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(*R*)-*O*-Aryllactic Acids: Convenient Chiral Solvating Agents for Direct ^{1}H NMR Determination of the Enantiomeric Composition of Amines and Amino Alcohols

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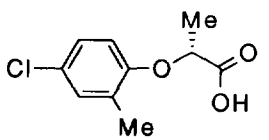
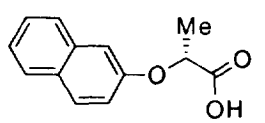
Abstract: (*R*)-*O*-(4-Chloro-2-methylphenyl)- and (*R*)-*O*-(2-naphthyl)lactic acids are very efficent chiral solvating agents for the direct ^{1}H NMR assay of the enantiomeric composition especially for primary and secondary amines and significant amino alcohols such as propranalol and fluoxetine.

Chiral recognition through diastereomeric salt formation between chiral amines and acids is a simple and rapid determination method of the enantiomeric composition of amines and acids by chemical shift differences in NMR spectroscopy[1]. The enantiomeric purity of chiral amines by ^{1}H NMR spectroscopy has been measured using (*R*)-*O*-acetylmandelic acid (ROAM)[1a] and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(+)-MTPA][1b,e]. In connection with our studies about asymmetric nitroaldol reaction we found that (*R*)-*O*-(4-chloro-2-methylphenyl)lactic acid (**1a**) was more adequate reagent that (+)-MTPA to determine the enantiomeric excess of 1-amino-4-methyl-2-pentanol[2]. (*R*)-*O*-Aryllactic acids (ROAL) are readily accessible reagents, because they can be easily prepared from very cheap lactic esters by a two-step procedure, which involves the arylation of the hydroxy function by Mitsunobu reaction with phenols followed by basic hydrolysis of the ester function[3]. ROAL acids have been used in the ^{1}H[4] and ^{19}F[5] NMR analysis of esters and amides derived from chiral alcohols and amines, respectively, and also in the kinetic resolution of racemic alcohols by DCC mediated esterification[6]. We study here the use of (*R*)-*O*-aryllactic acids (ROAL) as efficient chiral solvating agents to form soluble diastereomeric salts of amines and amino alcohols in order to measure their enantiomeric composition by ^{1}H NMR spectroscopy.

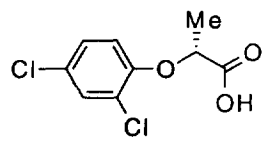
In a typical experiment a 0.1 M solution of the amine or amino alcohol **2** and the ROAL acid **1** in $CDCl_3$ was directly prepared in a NMR tube and its ^{1}H NMR (300 MHz) spectrum recorded at 300°K. Three representative ROAL acids have been attempted: (*R*)-*O*-(4-chloro-2-methylphenyl)lactic acid (**1a**), (*R*)-*O*-(2-naphthyl)lactic acid (**1b**) and (*R*)-*O*-(2,4-dichlorophenyl)lactic acid (**1c**), the best results being obtained with the two former, in general, with acid **1c** very broad signals were observed. The diastereomeric salts were soluble



1a



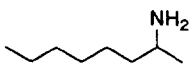
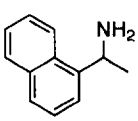
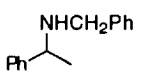
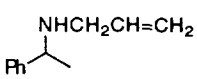
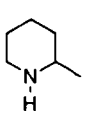
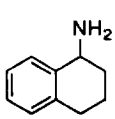
1b

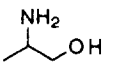
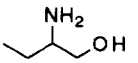
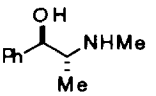
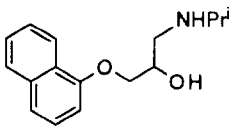
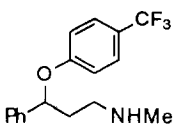


1c

in $CDCl_3$ and in general the known enantiomeric composition were in good agreement with NMR determined values (±1%). The compounds investigated are collected in Table 1. The detection limit was essayed with (*S*)-α-methylbenzylamine (**2d**) (Aldrich 96%) and it was possible to determine the 2% of the residual enantiomer with acids **1a** and **1b**.

Table 1. Magnitude of Nonequivalence for Racemic Chiral Amines and Amino Alcohols as ROAL Salts

Entry	Acid no.	Compound	No.	Δδ CH	Δδ Me	Solvent
1	**1a**		**2a**	0.110	0.036	C_6D_6
2	**1a**		**2b**	0.138	0.043	$CDCl_3$
3	**1a**		**2c**	0.242	0.054[a]	$CDCl_3$
4	**1a**		**2d**	0.300	0.097	$CDCl_3$
5	**1b**		**2d**	0.128	0.137	$CDCl_3$
6	**1a**		**2e**	0.092	0.043	$CDCl_3$
7	**1a**		**2f**	0.375[a]	0.230	$CDCl_3$
8	**1a**		**2g**	0.241	0.102	$CDCl_3$
9	**1a**		**2h**	0.004[a]	0.013[a]	C_6D_6
10	**1b**		**2h**	0.018[a]	0.036	$CDCl_3$
11	**1a**		**2i**	0.044	0.015	C_6D_6
12	**1b**		**2i**	-	0.032	$CDCl_3$
13	**1a**		**2j**	0.100	-	$CDCl_3$

14	**1a**		**2k**	-	0.035	$CDCl_3$
15	**1a**		**2l**	-	0.030[a]	$CDCl_3$
16	**1b**		**2l**	-	0.069	$CDCl_3$
17	**1a**		**2m**	0.052[b]	0.070[c]	$CDCl_3$
18	**1a**		**2n**	0.105[d]	-	$CDCl_3$
19	**1b**		**2n**	0.228[d], 0.229[b]	-	$CDCl_3$
20	**1a**		**2o**	0.082[b]	-	$CDCl_3$
21	**1b**		**2o**	0.113[b]	-	$CDCl_3$

[a] It could not be integrated. [b] For C*H*OH. [c] $\Delta\delta_{MeN} = 0.032$. [d] One of the CH_2O.

