JOC*Note*

Stereoselective Cyclization Reactions of IBX-Generated Alkoxyamidyl Radicals

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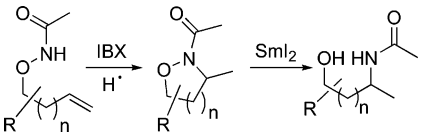
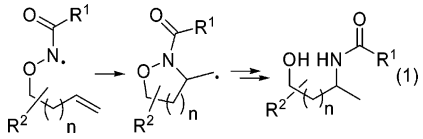


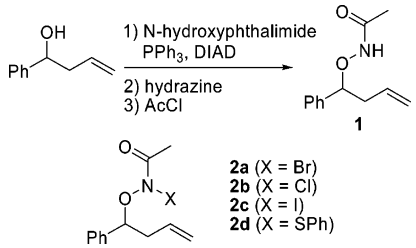
In this paper, a method for the generation of alkoxyamidyl radicals is presented. These N-centered radicals can efficiently be formed starting from the corresponding acylated alkoxyamines using IBX as an oxidant. Stereoselective 5-*exo* and 6-*exo* reactions with these N-heteroatom-centered radicals leading to isoxazolidines and [1,2]oxazinanes are discussed. The N−O bond in the heterocycles can readily be cleaved with SmI_2 to provide N-acylated 1,3-amino alcohols.

There are many reports in the literature on the application of N-centered radicals in organic synthesis.[1] In general, these heteroatom-centered radicals undergo H-abstraction or addition reactions. In particular, cyclizations leading to biologically important N-heterocyclic compounds are interesting. Newcomb showed that the rate of the 5-*exo* cyclization of an aminyl radical can be increased upon protonation or complexation of the aminyl radical.[2] Electronic effects are the reason for the acceleration. On the basis of these results, it is obvious that the more electrophilic amidyl radicals cyclize faster than aminyl radicals.[3] Amidyl radical cyclizations have been studied using *N*-chloroamides,[4] *N*-phenylthioamides,[5] *N*-hydroxypyridine-2(*1H*)thione derivatives,[6] *N*-nitrosoamides,[7] and other systems[8] as radical precursors. Herein we present our first results on cyclization reactions of alkoxy-substituted amidyl radicals (eq 1).[9] Since the O−N bond can be readily cleaved by various methods, a new entry into 1,3- and 1,4-amino alcohols should be opened (via 5-*exo* and 6-*exo* cyclizations, respectively). To the best of our knowledge, *N*-alkoxyamidyl radical cyclizations have not been reported to date.



As a model compound, acetylated alkoxyamine **1** was readily prepared from 1-phenyl-but-3-en-1-ol via Mitsunobu reaction using *N*-hydroxyphthalimide according to known procedures (Scheme 1).[10,11] All the compounds

SCHEME 1. Preparation of the Acetylated Alkoxyamine 1



described herein were prepared as racemates. Transformation of **1** into a suitable radical precursor was difficult to achieve. We tested several methods for the preparation of *N*-bromo amide **2a**. However, all attempts failed, probably due to instability of the bromide. Furthermore, under certain conditions, Br^+-induced electrophilic cyclizations were obtained.[11] We faced the same problems on the way to chloride **2b** and iodide **2c**. The *N*-phenylthioamide **2d** could not be prepared using established procedures for the preparation of *N*-phenylthioamides.

We therefore decided to generate the desired alkoxyamidyl radical directly from **1** under oxidative conditions.[9,12] Recently, Nicolaou and co-workers nicely demonstrated the potential of *o*-iodoxybenzoic acid (IBX) for the generation of N-centered radicals.[13,14] Pleasingly, we

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SCHEME 2. IBX-Mediated Radical Cyclization of 1

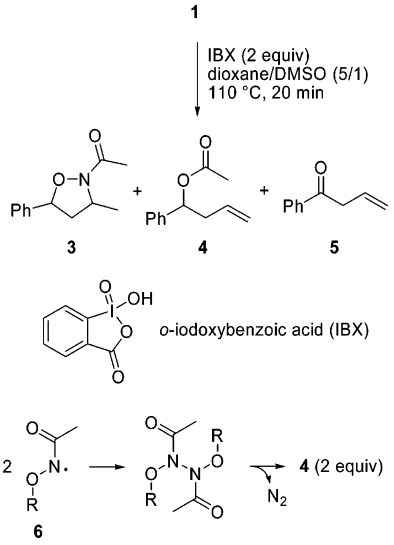


TABLE 1. IBX-Mediated Cyclization of 1: Variation of the Concentration

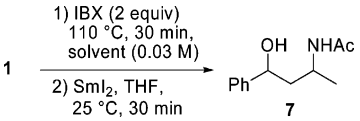
entry	concn (M)	conversion (%)	**3** (%)	**4** (%)	**5** (%)
1	0.01	83	71	28	1
2	0.02	82	67	29	4
3	0.03	95	64	32	4
4	0.05	99	60	34	6
5	0.10	99	54	36	10

