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Highly Efficient Photochemically Induced Thiyl Radical-Mediated Racemization of Aliphatic Amines at 30 °C

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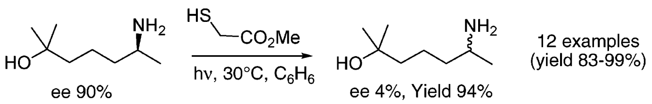

UV irradiation in the presence of thiol enables the performance of highly efficient aliphatic amines racemization, under mild conditions at 30 °C. The reaction proceeds via the reversible generation of prochiral α-aminoalkyl radicals. The latter may result either from a redox process between the thiyl radical and the amine or from direct hydrogen atom abstraction by thiyl radical. As hydrogen atom donor, the thiol plays a crucial role. While the racemization of both primary and secondary amines were fast processes, the racemization of tertiary amines was sluggish. A tentative rationale is based on the photostimulated amine-catalyzed oxidation of the thiol into the corresponding disulfide, which makes the hydrogen atom donor concentration in the reaction medium drop up to trace amount at a rate that depends on the nature of the amine.

Introduction

Racemization of amines is a field of major importance to industrial chemistry.[1] The study of thiyl radical-mediated amine racemization is an ongoing research topic in our group.[2] We have recently reported that the association of this radical process with enzymatic resolution by CAL-B enabled the synthesis of optically pure amides in good yields and high enantiomeric excesses.[3] Since the racemization was carried out at 80 °C using AIBN as radical initiator, the success of the dynamic kinetic resolution (DKR) process was intimately connected to the use of a thermostable lipase.[4] With the view to extend the scope of this DKR methodology by using other enzymes, we have investigated the feasibility of thiyl radical-mediated racemization at lower temperatures. To the best of our knowledge, aliphatic amine racemization proceeding at temperatures lower than 70 °C under mild conditions, in particular in the absence of strong bases, is unprecedented in the literature.[5]

Results and Discussion

Without going into the details of how the α-aminoalkyl intermediate radical is formed, the racemization process can be summarized according to Scheme 1.

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(1) (a) Lawrence, S. A. In *Amines: Synthesis, Properties and Applications*; Cambridge University Press: Cambridge, 2004. (b) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kesseler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788−824. (c) Hieber, G.; Ditrich, K. *Chim. Oggi* **2001**, *19*, 16−20.

(2) (a) Escoubet, S.; Gastaldi, S.; Vanthuyne, N.; Gil, G.; Siri, D.; Bertrand, M. P. *J. Org. Chem.* **2006**, *71*, 7288−7292. (b) Escoubet, S.; Gastaldi, S.; Vanthuyne, N.; Gil, G.; Siri, D.; Bertrand, M. P. *Eur. J. Org. Chem.* **2006**, 3242−3250.

(3) Gastaldi, S.; Escoubet, S.; Vanthuyne, N.; Gil, G.; Bertrand, M. P. *Org. Lett.* **2007**, *9*, 837−839.

(4) For DKR, see: (a) Reetz, M. T.; Schimossek, K. I. *Chimia* **1996**, *50*, 668−669. (b) Choi, Y. K.; Kim, M. J.; Ahn, Y.; Kim, M.-J. *Org. Lett.* **2001**, *3*, 4099−4101. (c) Kim, M.-J.; Kim, W.-H.; Han, K.; Choi, Y. K.; Park, J. *Org. Lett.* **2007**, *9*, 1157−1159. (d) Paetzold, J.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 17620−17621. (e) Parvulescu, A.; De Vos, D.; Jacobs, P. *Chem. Commun.* **2005**, 5307−5309. (f) Parvulescu, A. N.; Jacobs, P. A.; De Vos, D. E. *Chem.—Eur. J.* **2007**, *3*, 2034−2043. (g) Stirling, M.; Blacker, J.; Page, M. I. *Tetrahedron Lett.* **2007**, *48*, 1247−1250. (h) Crawford, J. B.; Skerlj. R. T.; Bridger, G. J. *J. Org. Chem.* **2007**, *72*, 669−671.

(5) Ebbers, E.; Ariaans, G. J. A.; Houbiers, J. P. M.; Brugginks, A.; Zwanenburg, B. *Tetrahedron* **1997**, *53*, 9417−9476.

