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KINETIC RESOLUTION OF RACEMIC CARBOXYLIC ACIDS WITH HOMOCHIRAL ALCOHOLS AND DICYCLOHEXYLCARBODIIMIDE

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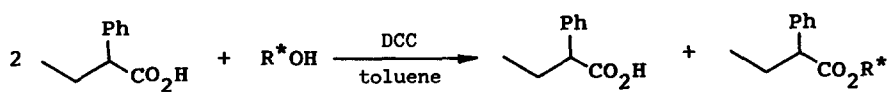
Abstract Racemic carboxylic acids have been kinetically resolved by means of homochiral alcohols using the DCC-esterification methodology The best results were obtained with commercially available homochiral 1-(4-pyridyl)ethanol <60% e e for enantiomerically enriched acids and <76% d e for diastereomerically enriched esters

One of the best methods for obtaining homochiral carboxylic acids involves (a) the transformation of the racemic acids into a diastereomeric salts or esters by reaction with an amine or an alcohol, (b) physical separation of both diastereoisomers (fractional crystallization, distillation, or chromatography), and (c) final regeneration of each enantiomeric acid by hydrolysis of the separated diastereoisomers [1] On the other hand, the kinetic resolution[2] of racemic carboxylic acid anhydrides can be accomplished with optically active alcohols [3] We have recently reported[4] the use of dicyclohexylcarbodiimide (DCC) esterification method[5] to resolve kinetically racemic alcohols using simple chiral carboxylic acids In this paper we describe the 'opposite' reaction, that is, the kinetic resolution of racemic acids by means of the DCC-methodology

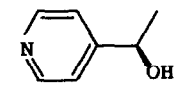
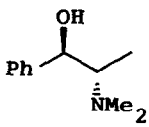
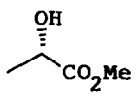
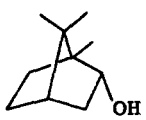
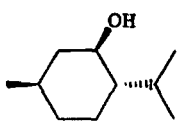
We first studied the resolution of racemic 2-phenylbutanoic acid **1a** with different chiral alcohols by means of DCC in toluene as solvent (Scheme 1) The results are summarized in Table 1 except in



(*R/S*)-**1a** **2a-f** (*S*) or (*R*)-**1a** **3aa-af**

Scheme 1

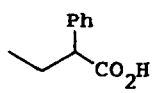
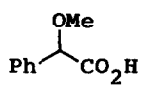
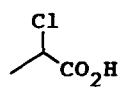
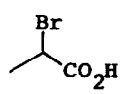
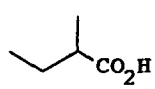
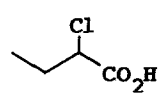
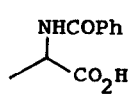
Table 1 Esterification of racemic **1a** with alcohols **2a-f** in toluene

Entry	Alcohol **2**		Reaction time (h)	Acid **1a**			Ester **3aa-af**	
	no	formula		yield (%)[a]	e e (%)[b]	config[b]	yield (%)[a]	d e (%)[c]
1	**2a**		6	92	60	*S*	86	73
2	**2b**		24	96	0	-	87	0
3	**2c**		4[d]	98	34	*R*	86	40
4	**2d**	Quinine	24[d,e]	99	39	*R*	51	76
5	**2e**		24[d]	98	38	*S*	83	51
6	**2f**		24[d]	93	30	*S*	89	38

[a] Isolated yield based on the starting alcohol **2** [b] From the $[\alpha]_D^{20}$ value in comparison with the literature data (see reference 9) $[\alpha]_D^{19}$ +92 (c=0 9, toluene) [c] From 300 MHz ^{1}H n m r and g l.c [d] A catalytic amount (*ca* 1%) of DMAP was added [e] In THF

the case of the alcohol **2a**[6] (entry 1) a catalytic amount of 4-(dimethylamino)pyridine (DMAP) is necessary It is noteworthy that no resolution was observed with N-methylephedrine (**2b**, entry 2) The best chemical and optical yields were obtained with (*R*)-1-(4-pyridyl)ethanol **2a**,[7] so we tried the resolution of different racemic acids with this alcohol Scheme 2 and Table 2 show the results obtained with this reaction The most significant observations are as follows (a) Toluene seems to be the optimal solvent, since tetrahydrofuran (THF) gives lower optical yield (entries 1 and 2), (b) When the reaction was carried out at low temperature (-80°C) no noticeable increment of the yields occurred (entries 1 and 3), (c) In the case of 2-methylbutanoic acid (entry 7) no resolution took place

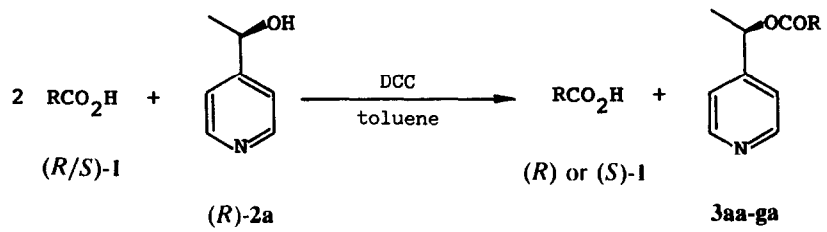
Table 2 Esterification of racemic acids **1** with (*R*)-**2a** in toluene