found that reaction of **1** with IBX (2 equiv, added in two portions) in dioxane/DMSO (5/1, 0.01 M) provided the desired cyclization product **3** (Scheme 2, Table 1, entry 1). Isoxazolidine **3** was obtained as a mixture of isomers (cis:trans = 6:1). The relative configuration of the major isomer was unambiguously assigned by NOE experiments. Under the applied conditions, 83% conversion was obtained as determined by GC analysis. Along with the cyclization product **3**, acetate **4** and ketone **5** were formed as side products (**3**:**4**:**5** = 71:28:1). The mechanism of the IBX-mediated generation of alkoxyamidyl radical **6** (R = 1-phenyl-but-3-en-1-yl) from **1** is currently not well understood.[13,14] The reduction of the alkyl radical obtained after cyclization is carried out by the solvent. Formation of **4** can be explained by the dimerization of alkoxyamidyl radical **6** (R = 1-phenyl-but-3-en-1-yl) to give the corresponding hydrazide derivative, which decomposes under liberation of N_2 to eventually give acetate **4**. Similar reactions have previously been described.[12] According to this mechanism, the formation of **4** should be enforced upon increasing the concentration. Indeed, a clear trend toward a higher percentage of **4** was observed upon going from 0.02 to 0.10 M (entries 2−5). Moreover, quantitative conversion was obtained at higher concentration under otherwise identical conditions (entries 4 and 5).

We next tested the IBX-mediated cyclization in various solvents. The radical reactions were conducted in sealed tubes at 110 °C (oil bath temperature, 0.03 M) using 2 equiv of IBX. After evaporation of the solvents, the crude product was treated with SmI_2 in THF to provide

(14) Reviews: Wirth, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 2812. Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523.

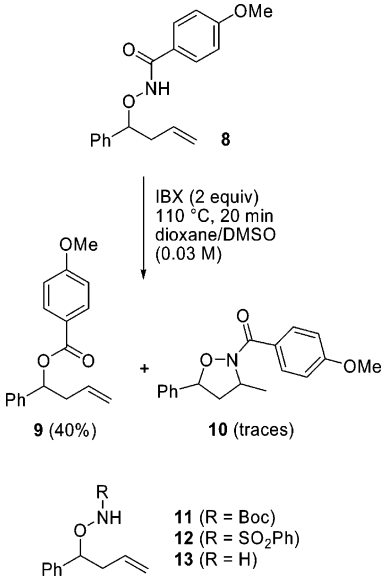
SCHEME 3. IBX-Mediated Radical Cyclization of 1 in Different Solvents



N-acetylated amino alcohol **7** (Scheme 3). The side products were not isolated in these experiments. Reaction in dioxane/DMSO (5/1) and reductive cleavage of the N−O bond provided **7** in 53% yield (syn:anti = 5:1). In CH_3CN, only 20% of **7** was isolated (syn:anti = 5:1). A slightly better yield was obtained for the experiment conducted in DMF (28% yield). In *t*-BuOH and in H_2O/acetone (5/1), no conversion was observed. The reaction in THP/DMSO (5/1) provided, after SmI_2 treatment, alcohol **7** in only 16% yield. Using THF/DMSO (5/1) gave a similar result (11%). Therefore, all the following experiments were conducted in dioxane/DMSO (5/1).

We also investigated the effect of the N-protecting group on the IBX-mediated alkoxyamidyl radical cyclization. To this end, benzoylated **8**, Boc-protected **11**, and sulfonylated alkoxyamine **12** were prepared. These compounds were treated under the optimized conditions with IBX. The reaction of **8** delivered the desired cyclization product **10** only in trace amounts. Ester **9** was isolated in 40% yield. With the Boc-protected alkoxyamine **11**, neither the ester nor the desired isoxazolidine was identified, and 77% of the starting material was recovered. A similar result was obtained using sulfonamide **12**. No products were identified, and the starting compound was recovered in 86%. The unprotected alkoxyamine **13** decomposed under the standard cyclization conditions. No major product was identified. Thus, the N-protecting group is very important for the reaction outcome. The IBX-mediated alkoxyamidyl radical generation works only for N-acylated alkoxyamines, probably due to electronic effects. Moreover, the *N*-acyl group influences the reactivity of the alkoxyamidyl radical. Due to delocalization, the N-centered radical derived from **8**