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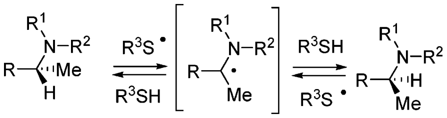
SCHEME 1. Racemization Mechanism



2-Amino-4-phenylbutane (**1**) and its secondary and tertiary derivatives (**2** and **3**) were selected as models to test different experimental conditions. The procedure was then applied to a series of related aliphatic amines bearing different functionalities (Figure 1).

We first examined the possibility to use diazenes known to decompose at low temperatures. 2,2′-Azobis(2,4-dimethyl-4-methoxyvaleronitrile (V70), whose half-life is 10 h at 37 °C,[6] was selected and used at 50 °C in degassed benzene. The results were quite disappointing since it was necessary to add up to 1 equiv of V70 in five portions (0.2 equiv each 2 h from t_0) over 8 h to only partially racemize amine **1** (28% ee and 17% ee with methyl thioglycolate and cyclohexanethiol, respectively, after 10 h at 50 °C). At a concentration 10 times higher than the concentration used in the previous experiments (0.67 M instead 0.067 M), amine **1** could be racemized in 6 h (in the presence of 0.8 equiv of V70), but purification was made difficult due to the formation of side products resulting from the initiator, and no further attempt was made.[7] In fact, at 50 °C the rate of hydrogen atom abstraction by thiyl radical was too slow for the radical chain mechanism to proceed efficiently. The slow rate and the necessity to use a large amount of initiator made the procedure prohibitive for any application at preparative scale.

Therefore, we turned our attention to photochemical initiation, which should enable direct homolytic cleavage of the S−H bond and continuous production of thiyl radical.[8] The reactions were carried out in a benzene solution containing the amine (**1**, **2**, or **3**; 0.067 M) and 1.2 equiv of thiol ($MeOCOCH_2SH$, $C_6H_{11}SH$, or *n*-OctSH) in a quartz tube surrounded by 16 RPR-3000 UV lamps in a Rayonet apparatus.[9] Blank experiments demonstrated without ambiguity that no racemization occurred when the amines were irradiated alone in the absence of thiol.

In literature data, photolytic cleavage of the S−H bond is generally performed with a low-pressure mercury lamp by irradiating at 254 nm.[8] We observed that racemization could be performed in a quartz reactor with our apparatus. The incidence of filtrating wavelengths below 300 nm by using Pyrex tubes instead of quartz ones was also investigated in the absence of any additional radical initiator.

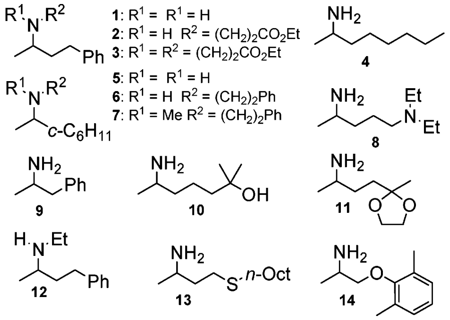


FIGURE 1. Amine structures.

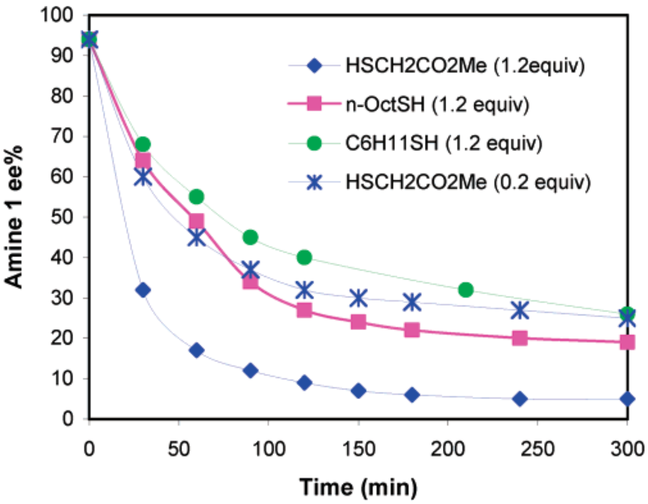


FIGURE 2. Plots of amine **1** enantiomeric excess (ee) versus time, during irradiation in the presence of octanethiol, cyclohexanethiol, and methyl thioglycolate at 47 °C in a quartz reactor.

