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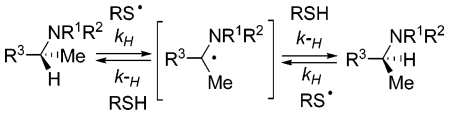
Thiyl Radical Mediated Racemization of Nonactivated Aliphatic Amines

Stéphanie Escoubet,[†] Stéphane Gastaldi,[†] Nicolas Vanthuyne,[‡] Gérard Gil,[‡] Didier Siri,[§] and Michèle P. Bertrand*,[†]

Laboratoire de Chimie Moléculaire Organique, UMR 6517 "Chimie, Biologie, et Radicaux Libres", Boite 562, Université Paul Cézanne, Aix-Marseille III, Faculté des Sciences St Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France, Laboratoire de Stéréochimie Dynamique et Chiralité, UMR 6180 "Chirotechnologies: Catalyse et Biocatalyse", Université Paul Cézanne, Aix-Marseille III, Faculté des Sciences St Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France, and Laboratoire de Chimie Théorique et Modélisation Moléculaire, UMR 6517, Université de Provence, Faculté des Sciences St Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France

michele.bertrand@univ-cezanne.fr

Received May 22, 2006



The racemization of nonactivated aliphatic amines has been mediated with alkanethiols and with methyl thioglycolate in the presence of AIBN. The process involves reversible H-abstraction at the chiral center, in a position α relative to nitrogen, by thiyl radical. The knowledge of the reaction enthalpy is critical to select the appropriate thiol. In the absence of experimental values, theoretical calculations of the α-C−H BDEs and the S−H BDE provide a useful guide.

The most common ways in industry to prepare enantiomerically pure compounds remain kinetic resolution and chiral chromatography of racemic mixtures. The recycling of the unwanted isomer through racemization is of critical importance from both an economical and an environmental point of view. With the exception of amino acids derivatives, the racemization of amines is generally performed by oxidation−reduction which can involve a complex multistep process or by base catalysis.[1−3] Both types of procedures often necessitate rather harsh conditions which may not tolerate other functional groups. Very few methods apply to nonactivated aliphatic amines.[4] The ruthenium-catalyzed methodology developed by Bäckvall and co-workers[2] is an exception. It was recently shown to be compatible with concomitant enzymatic resolution.[2e]

We have reported that chiral benzylic amines could be racemized by a free radical process, involving thiyl radical-mediated reversible H-abstraction at the chiral center in position α relative to nitrogen (Scheme 1).[5]

Thiols are very good hydrogen atom donors.[6] Hydrogen transfers from thiols to carbon-centered radicals have been the subject of numerous debates and theoretical studies.[7] Most of

[†] Laboratoire de Chimie Moléculaire Organique, Université Paul Cézanne.
[‡] Laboratoire de Stéréochimie Dynamique et Chiralité, Université Paul Cézanne.
[§] Laboratoire de Chimie Théorique et Modélisation Moléculaire, Université de Provence.

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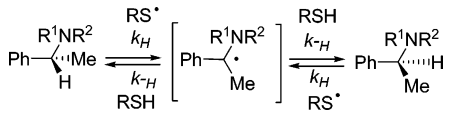
10.1021/jo061033l CCC: $33.50
Published on Web 08/24/2006

SCHEME 1



them are exothermic processes. However, thiyl radicals are able to abstract hydrogen atoms from electron rich C−H bonds.[8−11] Although the importance of hydrogen abstraction by thiyl radicals is now recognized in biological processes,[12] synthetic applications have not fully been explored yet.[8,9] Our group has reported that thiyl radicals enable the conversion of allylic amines into enamines through 1,3-hydrogen shift.[13] To the best of our knowledge, with the exception of an article published by Von Sonntag,[11] the few known examples of thiyl radical promoted epimerization at electron-rich chiral center in position α relative to an oxygen atom have been reported by Roberts.[10]

In the thiyl radical mediated racemization of amines, both the forward and the backward hydrogen transfers (Scheme 1) benefit from favorable polar factors (the strong nucleophilic character of the carbon-centered radical matches the electrophilic character of thiyl radical). A balance must be found between the activation barriers of the forward and backward steps to ensure the practical efficacy of the process.