Molar equivalency studies support a strong ion-pair interaction. Significant nonequivalence was observed with amine **2d** and acid **1a** at low acid/amine ratio 1/4 ($\Delta\delta_{CH} = 0.084$) which increases up to 1/1 ($\Delta\delta_{CH} = 0.300$) and decreased ($\Delta\delta_{CH} = 0.053$) when the ratio increases to 2/1. Effects of concentration on nonequivalence in the case of compound **2d** and acid **1a** were insignificant.

Primary and secondary chiral amines had the largest chemical shift differences. Acid **1a** shows a great influence in the methine group bonded to nitrogen and acid **1b** in the methyl group α- or β-bonded to the chiral carbon atom (Table 1, entries 5, 10, 12 and 16). In the case of amino alcohols **2k-o** (Table 1, entries 14-21) chemical shift nonequivalences have been observed in the proton bonded to the chiral carbon bonded to nitrogen, for propranalol[7] (**2n**) one of the protons of the CH_2O group split in two dd (Table 1, entries 18 and 19) and in the case of fluoxetine[8] (**2o**) the methine group was the only signal separated (Table 1, entries 20 and 21).

In general, the chemical shift differences between anisochronous resonances are in general greater than with (+)-MTPA[1b] or ROAM[1a] acids and the experiments can be carried out with ROAL acids in $CDCl_3$ (Table 2). It is possible to correlate the absolute configuration in the series of primary amines **2a,c-e** and the tertiary **2h** in these cases the methine and methyl groups for the (*R*)-enantiomer appear at lower fields than the *S*. For secondary amines **2f** and **2g** the opposite effect was observed.

In conclusion, we think that the simple and rapid method described here can become of practical use for the ^1H NMR determination of e.e.'s in chiral amines and amino alcohols.

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Table 2. Magnitude of Nonequivalence for Racemic Chiral Amines and Amino Alcohols as (+)-MTPA[1b], ROAM[1a] and ROAL Salts.

			Δδ		
Entry	Amine	Acid	CH	Me	Solvent
1	**2d**	(+)-MTPA	0.035	0.007	C_6D_6
2	**2d**	ROAM	0.075	0.063	C_6D_6
3	**2d**	ROAL **1a**	0.300	0.097	$CDCl_3$
4	**2d**	ROAL **1b**	0.128	0.137	$CDCl_3$
5	**2h**	(+)-MTPA	0.017	0.019	C_6D_6
6	**2h**	ROAM	0.061	0.058	C_6D_6
7	**2h**	ROAL **1b**	0.018	0.036	$CDCl_3$
8	**2m**	ROAM	-	0.060[a]	C_6D_6
9	**2m**	ROAL **1a**	0.052[b]	0.070, 0.032[a]	$CDCl_3$
10	**2n**	ROAM	0.017	-	C_6D_6-C_5D_5N
11	**2n**	ROAL **1b**	0.229	-	$CDCl_3$

[a] For MeN. [b] For *CH*OH.

REFERENCES AND NOTES

1. (a) Parker, D.; Taylor, R. J. *Tetrahedron* **1987**, *43*, 5451-5456. (b) Villani, F. J.; Costanzo, M. J.; Inners, R. R.; Mutter, M. S.; McClure, D. E. *J. Org. Chem* **1986**, *51*, 3715-3718. (c) Maryanoff, B. E.; McComsey, D. F. *J. Heterocycl. Chem.* **1985**, *22*, 911-914. (d) Mikolajczyk, M.; Omelanczuk, J.; Leitloff, M.; Drabowicz, J.; Ejchart, A.; Jurczak, J. *J. Am. Chem. Soc.* **1978**, *100*, 7003-7008. (e) Baxter, C. A. R.; Richards, H. C. *Tetrahedron Lett.* **1972**, 3357-3358. (f) Ejchart, A.; Jurczak, J.; Bankowski, K. J. *Bull. Acad. Pol. Sci.* **1971**, *19*, 731-734. (g) Dyllick-Brenzinger, R.; Roberts, J. D. *J. Am. Chem. Soc.* **1980**, *102*, 1166-1167. (h) Ejchart, A.; Jurczak, J. *Bull. Acad. Pol. Sci.* **1971**, *19*, 725-730.
2. Chinchilla, R.; Nájera, C.; Sanchez-Agulló, P. *Tetrahedron: Asymmetry* **1994**, *5*, 1393-1402.
3. Tottie, L.; Baeckström, P.; Moberg, C.; Tegenfeldt, J.; Heumann, A. *J. Org. Chem.* **1992**, *57*, 6579-6587.
4. (a) Tottie, L.; Moberg, C.; Heumann, A. *Acta Chem. Scand.* **1993**, *47*, 492-499. (b) Heumann, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1113-1115.
5. Heumann, A.; Faure, R. *J. Org. Chem.* **1993**, *58*, 1276-1279.
6. (a) Chinchilla, R.; Nájera, C.; Yus, M.; Heumann, A. *Tetrahedron: Asymmetry* **1990**, *1*, 851-854. (b) Mazón, A.; Nájera, C.; Yus, M.; Heumann, A. *Tetrahedron: Asymmetry* **1992**, *3*, 1455-1466.
7. Propranalol is a preparatory drug in which the *S* enantiomer acts as a β-blocker and the *R* as contraceptive.
8. Fluoxetine is a potent antidepresant.

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