Figure 2 gives a survey of the influence of the nature of the thiol on the racemization rate. The graphs show that methyl thioglycolate is far more efficient than *n*-OctSH, itself slightly more efficient than $C_6H_{11}SH$. With the former, amine **1** racemization was nearly completed in 3 h in a quartz tube when 1.2 equiv of thiol was used. Conversely, the enantiomeric excess never was less than 19% with *n*-OctSH and 25% with $C_6H_{11}SH$ after irradiation for 6 h. Owing to the less efficient radiative intensity when wavelengths below 300 nm were filtered, the racemization process was slowed down when irradiations were carried out in a pyrex tube.[10] In all cases, whenever racemization was not completed, the ee seemed to reach a limit that could not be overpassed upon prolonged irradiation without introducing and additional amount of thiol in the reaction medium.

If one admits that the racemization proceeds through reversible hydrogen atom abstraction from the amine by thiyl radical, then the initial rate should be related to the strength of the S−H bond that is formed. The slowing of the racemization rate should therefore be expected when going from methyl thioglycolate to alkanethiols since the S−H bond dissociation enthalpy (BDE) is stronger in methyl thioglycolate than in the other aliphatic thiols.[11] This implicitly admits that the forward hydrogen abstraction is rate limiting for the process, at least at the initial stage of the reaction. This is in accordance with experimental observations. The slight difference observed between *n*-OctSH and $C_6H_{11}SH$ is likely to reside more in their compared steric bulk than in the difference between their S−H BDEs. In regard

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(6) Feray, L.; Bertrand, M. In *e-Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Crich, D., Fuchs, P., Molander, G., Eds.; Wiley: Chichester, 2005; DOI:10.1002/047084289X.m00633.

(7) The ^{1}H NMR spectrum of the crude mixture showed that amine was degraded. The residual amine was difficult to quantify with respect to the internal standard owing to the complexity of the mixture.

(8) For the photoinitiated cyclization of thiyl radicals, see: (a) Surzur, J.-M. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum: New York, 1981; Vol. 2, Chapter 3, pp 177−186 and references cited therein. (b) Kirpichanko, S. V.; Tolstikova, L. L.; Suslova, E. N.; Voronskov, M. G. *Tetrahedron Lett.* **1993**, *34*, 3889−3892.

(9) Spectral distribution ranges from 250 to 350 nm with maximum intensity of irradiance at 300 nm.

(10) In the presence of methyl thioglycolate, amine **1** racemization reached completion in 5 h in a Pyrex vessel. The final ee was only 45% in the presence of cyclohexane thiol under the same experimental conditions.

(11) Calculated S-H bond dissociation energies at 298 K according to the G3B3(MP2) level of theory are 359.9 and 364.4 kJ/mol for *n*-BuSH and $HSCH_2CO_2Me$, respectively; see ref 2.

to the use of a catalytic amount of thiol, the reaction rate is likely to be limited in this case by the rate of the backward hydrogen transfer from the thiol to the α-amino radical.

Whatever the intimate mechanism is, the thiol concentration is critical to ensure a complete racemization. The evolution of the amounts of thiol and of the corresponding disulfide in the reaction medium will be discussed later on.

An alternative pathway might involve electron transfer from the amine to thiyl radical immediately followed by proton abstraction by thiolate anion according eqs 5 and 6 (see below). If a photostimulated (or a spontaneous) charge transfer from the amine toward thiyl radical was responsible for the efficacy of the process, then the rate of the reaction should be affected both by the reduction potential of the thiyl radical intermediate[12] and by the oxidation potential of the amine.[13] According to these values, methyl thioglycolate should be the most efficient thiol in the series, but one would expect the tertiary amine to be more reactive, which is not the case.

The influence of the nature of the amine on racemization was investigated. The comparative data are shown in Figure 3 for the reactions carried out on amines **1**−**3**, **12**, and **7** in a quartz vessel. Plots already given for amine **1** have been reproduced to facilitate the comparison. For this reason, all experiments were carried out at 47 °C.