The information gathered from the experiments performed with benzylic amines[5] can be summarized by the following statements. The racemization of chiral benzylic amines can be achieved in the presence of aromatic or aliphatic thiols, but only the best hydrogen donors enable the racemization to proceed in the presence of a catalytic amount of thiol. In the case of primary benzylic amines, the main limitation comes from the fast competitive oxidation of the carbon-centered radical. Thus, the backward transfer must be fast enough to compete with oxidative degradation. The knowledge of the reaction enthalpy has proved useful to rationalize reactivity. The forward hydrogen transfer in Scheme 1 is generally an endothermic reaction, it is rate limiting and must not be too slow for the reaction to proceed in a reasonable time.

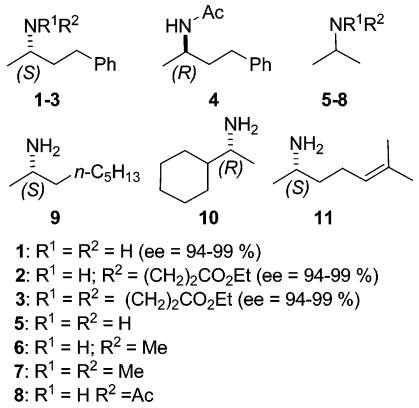


FIGURE 1. Structures of amines **1**−**11**.

TABLE 1. Experimental and Calculated Value of the α-C−H BDEs in Methyl Amines (kJ mol^{-1})

H_2NCH_2−H	$MeHNCH_2$−H	Me_2NCH_2−H
393 ± 8[a]	364 ± 8[a]	351 ± 8[a]
388[b]	386[b]	387[b]
389.5[c]	387.4[c]	387.8[c]

[a] Reference 16. [b] G2(MP2) calculations at 298 K, from ref 18. [c] Average values from G3 and CBS-(Q) calculations, ref 19.

We describe herein the results obtained with (*S*)-2-amino-4-phenylbutane (**1**) and its derivatives (**2**, **3**) that were prepared from **1** by mono- and double-Michael addition to ethyl acrylate, respectively (Figure 1). Compound **1** was obtained in 94−99% ee through the enzymatic resolution of a racemic mixture using *Candida antartica* lipase B (Novozym 435) as the catalyst in the presence of ethyl acetate as the acyl donor.[14] The enzymatic resolution led concomitantly to amide **4** (86% ee). Additional experiments were performed on the commercially available amines **9** and **10** and on amine **11**.

Results and Discussion

As stated above, previous investigations of thiyl radical-mediated racemization of α-branched benzylic amines have shown that the choice of the appropriate thiol was critical. A series of values for the α-C−H BDE in aliphatic amines were available from different sources. They are gathered in Table 1.

It seemed reasonable to assume that the α-C−H bonds should be stronger in aliphatic amines than in benzylic amines, even though the few values reported in the literature did not support this assumption.[15] It must be reminded that the influence of substitution at nitrogen on the α-CH BDE has been controversial for more than twenty years. It has long been admitted that the stabilization of α-amino radicals increased with substitution at nitrogen, i.e., going from primary to tertiary amines. The stabilization energies relative to methyl radical have been determined by Burkey et al. by electron impact mass spectrom-

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TABLE 2. α-C−H BDEs and Energies of the SOMOs of the Corresponding α-amino Radicals Calculated for Amines 5−7 and Acetamide 8

amine	5	6	7	8
BDE_{298K} (kJ mol^{-1})	371.9[a]	372.2[a]	372.4[a]	389.1[a]
	382.8[b]	383.1[b]	384.5[b]	
α-amino radical SOMO[a] (eV)	−4.5	−4.3	−4.2	−5.1

[a] UB3P86/6-311++G (d,p)//UB3LYP/6-31G(d). [b] G3B3.

etry.[16,17] However, the values calculated by Rauk and Armstrong by the G2(MP2) method did not confirm this trend. According to these data, the gap between the extreme values would be only 2 kJ mol^{-1}.[18] Recent calculations performed by Guo are consistent with the latter (Table 1).[19]

The most recent experimental measurements, reported by Lalevée et al.,[20] have led to the conclusion that substitution at nitrogen has little influence on the α-C−H BDE. According to these data, *N*-alkylation would stabilize the α-amino radical by less than 4 kJ mol^{-1}. The additional substituent in tertiary amines would have a negligible effect on the stability of the carbon-centered radical.

Since none of the above-mentioned data could be transposed directly to our series involving the formation of secondary α-aminoalkyl radicals, α-C−H BDEs calculations were performed, first at the UB3P86/6-311++G(d,p)//UB3LYP/6-31G(d) on the series of amines **5**−**7** (taken as models for compounds **1**−**3)** and on acetamide **8** (selected as a model for amide **4**) using the Gaussian 03 package.[21] These data are reported in Table 2. The DFT calculations are known to underestimate the BDE values, but they give a reliable trend in the series.[19] Since it was difficult to appreciate the underestimation in the absence of experimental values, G3B3 calculations known to give BDE values very close to the experimental ones,[22] were also performed on amines **5**−**7**.

