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Efficient Racemization of 1-Phenylethylamine and Its Derivatives[1]

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Abstract—We report on simple and efficient procedure for the racemization of 1-phenylethylamine and its derivatives. In the presence of trichloroisocyanuric acid, *N*-chloroimine derivative is formed as the intermediates, with subsequent hydrogenation catalyzed by Pd–C leading to the racemic product.

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Enantiomerically pure amines and alcohols are key intermediates in the preparation of biologically active pharmaceuticals and agrochemical products [1–5]. To prepare enantiomerically pure amines, separation by chiral chromatography, diastereomeric crystallization, or kinetic resolution as well as asymmetric hydrogenation of imines, enamines, or oximes are the well known methods [3].

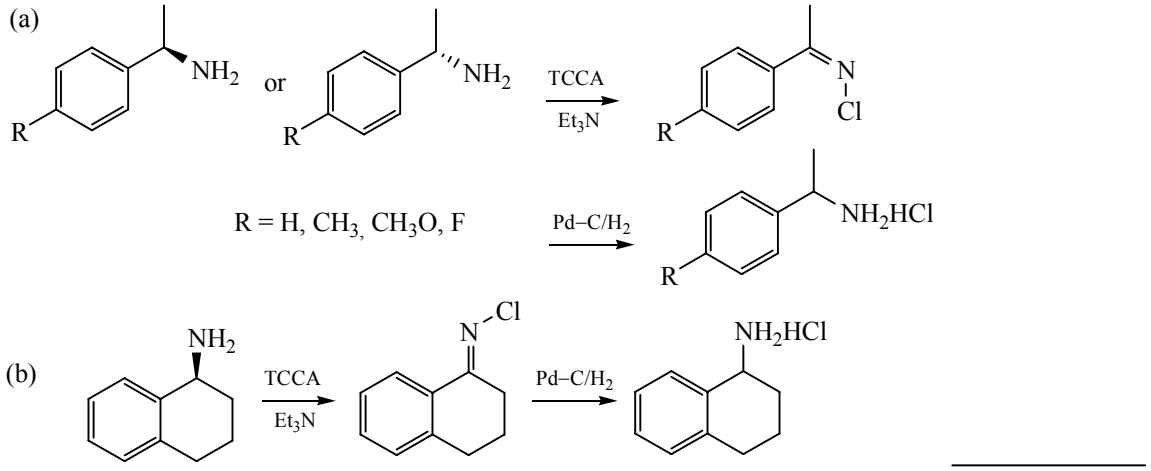
On the other hand, processing of the undesired enantiomers through racemization is of critical importance from both economical and environmental points of view [6, 7]. Racemization of chiral compounds is a useful technique to increase the yield of the desired product: the undesired enantiomer can be racemized, and additional portions of the desired one can be obtained from the racemate [8]. The resolution process accompanied by continuous racemization is referred to as dynamic kinetic resolution (DKR). Reports on selective racemization and DKR of amines are scarce; therefore development of highly selective and active racemization catalyst is still a challenge [9, 10]. So far, four routes have been identified for racemization of chiral amines, including redox, radical, base-catalyzed, and enzymatic racemization, redox racemization being the most promising [8, 10–17]. In 1996, palladium was used as racemization catalyst in DKR of amines [18]. From then on, palladium was considered an attractive catalyst for racemization of many primary amines [19, 20]. Besides palladium, other transition metals were used as racemization catalysts. In particular, nickel nanoparticles allowed for excellent selectivity in racemization of benzyl and aliphatic amines [9]. Ruthenium-catalyzed racemization of amines under transfer hydrogenation conditions was reported in [21], the advantage of them being that ruthenium catalysts were highly tolerant to other functional groups, and both primary and secondary amines could be efficiently racemized. In the presence of metal catalysts, racemization occurred via redox reactions [11, 22–24]. Under either heterogeneous or homogeneous catalytic conditions, the redox process could be performed via prochiral imines or iminium ion intermediates [25]. Amines could be easily transformed into *N*-chloroimines in the presence of trichloroisocyanuric acid (TCCA) [26]. This reaction was used in this work to perform the chiral amines racemization.

Seven enantiomerically pure amines were used in racemization reactions (see table). At the first step, the substrates were converted into *N*-chloroimine derivatives in the presence of trichloroisocyanuric acid. Then, the prepared intermediates were reduced to racemic amine by hydrogen in the presence of Pd–C (see Scheme 1).

The products structures were confirmed by ESI-MS and ^{1}H NMR spectroscopy. The HPLC retention time of the mixtures components and the corresponding enantiomeric excess values are collected in the table. From each racemic mixture, two enantiomers were isolated by HPLC (the retention times differed by about 2 min). In the case of 1-phenylethylamine, the enantiomeric excess of the racemate mixtures derived

[1] The text was submitted by the authors in English.