Amine **2** behaved rather similarly to amine **1** as regard to racemization in the presence of methyl thioglycolate. But the racemization of secondary amine **2** was faster than the racemization of primary amine **1** in the presence of cyclohexane thiol. The racemization of amine **3** was much slower, and what is more, amine **3** was partially degraded when the reaction was performed in the presence of methyl thioglycolate. No degradation, but at the same time no racemization at all, was registered when amine **3** was irradiated in a pyrex tube whatever thiol was used. Thereby the class of the amine has a very significant impact on the rate of the photochemically induced racemization process.

Owing to the presence of the electron-withdrawing carbethoxy groups in γ-position relative to the reactive center, the behavior of amines **2** and **3** might be considered as anomalous; therefore, amines **12** and **7** racemizations were also monitored. Racemization in the presence of methylthioglycolate was slightly faster for amine **12** than for amine **2**. Although faster than with amine **3** the racemization of tertiary amine **7** did not reach completion. The final ee was 28% after 3 h.

Our initial choice of secondary amine **2** and tertiary amine **3** as models was essentially governed by their easy access from amine **1** via Michael addition to ethyl acrylate. The racemization process, initiated thermally at 80 °C in the presence of AIBN and a stoichiometric amount of thiol, was as efficient for amine **1** as for amines **2** and **3**.[2b] However, the influence of one or two electron withdrawing groups in position β relative to the nitrogen atom, became significant at lower temperature.

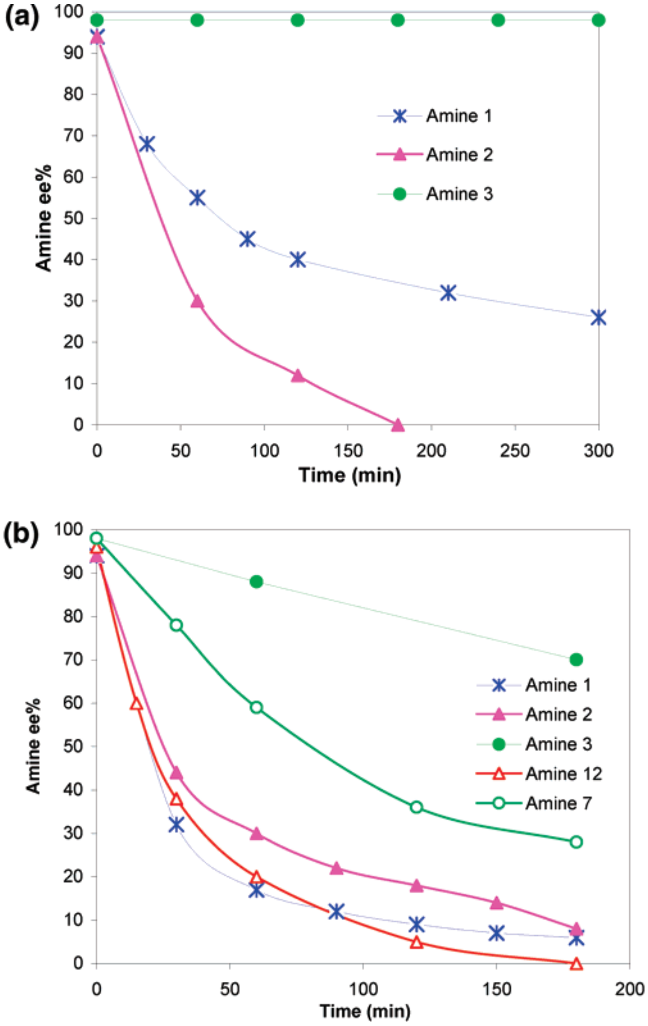

FIGURE 3. Comparative plots of amine ee versus time for amines **1**−**3**, **12**, and **7** (quartz vessel, 47 °C) in the presence of 1.2 equiv of $C_6H_{11}SH$ (Figure 3a) or methyl thioglycolate (Figure 3b).

Several tracks could be followed to propose a tentative rationale to these experimental observations. Recent experimental data and theoretical calculations came to the conclusion that the class of the amine had little influence of the α-CH BDE.[14,2b] This was in contradiction with previous reports that stated the α-C−H BDE decreased in the order primary amine > secondary amine > tertiary amine.[15] Interpreting our data according to α-C−H bond strength would contradict both since racemization was faster for the secondary amine and the primary amine than for the tertiary one.[16]

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[12] The electron affinities of thiyl radicals were shown to give linear correlation with S-H BDEs and with proton affinities; see: (a) Fattahi, A.; Kass, S. R. *J. Org. Chem.* **2004**, *69*, 9176−9183. (b) Janousek, B. K.; Reed, K. J.; Brauman, J. I. *J. Am. Chem. Soc.* **1980**, *102*, 3125−3129.