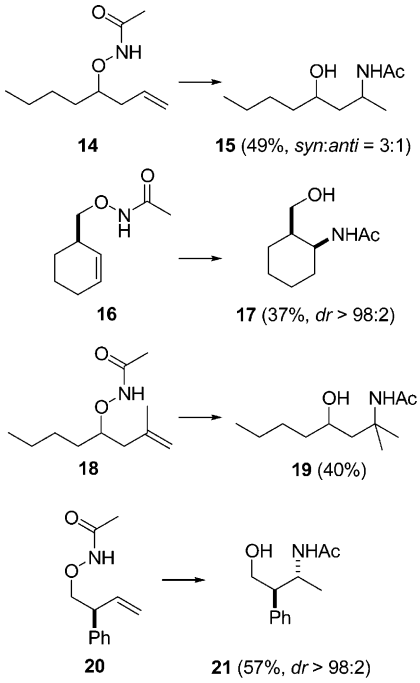
SCHEME 4. Variation of the N-Substituent



is more stable than the acetylated N-radical **6** (R = 1-phenyl-but-3-en-1-yl). For the highly conjugated radical derived from **8**, the 5-*exo* cyclization cannot efficiently compete with dimerization to give the corresponding hydrazide derivative, which eventually delivers ester **9** as major product.

To study the scope and limitations of our new method, the acylated alkoxyamines **14**, **16**, **18**, and **20** were prepared as described in the Supporting Information. Radical cyclization and reductive ring-opening were performed under the above optimized conditions. Reaction of **14** afforded acylated 1,3-amino alcohol **15** in 49% yield as a 3:1 (syn:anti) mixture of isomers (Scheme 5).

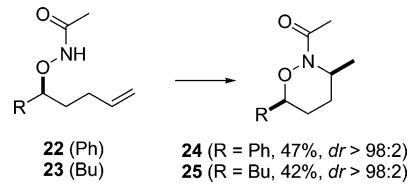
SCHEME 5. Alkoxyamidyl Radical Cyclizations Followed by Reductive Ring-Opening



As expected, cyclization of **16** occurs highly diastereoselectively providing, after N−O bond cleavage, alcohol **17** in 37% yield. Pleasingly, our method can also be used for the synthesis of quaternary C-centers (→ **19**, 40%). Reaction of alkoxyamine **20** afforded **21** in an excellent stereoselectivity with a good yield (dr > 98:2, 57%). The relative configuration was assigned prior to ring-opening by NOE experiments.

6-*exo* Cyclizations were successfully performed using olefins **22** and **23**. The corresponding cyclization products **24** and **25** were isolated in 47 and 42% yield, respectively (Scheme 6). Pleasingly, the cyclization occurred with a

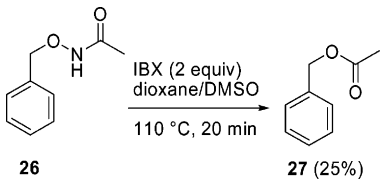
SCHEME 6. 6-*exo* Cyclizations



high degree of stereocontrol, affording the cis product as the only detectable isomer. (dr (**24**) > 98:2, dr (**25**) > 98:2). The relative configuration of the [1,2]oxazinane **24** was assigned by NOE experiments (isomer **25** was assigned by analogy).

Finally, we attempted homolytic aromatic substitution[15] using acetylated alkoxyamine **26** under standard conditions. The desired cyclization product was not identified. Along with starting **26** (55% recovered), ester **27** was isolated in 25% yield (Scheme 7). Thus, homolytic aromatic substitution is obviously too slow to compete with dimerization of the alkoxyamidyl radical derived from **26**.

SCHEME 7. Attempted Homolytic Aromatic Substitution



We have shown that alkoxyamidyl radicals cannot be generated using established procedures for the generation of amidyl radicals. However, the alkoxyamidyl radicals can efficiently be formed from the corresponding acylated alkoxyamines using IBX. Typical 5-*exo* and 6-*exo* cyclization reactions can be conducted using these N-centered radicals leading to five- and six-membered heterocycles. Moderate to excellent stereoselectivities were obtained for the cyclization reactions. As a side reaction, dimerization of the alkoxyamidyl radical occurs, leading to the corresponding hydrazide. The bisacylated *N*,*N*′-bisalkoxyl-substituted hydrazides decompose under N_2-extrusion to form esters. For slow cyclizations, the dimerization becomes the dominant process. The isoxazolidines can be reductively cleaved to give N-protected 1,3-amino alcohols.