SCHEME 2

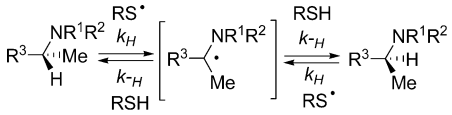

TABLE 3. Calculated and Experimental Values for S−H BDEs and Energies of the SOMOs of Thiyl Radicals[5,24,13b]

thiol	BuSH	MeO_2CCH_2SH
S−H BDE (kJ mol^{-1})	358.2[a]	364.9[a]
	359.9[b]	364.4[b]
	358.5[c]	363.2[c]
	360.9[d]	
	370.7 ± 8.4[e]	
RS•SOMO[a] (eV)	−7.3	−7.7

[a] UB3P86/6-311++G(d,p)//UB3LYP/6-31G(d) (this work). [b] G3B3(MP2) (ref 5). [c] G3B3 (this work). [d] G3 calculated value at 298 K for *n*-BuSH (ref 13b). [e] Experimental values (ref 24).

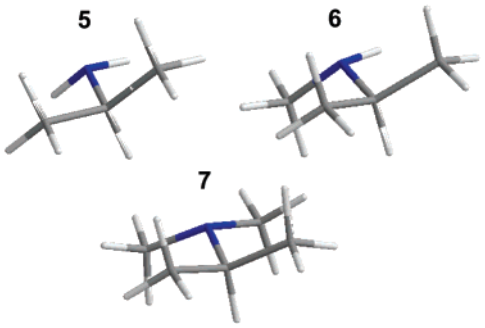

FIGURE 2. Preferred conformations of amines **5**−**7**.

In agreement with the above-mentioned literature data,[18−20] the class of the amine has little incidence on the BDE value (less than 2 kJ mol^{-1} between the primary and the tertiary amine). It is important to note that, in this regard, they differ from benzylic amines. The α-C−H BDEs of the latter vary within a larger range (16.4 kJ mol^{-1} according to G3B3(MP2) calculations[5]). Owing to the lack of benzylic stabilization in the radical, the α-C−H BDEs are stronger in aliphatic amines than in benzylic ones by ca. 36 kJ mol^{-1} in the case of the primary amine (based on G3B3 calculations[5]). Thus, thiols having stronger S−H bonds should be needed to achieve the racemization of aliphatic amines (Scheme 2).

As expected, thiocresol (339.6 kJ mol^{-1} S−H BDE according to G3B3(MP2) calculations[5]) was inefficient to racemize amine **1**. The racemization experiments were performed with octanethiol,[23] and with thioglycolic methyl ester (Table 3, *n*-BuSH was selected as a model for *n*-OctSH).

The preferred conformations of the amine and the corresponding α-amino radicals are shown in Figures 2 and 3.

In all cases, the preferred conformation of the amine corresponds to the antiperiplanar arrangement of the α-C−H bond and the lone pair. According to NBO calculations,[25] the

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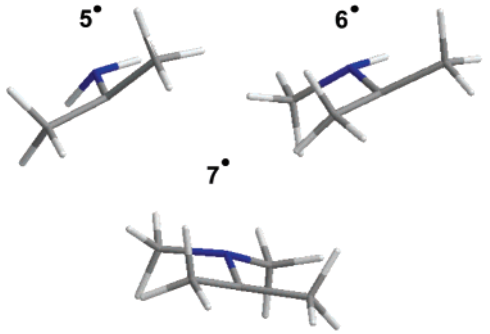

FIGURE 3. Preferred conformations of α-amino radicals **5**•**−7**•.

TABLE 4. Hyperconjugative Effects Affecting the α-C−H Bond Determined by the NBO Method for the Lowest Energy Conformers of Amines 5−7 (Models for 1−3) and Amide 8 Calculated at the UB3LYP/6-311++G(d,p)//UB3LYP/6-31+G(d) Level and Bond Lengths

amine	$n \rightarrow \sigma^*_{C-H}$ (kJ mol^{-1})	d_{C-H}[b] (Å
5	30.5	1.106
6	33.1	1.108
7	39.0	1.110
8	8.3	1.009

overlap between the σ^* C−H orbital and the lone pair stabilizes the system by ca. 30−39 kJ mol^{-1}. These effects account for the variation of the C−H bond length in the series (Table 4).