Scheme 1.



from (*S*)-l-phenylethylamine and (*R*)-l-phenylethylamine were equal (*ee* = 2%). In the case of other amine substrates, the enantiomeric excess values were low as well (below 4%), thus confirming the efficient racemization process. However, in the case of (*S*)-β-naphthylamine the desired racemic product was not obtained under the similar conditions. This fail will be further investigated and reported separately.

EXPERIMENTAL

The starting materials: (*S*)-1-phenylethylamine, (*R*)-1-phenylethylamine, (*S*)-1-(4-methylphenyl)ethylamine, (*R*)-1-(4-methylphenyl)ethylamine, (*R*)-1-(4-methoxyphenyl)ethylamine, (*S*)-1-(4-fluorophenyl)ethylamine, (*S*)-1,2,3,4-tetrahydronaphthyl-1-amine, trichloroisocyanuric acid, and Pd-C were purchased from J&K. All organic solvents used in this work including anhydrous methanol and anhydrous dichloromethane were of analytical pure grade and were used directly without further purification.

The enantiomeric excess (*ee*) was determined by using HPLC with a UV-Vis DAD detector and a chiral column (Chiralcel AD). The mobile phase was a mixture of hexane, isopropanol, trifluoroacetic, and triethylamine 375 : 25 : 0.8 : 0.4. The detection wavelength was 215 nm, and flow rate was 1 mL/min. The relative content of each enantiomer (α and β) was calculated from the peak area in the chromatogram.

$$ee\ (\%) = \frac{\alpha - \beta}{\alpha + \beta} \times 100\%.$$

***N*-Chloroimine intermediates preparation** *(general procedure).* Enantiomerically pure amine (1 mmol) was dissolved in dichloromethane (5 mL), and trichloroisocyanuric acid (0.16 g, 0.7 mmol) was added at 0°C. Then, the mixture was stirred at ambient temperature during 1 h. Triethylamine (0.30 g, 0.3 mol) dissolved in dichloromethane (5 mL) was added, and the resulting mixture was washed with water (10 mL) and hydrochloric acid (1 M, 10 mL) successively. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuum to give the *N*-chloroimine derivative.

***N*-Chloro-1-phenylethanimine (I).** Transparent liquid. Yield 80%. ESI-MS: *m/z* 154.07 ([*M* + H]$^+$, C_8H_9ClN is 154.04). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, TMS), δ, ppm: 7.39–7.71 m (5H), 2.60 s (3H).

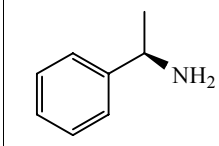
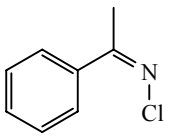
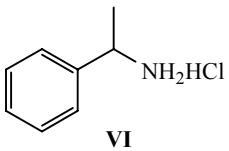
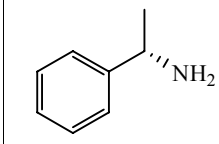
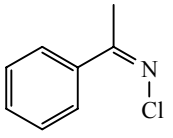
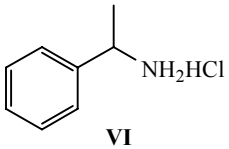
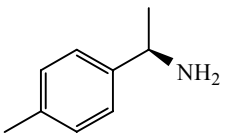
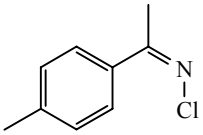
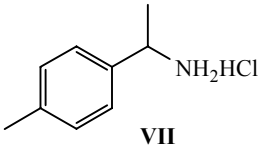
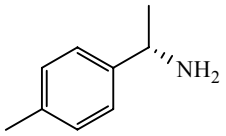
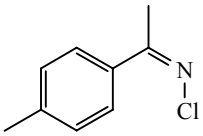
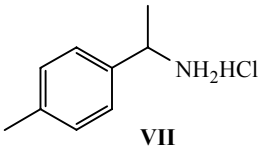
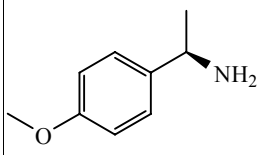
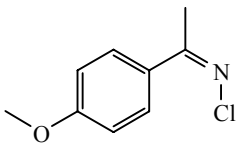
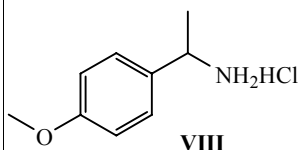
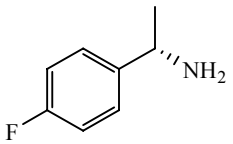
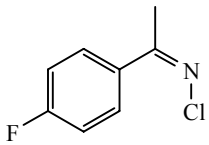
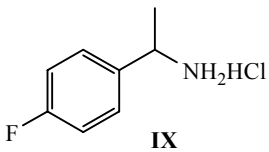
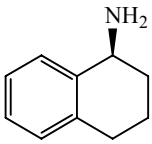
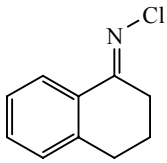
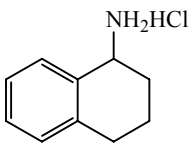
***N*-Chloro-1-(4-methylphenyl)ethanimine (II).** Transparent liquid. Yield 81%. ESI-MS: *m/z* 168.07 ([*M* + FT], $C_9H_{11}ClN$ is 168.06). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, TMS), δ, ppm: 7.15–7.61 m (4H), 2.57 s (3H), 2.37 s (3H).