[13] The oxidation potentials of primary, secondary, and tertiary amines have been calculated by Fu et al.; see: (a) Fu, Y.; Liu, L.; Yu, H.-Z.; Wang, Y.-M.; Guo, Q.-X. *J. Am. Chem. Soc.* **2005**, *127*, 7227−7234. The calculated IP determined in acetonitrile for *n*-propylamine, di-*n*-propylamine, and tri-*n*-propylamine at the B3LYP/6311++G(2df,2p)//B3LYP/6-31G(d) level of theory, using the PCM solvation model, are 8.81, 8.03, and 7.38 eV, respectively. The corresponding E^0 vs NHE values are 1.63, 1.43, and 1.02 eV. The values are very close to experimental ones. For a quantitative approach to IE and gas-phase basicity, see: (b) Cherkasov, A. R.; Jonsson, M.; Galkin, V. *J. Mol. Graphics Mod.* **1999**, *17*, 28−42.

[14] (a) Wayner, D. D. M.; Clark, K. B.; Rauk, A.; Yu, D.; Armstrong, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 8925−8932. (b) Lalevée, J.; Allonas, X.; Fouassier, J.-P. *J. Am. Chem. Soc.* **2002**, *124*, 9613−9621. (c) Feng, Y.; Wang, J.-T.; Huang, H.; Guo, Q.-X. *J. Chem. Comput. Sci.* **2003**, *43*, 2005−2013.

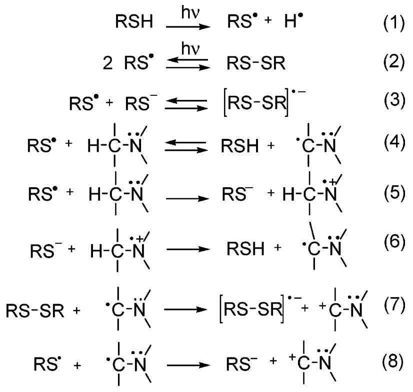
[15] (a) Burkey, T. J.; Catelhano, A. L.; Griller, D.; Lossing, F. P. *J. Am. Chem. Soc.* **1983**, *105*, 4701−4703. (b) Griller, D.; Lossing, F. P. *J. Am. Chem. Soc.* **1981**, *103*, 1586−1587.

[16] For the influence of amine class on the catalysis by aliphatic thiols of the photoreduction of triplets carbonyls, see: (a) Stone, P. G.; Cohen, S. *J. Am. Chem. Soc.* **1980**, *102*, 5686−5688. (b) Stone, P. G.; Cohen, S. *J. Am. Chem. Soc.* **1982**, *104*, 3435−3440. (c) Khan, J.; Cohen, S. G. *J. Org. Chem.* **1991**, *56*, 938−943.

Other parameters might be taken into account such as amine basicity[17,18] or amine ionization potential.[13,19] Since all properties are intimately correlated, it is difficult to define which parameter best accounts for the results.

The rate of formation of disulfide in the reaction medium seems to be the most critical factor. The higher the amount of disulfide is, the lower the amount of free thiol, i.e., the lower the amount of hydrogen atom donor in the medium is. Even though the homolytic cleavage of either the thiol or the disulfide may initiate the production of thiyl radical, the reaction cannot proceed unless the concentration of hydrogen donor enables hydrogen atom transfer to the intermediate α-aminoalkyl radical to become more efficient than competitive side reactions.

As the reaction proceeds, an increasing amount of disulfide is formed at the expense of the thiol. Even spontaneous formation of a small amount of disulfide was observed upon mixing the reagents together at t_0 just before starting irradiation. The formation of disulfide can occur through different pathways.[20] Equations **1−8** illustrate a panel of elementary steps the occurrence of which may be envisaged in the reaction medium. Thiyl radical and disulfide radical anions are closely related to each other through an equilibrium which comes into play any time thiyl radicals are generated through a redox process from either thiols or disulfides (eq 3). Due to the involvement of thiolate anion the equilibrium depends on the concentration of the anion and thus, in our case, on the pK_a of the amine and on its concentration. It depends also on the nature of the R group and, thus, on the acidity of the thiol. Reductive generation of thiyl radical through direct electron transfer to disulfide can be initiated with one electron reducing species such as α-aminoalkyl radicals (eq 7). Although less likely, direct reduction of thiyl radical to thiolate anion can also be envisaged with these alkyl radicals known as being powerful reducing agents[13,15,21] (eq 8).