The planarity of the radical increases in the series going from the primary to the tertiary amine. The structural parameters are also reflected in the relative energies of the SOMOs. The carbon-centered radical corresponding to the tertiary amine is likely to be more nucleophilic than the secondary and the primary ones (Table 2).

The radical reactions were performed under the standard conditions previously applied to benzylic amines, i.e., a benzene solution of amine (0.6−0.7 mmol, 0.067 M) containing the selected thiol (1.2 or 0.2 equiv) was heated at reflux for 2−7 h in the presence of AIBN (20 mol %). A series of experiments were carried out over 6 h according to the experimental protocol previously used for benzylic amines,[5] i.e., adding the overall 20 mol % of AIBN in three equal portions every 2 h. Then, reactions were monitored and analyzed by chiral chromatography (cf. Supporting Information), adding the whole quantity of initiator at the beginning of the reaction. Monitoring (ee/ee$_0$) versus time has shown that in the presence of a stoichiometric amount of thiol, racemization was completed within ca. 2 h (cf. Supporting Information; the superimposing of the plots obtained for the racemization of amines **1** and **3** mediated by *n*-OctSH indirectly confirmed the α-CH BDEs calculations).

The results are summarized in Table 5.

In the case of the primary amine the recovery was low, but the yields in isolated product after an additional step of trifluoroacetylation reached ca. 70% (entries 1/3, 4). In all cases, ^{1}H NMR yields were determined by using pentamethyl benzene as internal standard. Both octanethiol and methyl thioglycolate were efficient in the presence of a stoichiometric amount of thiol (entries 1, 3). Amine **1** was also racemized in the presence of a catalytic amount of thiol (entries 2, 4, 5). However 7 h were necessary to complete racemization when 0.2 equiv of thiol were used. It is noteworthy that no oxidative degradation was detected, contrary to what happened in the case of benzylic primary amines.[5]

TABLE 5. Racemization of Amines 1−3, 9, and 10

entry	amine	RSH (n equiv)	time (h)	isolated yield (%) (NMR)	*S*/*R* (ee)
1	**1**[b]	*n*-OctSH (1.2)	2	40 (62)	51:49 (2)
2	**1**[b]	*n*-OctSH (0.2)	6	38 (55)	79:21 (58)
3	**1**[b]	MeO_2CCH_2SH (1.2)	2	67[a] (100)	50:50 (0)
4	**1**[b]	MeO_2CCH_2SH (0.2)	3	68[a] (82)	76:24 (52)
5	**1**[b]	MeO_2CCH_2SH (0.2)	7	30 (70)	50:50 (0)
6	**2**[b]	*n*-OctSH (1.2)	6	70 (94)	52:48 (4)
7	**2**[b]	MeO_2CCH_2SH (1.2)	6	80 (100)	52:48 (4)
8	**2**[b]	*n*-OctSH (0.2)	6	43 (75)	54:46 (8)
9	**2**[b]	MeO_2CCH_2SH (0.2)	6	70 (88)	59:41 (18)
10	**3**[b]	*n*-OctSH (1.2)	6	70 (89)	53:47 (6)
11	**3**[b]	MeO_2CCH_2SH (1.2)	6	70 (98)	53:47 (6)
12	**3**[b]	*n*-OctSH (0.2)	6	70 (89)	78:22 (56)
13	**3**[b]	MeO_2CCH_2SH (0.2)	6	84 (100)	74:26 (52)
14	**4**[c]	MeO_2CCH_2SH (1.2)	6	95 (100)	93:7 (86)
15	**9**[d]	MeO_2CCH_2SH (1.2)	2	51 (73)	55:45 (10)
16	**10**[e]	MeO_2CCH_2SH (1.2)	2	64 (83)	53:47 (6)
17	**11**[f]	MeO_2CCH_2SH (1.2)	3	46 (78)	51:49 (6)

[a] Isolated yield after derivatization with trifluoroacetic anhydride. [b] (ee)$_0$ = 94%. [c] (ee)$_0$ = 86%. [d] (ee)$_0$ = 99%. [e] (ee)$_0$ = 95%. [f] (ee)$_0$ = 99%.

The secondary amine **2** behaved similarly to **1**. It was racemized by both thiols in the presence of either 1.2 equiv or 0.2 equiv of thiol (entries 6−9).