Experimental Section

General Procedure for Alkoxyamidyl Radical Cyclization Followed by Reductive Ring Opening. The acetylated alkoxyamine was dissolved in a mixture of dioxane/DMSO, 5:1 (0.03 M). IBX (1 equiv) was added, and the suspension was heated at 110 °C for 15 min. A second equivalent of IBX was added, and the mixture was heated for another 15 min. After the solvent was evaporated, the residue was dissolved in Et_2O and washed with saturated aqueous $NaHCO_3$. The organic layer was separated and dried ($MgSO_4$). After evaporation of the solvent, SmI_2 (0.1 M in THF) was added until a blue color persisted. Stirring was then continued for 30 min. The reaction mixture was poured onto saturated aqueous NH_4Cl. The organic layer was separated, washed with saturated aqueous $Na_2S_2O_3$ and brine, and dried ($MgSO_4$). After evaporation of the solvent, the crude product was purified by FC.

Typical Experiment: *N*-(3-Hydroxy-1-methyl-3-phenylpropyl)acetamide (7). Performed according to the general procedure using *N*-(1-phenylbut-3-enyloxy)acetamide (**1**) (121 mg, 0.59 mmol), IBX (2 × 165 mg, 1.17 mmol), dioxane/DMSO, 5:1 (20 mL), and SmI_2 (ca. 0.1 M in THF, 19 mL). FC (acetone/dichloromethane, 2:8) afforded *cis*-**7** (54 mg, 44%) and *trans*-**7** (11 mg, 9%) [dr (cis/trans) = 5:1].

***cis*-Isomer.** IR (film): 3280*m*, 3216*m*, 3087*w*, 2973*m*, 2922*w*, 1636*s*, 1558*s*, 1454*m*, 1373*m*, 1152*m*, 1082*m*, 979*m* cm^{-1}. ^1H

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NMR (200 MHz): δ = 7.36−7.30 (*m*, 5 H), 5.65−5.62 (*br m*, 1 H), 4.80 (*dd*, *J* = 7.7, 4.8 Hz, 1 H), 4.67−4.05 (*m*, 1 H), 3.11 (*br s*, 1 H), 2.04−1.91 (*m*, 1 H), 1.89 (*s*, 3 H), 1.86−1.81 (*m*, 1 H), 1.21 (*d*, *J* = 6.6 Hz, 3 H). ^{13}C NMR (50 MHz): δ = 170.1, 144.7, 128.4, 127.4, 125.6, 72.4, 46.6, 44.0, 23.4, 21.4. MS (EI): *m/z* = 207 (9, $[M]^+$), 148 (8), 133 (6), 101 (44), 87 (57), 72 (25), 60 (30), 44 (90), 28 (100). HRMS: *m/z* = $[M + Na]^+$ calcd for $C_{12}H_{17}NaNO_2$ 230.1157, found 230.1159.

***trans*-Isomer.** IR (film): 3275*m*, 3204*m*, 2966*w*, 2919*m*, 2852*w*, 1632*s*, 1562*s*, 1448*m*, 1375*m*, 1307*m*, 1224*w*, 1058*m*, 1022*m*, 961*m* cm^{-1}. ^{1}H NMR (200 MHz): δ = 7.35−7.33 (*m*, 5 H), 5.60−5.58 (*m*, 1 H), 4.65 (*dd*, *J* = 10.9, 2.5 Hz, 1 H), 4.48 (*br s*, 1 H), 4.38−4.29 (*m*, 1 H), 2.06 (*s*, 3 H), 1.96−1.82 (*m*, 1 H),1.64−1.55 (*m*, 1 H), 1.24 (*d*, *J* = 6.7 Hz, 3 H). ^{13}C NMR (50 MHz): δ = 170.1, 144.7, 128.4, 127.4, 125.6, 72.4, 46.2, 44.0, 23.4, 21.5. MS (EI): *m/z* = 207 (2, $[M]^+$), 147 (8), 101 (27), 87 (63), 72 (30), 60 (36), 44 (100). HRMS: *m/z* = $[M]^+$ calcd for $C_{12}H_{17}NO_2$ 207.1259, found 207.1259.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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