The evolution of the amounts of thiol and that of the corresponding disulfide was investigated under different experimental conditions monitoring the reaction by ^{1}H NMR using pentamethylbenzene as internal standard in C_6D_6.[22] When methyl thioglycolate was irradiated alone for 3 h, less than 10% of thiol was consumed to give the disulfide. When the thiol and MeN-(*n*-Oct)$_2$ (taken as a model for tertiary amine) were mixed in the absence of irradiation, less than 6% of thiol was consumed and converted into disulfide within 3 h. Figure 4 illustrates how the irradiation of the thiol in the presence of the different types of amines stimulates the formation of disulfide.

There is a clear relationship between the nature of the amine and the rate of formation of the disulfide which argues in favor of the hypothesis of a photostimulated electron-transfer mechanism in eqs 5 and 6. However, the ionization potential of the amine does not correlate with the rate of formation of the disulfide. The formation of disulfide is slower in the presence of primary amine **1** than in the presence of a tertiary one (*N*-methyl-*N*,*N*-di-*n*-octylamine), but the formation of the disulfide and the concomitant disappearance of the thiol go slightly slower in the presence of a secondary amine (*i*-Pr$_2$NH taken as model) than with amine **1**.

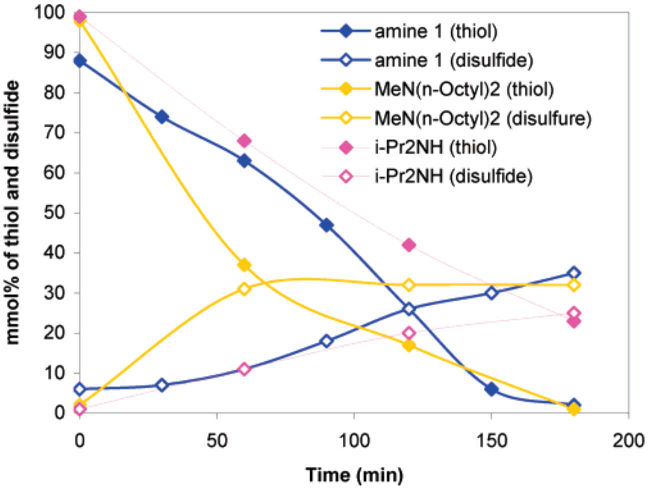


FIGURE 4. Plots for the disappearance of methyl thioglycolate and for the formation of the corresponding disulfide upon irradiation in the presence of amines at 30 °C.

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[17] pK_a values in water are 10.69 for *n*-propylamine, 11.09 for diethylamine, and 11.09 for triethylamine; see: (a) Lu, G.; Grossman, J. E.; Lambert, J. B. *J. Org. Chem.* **2006**, *71*, 1769−1776. The corresponding pK_a values in acetonitrile are 18.4 for ethylamine, 18.8 for diethylamine, and 18.5 for triethylamine; see: (b) Li, J.-N.; Fu, Y.; Liu, L. Guo, Q.-X. *Tetrahedron* **2006**, *62*, 11801−11813. Solvent effect on amine basicity is well known. A subtle differentiation, according to the nature of the alkyl substituent, might be induced by a solvent of low dielectric constant like benzene. See: (c) Headley, A. D. *J. Org. Chem.* **1991**, *56*, 3688−3691. (d) Safi, B.; Choho, K.; Geerlings, P. *Chem. Phys. Lett.* **1999**, *300*, 85−92. (e) Caskey, D. C.; Damrauer, R.; McGoff, D. *J. Org. Chem.* **2002**, *67*, 5098−5105.

[18] Proton transfer would induce the formation of an unreactive salt in the reaction medium (the α C-H BDE is strengthened when the amine lone pair is protonated). The formation of the ammonium thiolate is an equilibrium. The more basic the amine is and the more acidic the thiol is, the more the equilibrium should be displaced to the right and, as a consequence, the least efficient the hydrogen abstraction should be. The pK_a value for methyl thioglycolate is 7.8, and the pK_a value for *n*-BuSH is 10.9; see: McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493−532.