The tertiary amine was completely racemized in 6 h in the presence of 1.2 equiv of either octanethiol or methyl thioglycolate (entries 10, 11). It was only partially racemized after 6 h in the presence of 0.2 equiv of thiol (entries 12, 13).

According to literature data,[26] acetylation increases the α-C−H BDE in aliphatic amines by approximately 17 kJ mol^{-1} (this was confirmed by theoretical calculations, cf. Table 2). The chiral center in the acetylated derivative **4** could not be epimerized whatever thiol was used (*n*-OctSH or thioglycolic acid methyl ester under stoichiometric conditions (entry 14)).

The reaction was generalized to primary amines **9**, **10** and **11** (entries 15−17).

The theoretical calculations corroborate quite well the experimental results and a rationale can be based on the reaction enthalpy. According to the G3B3 calculations, the α-C−H bonds are stronger than the S−H bonds by 24.3−26 kJ mol^{-1} in the case of octanethiol and by 19.6−21.3 kJ mol^{-1} in the case of methyl thioglycolate. The forward hydrogen transfer is endothermic, it should be rate determining. Although the forward H-abstraction should go slightly faster in the case of the thioglycolic ester than in the case of *n*-OctSH, no significant impact was noted on the racemization in the presence of a stoichiometric amount of thiol. In the presence of 0.2 equiv of thiol, the lower degree of racemization of amine **3** points to the importance of enthalpy. The backward hydrogen transfer might be too slow in this case. Additional competitive experiments were achieved in the presence of a catalytic amount of octanethiol. They are summarized in Table 6.

These data confirm the trend revealed in Table 5, i.e., amine **2** is racemized faster than amines **1** and **3** in the presence of a catalytic amount of thiol. Because calculated α-CH BDEs are not significantly different, no rationale can be based on the variation of the reaction enthalpy in the series. The interplay between slightly different polar and steric effects might be responsible for the selective of racemization the secondary amine.

(26) Cf. ref 17, pp 73 and 85.

TABLE 6. Variation of ee versus Time in Competitive Experiments Performed in the Presence of a Catalytic Amount of *n*-OctSH

competition[a] time (h)	**2**/**1**[b] ee **(2)**[e]/ee (**1**)[d]	**2**/**3**[c] ee **(2)**[e]/ee (**3**)[e]
0	99/99	99/99
2	20/76	20/86
4	0/70	0/76
6	0/68	0/74
8	0/64	0/72

[a] **1** (0.07M), **2** or **3** (0.07M), *n*-OctSH (0.2 equiv) in benzene. [b] NMR yields after 8 h: **1** (52%), **2** (58%). [c] NMR yields after 8 h: **2** (64%), **3** (76%). [d] ee determined by GC. [e] ee determined by HPLC.

It is not possible to estimate the variation in polar effects contribution in the series. One would expect them to lower the activation barrier for the hydrogen transfer between the most electrophilic thiyl radical, i.e., $MeO_2CCH_2S^{\bullet}$ and the amine leading to the most nucleophilic α-amino radical, i.e., **3**. Even without taking into account the possible contribution of steric effects, the interplay between polar- and enthalpy effects that are varying within very small ranges is complex, and a qualitative prediction becomes difficult.

Conclusion

Reversible H-abstraction at the chiral center, in position α relative to nitrogen, by thiyl radical provides a general method to racemize aliphatic amines. The reaction can be complete in 2 h, and it is carried out under mild conditions. Theoretical calculations have considerable interest since they enable one to evaluate BDEs that have not been determined yet. Owing to the strengthening of the α-C−H bond, the thiyl radical-mediated H-abstraction does not proceed with acetylated primary amines. Further developments will be reported in due course.

Experimental Section

General Procedure for the Racemization Experiments. A 0.06 M solution of amine (100 mg) and thiol (1.2 or 0.2 equiv) in benzene was refluxed for 2 h (stoichiometric condition) or 7 h (catalytic condition) in the presence of AIBN (an overall quantity of 20 mol % of AIBN was divided into three equal portions (when reaction time > 2 h) that were added successively each 2 h). After concentration, the residue was diluted with HCl (1 M), and the solution was washed with Et_2O. The aqueous phase was basified with saturated sodium carbonate and extracted with Et_2O. The pure amine was isolated after drying on $MgSO_4$ and concentration.

Supporting Information Available: Plots for the variation of ee/ee_0 versus time and plots for the variation of $\ln(ee/ee_0)$ versus time for the racemization of amines **1** and **3** in the presence of 1.2 equiv of *n*-OctSH. Experimental procedures. NMR spectra for new compounds. Computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061033L