***N*-Chloro-1-(4-methoxyphenyl)ethanimine (III).** Transparent liquid. Yield 80%. ESI-MS: *m/z* 184.07 ([*M* + H]$^+$, $C_9H_{11}ClNO$ is 184.05). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, TMS), δ, ppm: 6.89–7.69 m (4H), 3.84 s (3H), 2.56 s (3H).

***N*-Chloro-1-(4-fluorophenyl)ethanimine (IV).** Transparent liquid. Yield 78%. ESI-MS: *m/z* 172.05 ([*M* + H]$^+$, C_8H_8ClFN requires 172.03). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, TMS), δ, ppm: 7.07–7.73 m (4H), 2.58 s (3H).

***N*-Chloro-3,4-dihydronaphthyl-1(2H)-imine (V).** Transparent liquid. Yield 82%. ESI-MS: *m/z* 180.09 ([*M* + H]$^+$, $C_{10}H_{11}ClN$ is 180.06). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, TMS), δ, ppm: 7.18–8.08 m (4H), 2.96 t (2H), 2.80 t (2H), 1.95 m (2H).

Structures of compounds, retention times, and enantiomeric excess (*ee*) of the racemic products

Run no.	Substrate	Intermediate	Racemization product	Retention time, min		*ee*, %
				t_R(S)	t_R(R)	
a		 **I**	 **VI**	10.913	12.956	2
b		 **I**	 **VI**	10.913	12.956	2
c		 **II**	 **VII**	10.296	11.787	4
d		 **II**	 **VII**	10.296	11.787	3
e		 **III**	 **VIII**	18.126	15.557	1
f		 **IV**	 **IX**	10.500	13.763	3
g		 **V**	 **X**	11.332	10.059	3

Preparation of 1-phenylethylamine derivatives racemate *(general procedure).* The prepared *N*-chloroimine and Pd–C (0.012 g) were mixed in 6 mL of methanol and stirred at ambient temperature under hydrogen during 2 h. Then the mixture was filtered and concentrated in vacuum to give the racemic product.

1-Phenylethylamine (VI). White powder. Yield 95%. ESI-MS: *m/z* 121.99 ($[M + H]^+$, C_8Hi_2N is 122.10). ^{1}H NMR spectrum (400 MHz, CD_3OD, TMS), δ, ppm: 7.09–7.59 m (5H), 4.23 m (1H), 1.38 d (3H).

1-(4-Methylphenyl)ethylamine (VII). White powder. Yield 95%. ESI-MS: *m/z* 136.08 ($[M + H]^+$, $C_9H_{14}N$ is 136.11). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, TMS), δ, ppm: 7.01–7.56 m (4H), 4.23 m (1H), 2.35 s (3H), 1.38 d (3H).

1-(4-Methoxyphenyl)ethylamine (VIII). White powder. Yield 93%. ESI-MS: *m/z* 151.85 ($[M + H]^+$, $C_9H_{14}NO$ is 152.11). ^1H NMR spectrum (400 MHz, $CDCl_3$, TMS), δ, ppm: 6.86–7.28 m (4H), 4.09 m (1H), 3.77 s (3H), 1.37 d (3H).

1-(4-Fluorophenyl)ethylamine (IX). White powder. Yield 90%. ESI-MS: *m/z* 139.91 ($[M + H]^+$, $C_8H_{11}FN$ is 140.09). ^1H NMR spectrum (400 MHz, $CDCl_3$, TMS), δ, ppm: 7.00–7.27 m (4H),4.25 m (1H),1.37 d (3H).

1,2,3,4-Tetrahydronaphthyl-l-amine (X). Pink powder. Yield 90%. ESI-MS: *m/z* 147.98 ($[M + H]^+$, $C_{10}H_{14}N$ is 148.11). ^1H NMR spectrum (400 MHz, $CDCl_3$, TMS), δ, ppm: 7.22–8.10 m (4H), 1.50 m (2H), 4.36 m (1H), 2.77 t (2H), 1.90 m (2H).

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