[19] For other photoinduced electron transfer processes involving amines, see: (a) Pischel, U.; Nau, W. M. *J. Am. Chem. Soc.* **2001**, *123*, 9727−9737. (b) Pishel, U.; Nau, W. M. *J. Phys. Org. Chem.* **2000**, *13*, 640−647. (c) Dossot, M.; Allonas, X.; Jacques, P. *Phys. Chem. Chem. Phys.* **2002**, *4*, 2989−2993.

[20] For general reviews, see: (a) Asmus, K.-D.; Bonifačić, M. In *S-Centered Radicals*; Alfassi, Z. B., Ed.; Wiley: Chichester, 1999; Chapter 5. (b) Chatgilialoglu, C.; Guerra, M. Thiyl radicals. In *Chemistry of Sulphur-Containing Functional Groups*; Patai, S.; Rappoport, Z., Eds.; Wiley: Chichester, New York, 1993; pp 363−94. (c) For EPR studies of photoreaction of aliphatic thiols leading to disulfide radical anions, see: Cremonini, M. A.; Lunazzi, L. Placicci, G. *J. Org. Chem.* **1993**, *58*, 3805−3810.

[21] (a) Wayner, D. D. M.; Dannenberg, J. J.; Griller, D. *Chem. Phys. Lett.* **1986**, *131*, 189−191. (b) For the theoretical prediction of the absolute standard redox potentials of a series of α-amino radicals, see ref 13. The values calculated in solution in acetonitrile, at the B3LYP/6-311++G-(2df,2p)//B3LYP/6-31G(d) level of theory using the PCM solvation model, range from − 1.5 V to 0.36 V ($E° = −0.66$ V for $H_2NCH_2^•$; − 1.47 V for $(Me)_2NCH_2^•$). (c) Armstrong, D. A.; Rauk, A.; Yu, D. *J. Am. Chem. Soc.* **1993**, *115*, 666−673.

TABLE 1. Quantitative Data for the Racemization of Amines 1−14 upon Irradiation in the Presence of Methyl Thioglycolate[a]

entry	amine (ee$_0$, %)	time (h)	yield (%)		ee (%)
			NMR[b]	isolated[c]	
a	**1** (94)	2.5	99	83	13
a′	**1** (94)[e]	3.5	92	63	8
b	**2** (94)	3	99	95	<0.5
c	**3** (94)	3	96	79	33
d	**4** (99)	3	96	82	4
d′	**4** (99)[e]	3.5	83	62	5
e	**5** (98)	3	97	81	6
e′	**5** (98)[e]	3.5	86	76	7
f	**6** (98)	1	99	84	15
g	**7** (98)	3	nd	85	30
h	**8** (>99.5)	1	96	63[d]	21
i	**9** (93)	2.5	97	77	10
k	**10** (90)	3	94	62	4
l	**11** (93)	3	degradation		
l′	**11** (93)[e]	4	87	53	17
m	**12** (91)	3	97	84	2
n	**13 (**>99)[f]	3.5	88	74	16
o	**14** (>99.5)		degradation		

[a] Conditions: amine (0.067M); thiol (1.2 equiv); solvent: benzene; 30 °C; *hν* (quartz vessel, unless otherwise stated). [b] Determined using pentamethylbenzene as internal standard. [c] Yields were determined after derivatization in trifluoroacetamide unless otherwise stated. [d] Isolated without derivatization. [e] The reaction was carried out in a Pyrex vessel at 47 °C. [f] The reaction was carried out in a Pyrex vessel at 30 °C.

It must be noted that in the case of amine **3**, the disappearance of the thiol is by far much slower than in the other cases. The presence of the two carboxylic esters in position β-relative to the nitrogen atom in **3** modifies the properties in such a way that the formation of disulfide has little incidence after irradiating for 3 h (less than 5%). In this case, the incidence of the substituents on either the α-CH BDE or the amine ionization potential could provide a rationale.

The racemization efficiency is undoubtly connected with the disappearance of the thiol from the reaction medium. Partial racemization of amine **1** could be achieved when starting from the thioglycolic disulfide, i.e., in the absence of thiol, but the ee was only 36% after 7 h, and partial degradation occurred (47% ^{1}H NMR yield). Conversely, starting with 1.2 equiv of methyl thioglycolate, **1** was racemized in 2.5 h (13% ee, Table 1, entry a).