Entry	Acid **1**		Reaction time (h)	Acid **1**			Ester **3aa-ga**	
	no	formula		yield (%)[a]	e.e (%)[b]	config[b]	yield (%)[a]	d.e.(%)[c]
1	**1a**		6[d]	95	34[e]	*S*	75	59
2			6	92	60[e]	*S*	86	73
3			8[f]	95	41[e]	*S*	75	76
4	**1b**		4	82	27[g]	*R*	77	45
5	**1c**		19	99	49[h]	*R*	72	63
6	**1d**		19	97	[i]	*R*	83	30
7	**1e**		24	64	0[j]	-	61	0
8	**1f**		4	95	67[k]	*R*	70	74
9	**1g**		24[d]	82	16[l]	*S*	58	33

[a] Isolated yield based on the starting alcohol **2a** [b] From the $[\alpha]_D^{20}$ value in comparison with the literature data (see references 9-14) [c] From 300 MHz ^{1}H n.m.r. and g.l.c. [d] In THF [e] Lit.[9] $[\alpha]_D^{19}$ +92 (c=0.9, toluene) [f] At -80°C [g] Lit.[10] $[\alpha]_D^{17}$ +150 (c=1, ethanol) [h] Lit.[11] $[\alpha]_D^{25}$ -14 (neat), Lit.[12] -11.3 (c=2.17, H_2O) [i] $[\alpha]_D^{20}$ +9.5 (c=2.1, ethanol), Lit.[13] $[\alpha]_D^{25}$ +27.2 (neat) [j] Lit.[14] $[\alpha]_D^{20}$ -24 (c=0.9, H_2O) [k] Lit.[13] $[\alpha]_D^{27}$ -9.7 (methanol) [l] Lit.[14] $[\alpha]_D^{25}$ +37.3 (NaOH)

Concerning the stoichiometry of the process, we have found that in the absence of alcohol and working with a 2:1 acid:DCC molar ratio, the *in situ* formation of the corresponding anhydride takes place.[5,15] Consequently, these are the best conditions, since with 1:1 molar ratios and in the presence of

the alcohol (0 5 equivalents) the corresponding *O*-acylurea[8] was formed together with the ester The simple isolation of the enriched acid becomes thus impossible



Scheme 2

Finally, we have studied the change of both diastereomeric and enantiomeric excess when the process is repeated Thus when the reaction indicated in Scheme 2 was performed with the acid (*S*)-**1a** (50% e e) the expected ester **3** (83% yield) and (*S*)-**1a** (96% yield) were isolated with 35% d e and 68% e e , respectively So, logically an increment of e e implies a decrease in the d e

From the results described in this paper, we conclude that this procedure simplifies the kinetic resolution of carboxylic acids by means of chiral alcohols, since it is not necessary to start from the corresponding anhydrides[16]

References and Notes

1 E W Colvin in *Comprehensive Organic Chemistry*, D Barton and W A Ollis Eds , Pergamon Press, Oxford, 1979, p 626
2 J D Morrison in *Asymmetric Synthesis*, vol 1, J D Morrison Ed , Academic Press, New York, 1983, p 6
3 (a) H B Kagan, J C Fiand in *Topics in Stereochemistry*, vol 18, E L Eliel and S H Wilen, Eds , 1988, p 313 (b) The most known procedure involving this reaction is the Horeau's method A Horeau *Tetrahedron Lett* , **1961**, 506
4 R Chinchilla, C Nájera, M Yus, A Heumann, *Tetrahedron Asymmetry*, **1990**, 851
5 See, for instance (a) B Neises, W Steglich, *Angew Chem , Int Ed Engl* , **1978**, *17*, 522 (b) A Hassner, V Alexanian, *Tetrahedron Lett* , **1978**, 4475
6 H Gartner, U Saltz, C Ruchart, *Angew Chem , Int Ed Engl* , **1984**, *23*, 162.
7 Fluka, e e >99%
8 J March in *Advanced Organic Chemistry*, 3rd Ed , J Wiley & Sons, New York, 1985, p 350
9 *Beilstein*, **9**(3), 2461
10 *Beilstein*, **10**(1), 84
11 *Beilstein*, **2**(1), 110
12 H J Lucas, H K Garner, *J Am Chem Soc* **1948**, *70*, 990
13 *Dictionary of Organic Compounds*, 5th Ed , Chapman & Hall, New York, 1982
14 *Handbook of Chemistry and Physics*, 70th Ed , CRC Press Inc , Cleveland, Ohio (1989-90)
15 N -Y Wang, C -T Hsu, C J Sih, *J Am Chem Soc* , **1981**, *103*, 6538
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