] 17 equiv of **1** was used. [e] 3 equiv of Et_3B was used. [f] The reaction was carried out under open-air conditions. [g] Not obtained.

derivatives as 1,3-dimethyl-2-imidazolidinone (**8**) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (**9**) provided α-alkylated compounds **16** (75%) and **17** (8%), and **18** (72%) and **19** (11%), respectively (entries 1 and 2). 1-Methylpyrrolidine (**10**) and triethylamine (**11**) were also efficiently transformed into alkylation products (entries 3 and 4).[9] The hydroxyalkylation of *N*,*N*-diethylaniline (**12**), an aromatic tertiary amine, gave phenyl-protected β-amino alcohol **23** in 65% yield (dr 83:17). Interestingly, the hydroxyalkylation of 4-methylmorpholine (**13**) was found to selectively take place at the position α to nitrogen; the regioselectivity in this case indicates that the C−H bond adjacent to nitrogen is more susceptible to hydrogen abstraction than that adjacent to the ethereal oxygen, although the C−H bonds α to nitrogen and oxygen have similar dissociation energies.[5d] In general, undesirable side reactions, such as ethyl radical addition and aldehyde reduction, occurred only modestly in the above conditions (see Supporting Information). 3-Methyl-2-oxazolidinone (**14**) and acyclic *N*,*N*-dimethylacetamide (**15**) were found to be somewhat poor substrates for the present hydroxyalkylation reaction (43 and 40% yields, entries 7 and 8). The reason for the low yield in the reaction of **14** is unclear, whereas the inefficient conversion of **15** may be attributed to thermochemical factors that retard the hydrogen abstraction at the *N*-CH_3 sites, where radical stabilization is less available.

One plausible mechanism of this reaction, which is analogous to that proposed for ether hydroxyalkylation,[2b,d] is shown in Scheme

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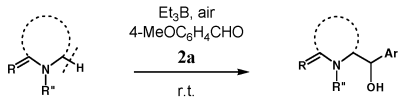
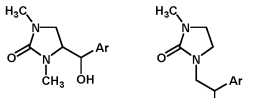
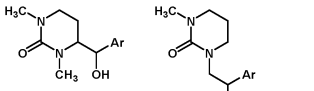
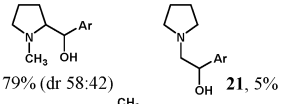
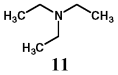
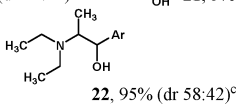
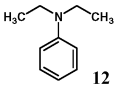
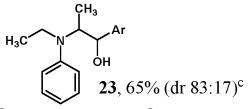
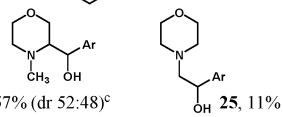
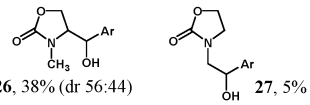
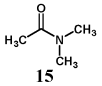
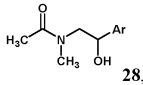
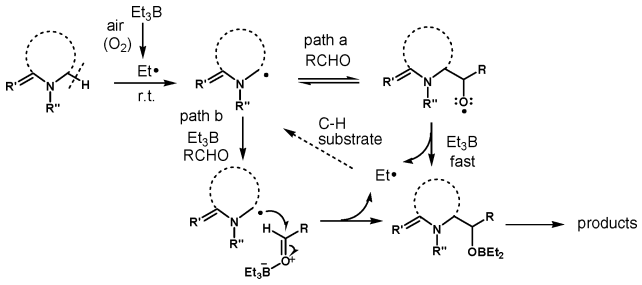
Table 2. Substrate Scope



entry	substrate[a]	time (h)	product[b] yield (dr: *threo*:*erythro*)
1	 **8**	10	 **16**, 75% (dr 62:38) **17**, 8%
2	 **9**	16	 **18**, 72% (dr 79:21) **19**, 11%
3	 **10**	36	 **20**, 79% (dr 58:42) **21**, 5%
4	 **11**	16	 **22**, 95% (dr 58:42)[c]
5	 **12**	21	 **23**, 65% (dr 83:17)[c]
6	 **13**	36	 **24**, 57% (dr 52:48)[c] **25**, 11%
7	 **14**	36	 **26**, 38% (dr 56:44) **27**, 5%
8	 **15**	41[d]	 **28**, 40%

[a] C−H substrate (35 equiv) and Et_3B (6 equiv) were used except entry 8. [b] Isolated yield based on aldehyde. [c] Stereochemistry of major product has yet to be determined. [d] 70 equiv of **15** was used.

Scheme 2. Plausible Mechanism of Radical C−H Hydroxyalkylation of Nitrogen Compounds



2. An ethyl radical generated from Et_3B/air abstracts the α-hydrogen of the nitrogen compound to produce nucleophilic α-aminoalkyl radicals. Then, the α-aminoalkyl radicals irreversibly undergo addition to aldehyde via two possible pathways that involve the rapid capture of oxyradicals with Et_3B (path a) and/or the precoordination of aldehyde with Et_3B followed by the addition of α-aminoalkyl radicals (path b).[10]

In conclusion, we have devised a new radical alkylation reaction that occurs via the selective abstraction of the hydrogen α to the nitrogen atom by using Et_3B/air. The present C−H transformation features the direct generation of α-aminoalkyl radicals from the C−H substrates, which may potentially serve as an alternative to the homolysis of C−X (X = SR, SeR) bonds, the radical translocation, and the single electron transfer (SET) processes. It should be noted that this radical reaction enables the rapid construction of contiguous stereocenters functionalized with heteroatoms, which is not readily achieved by other C−H functionalization methods. Studies on the scope of this reaction are underway with focus on the application to evolutional organic synthesis.

Acknowledgment. This work is dedicated to the memory of Professor Satoru Masamune. We thank Mr. Atsushi Kishida and Dr. Kazuhiko Takatori for X-ray crystallographic analysis.

Supporting Information Available: Experimental procedures, characterization data, and $^1H/^{13}C$ NMR spectra of hydroxyalkylation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The hydroxyalkylation of 1-methylpiperidine provided alkylation products in ca. 60% yield (dr 58:42; regioisomeric ratio ca. 5.5:1). Further studies on the substrate scope will be reported in due course.

(10) The coordination of Et_3B with aldehyde in path b remains a matter of speculation. However, the formation of 4-methoxybenzyl alcohol from 4-methoxybenzaldehyde in some cases under the Et_3B/air conditions possibly indicates the intermediacy of the "ate" complex of Et_3B with aldehyde that is capable of *β*-hydride transfer. Studies aimed at elucidating the details are ongoing.

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