Finally, the influence of the temperature upon the racemization of amine **1** was investigated. Lowering the temperature to 30 °C had no significant effect on the characteristic feature of the reaction, as far as it was carried out in quartz vessel. The optimized conditions at 30 °C were applied to the series of aliphatic amines given in Figure 1. The results (final ee, and isolated yields) are reported in Table 1. For sake of comparison, some satisfying results obtained at 47 or 30 °C in a Pyrex vessel are also given (entries a′, d′, e′, l′, and n).

The racemization of primary and secondary amines proceeded in high yield, and all reactions were very clean and fast processes. The lowest isolated yield was registered for amine **8** (bearing an additional tertiary amine group, entry h). It can be noted that the racemization of amphetamine **9** (that could not be performed at 80 °C without degradation) was also very efficient (entry i). The bifunctional amines **11**, **13**, and **14** were degraded when irradiation was carried out in quartz vessel. However, **11** and **13** could be racemized without too much degradation in a Pyrex vessel at 47 °C and 30 °C, respectively (entries l′ and n).

The racemization of tertiary amines was slow and could not be completed (final ee close to 30% after irradiating for 3h) (entries c and g).

Conclusion

The thiyl radical mediated racemization of aliphatic amines could be performed under mild experimental conditions at 30 °C under photochemical initiation. The racemization of primary and secondary amines proceeded in high yield, and all experiments reported herein were very clean and fast. Tertiary amine racemization was slower. Thioglycolic derivatives are among the most efficient aliphatic thiols. The reaction proceeds through the reversible formation of a α-aminoalkyl radical. Therefore, the concentration of thiol as the hydrogen atom donor must be kept at such a level as to avoid competitive evolutions of the prochiral intermediate radical. Any oxidative transformation of the thiol into the corresponding disulfide is detrimental to the racemization process. Therefore, the efficiency of the racemization depends on the complex interplay of several factors such as α C−H BDE, amine ionization potential, amine basicity, thiol acidity. The low-temperature range opens perspectives regarding the performance of dynamic kinetic resolutions associating the photochemically induced reaction with enzymatic resolution by thermolabile enzymes. Assays are currently under investigation, results will be reported in due course.

Experimental Section

General Procedure for Racemization Experiments. In a typical experiment, a 0.06 M benzene solution of amine (100 mg) and methyl thioglycolate (1.2 equiv) was irradiated at 30 °C in a quartz tube (or Pyrex tube depending on the stability of the substrate (see Table 1)) in a Rayonet apparatus (RPR-200, 16 UV lamps RPR-3000) for 1−4 h. The workup was adapted according to the nature of the amines. For primary amines, after concentration, the residue was diluted with CH_2Cl_2 (5 mL). Triethylamine (3.2 equiv) and trifluoroacetic anhydride (3 equiv) were added at 0 °C. The solution was stirred for 3 h at room temperature. The solvent was removed in vacuo and the crude material was diluted with Et_2O, washed with HCl (0.1 N) and brine, and dried under Na_2SO_4. After concentration, the crude material was subjected to flash column chromatography on silica gel (AcOEt/pentane) to give the trifluoroacetamide. For secondary and tertiary amines, after concentration, the crude material was purified by flash column chromatography on silica gel (Et_3N/pentane) to give the pure amine.

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Supporting Information Available: Experimental procedures and NMR spectra for compounds **1**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Only methyl thioglycolate enabled the monitoring of the reaction by ^{1}H NMR while irradiating in C_6D_6 in the presence of pentamethylbenzene as internal standard. The signals of the methylene protons and of the methoxy group in both compounds are distinct from each other. The δ values for the methoxy group and the methylene protons are 3.20 and 2.66, respectively, in methyl thioglycolate. The δ values for the methoxy group and the methylene protons are 3.25 and 3.17, respectively, in the corresponding disulfide. It can be noted that the methylene signal in methyl thioglycolate remains a doublet ($J = 8.1$ Hz) in the presence of amine **3**, but due to a fast exchange of the SH proton, no coupling is observed in the presence of amine **1** and the other amines in the series. This confirms the low basicity of amine **3**.