Kinetic resolution of heterocyclic amines by reaction with optically active acid chlorides. The effect of reaction conditions on the diastereoselectivity of acylation of (±)-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazine

V. P. Krasnov, G. L. Levit, M. A. Korolyova, I. M. Bukrina, L. Sh. Sadretdinova, I. N. Andreeva, V. N. Charushin, and O. N. Chupakhin*

I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 22, ul. S. Kovalevskoi, 620219 Ekaterinburg, Russian Federation. Fax: +7 (343) 374 1189. E-mail: ca@ios.uran.ru

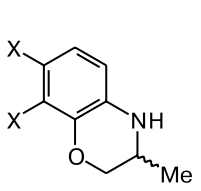
The influence of the reaction conditions (solvent, base) on the diastereoselectivity of acylation of (±)-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazine with (*S*)-naproxen and *N*-tosyl-(*S*)-proline chlorides was studied. The highest diastereoselectivity was observed for the reaction carried out in benzene in the presence of aliphatic tertiary amines.

Key words: kinetic resolution of racemates, 3-methyl-2,3-dihydro-4*H*-1,4-benzoxazine, acid chlorides, (*S*)-naproxen, *N*-tosyl-(*S*)-proline, acylation.

The methods for kinetic resolution of racemates based on different rates of reaction of the enantiomers with a nonsymmetrical reagent and/or catalyst are actively used to prepare optically pure biologically active chiral substances and intermediates.[1,2] Acylating enzymes (amidases, proteases, esterases and lipases) have found extensive use in these processes.[2—4] In recent years, studies aimed at the synthesis of catalysts for asymmetric acylation have been in progress.[5—11]

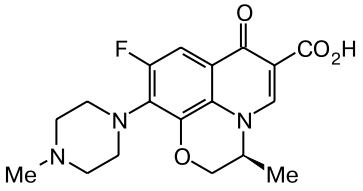
Reactions with enantiopure acylating reagents represent an alternative to the methods involving enzymes and chiral catalysts for the resolution of alcohols and amines. Usually, it is required that the chiral reagent can be easily detached from the product. Although the kinetic resolution of amines and alcohols by reactions with anhydrides of optically active acids has previously been regarded as having low preparative value,[1] it is the use of these compounds that has been repeatedly reported in recent years.

In particular, we proposed methods for the kinetic resolution of racemic heterocyclic amines **1a** and **1b**, which are of interest as fragments of compounds exhibiting biological activities.[12,13] (*S*)-7,8-Difluoro-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazine ((*S*)-**1b**) is a key intermediate in the synthesis of levofloxacin **2**, a highly potent antibiotic of the fluoroquinolone series.[14]



1a,b

X = H (**a**), F (**b**)



2

We showed[12,13] that chlorides of (*S*)-2-(6-methoxy-2-naphthyl)propionic acid ((*S*)-naproxen, **3**) and *N*-tosyl-(*S*)-proline (**4**) can act as effective resolving agents for the kinetic resolution of amines **1a,b**.

Racemic amine **1a** was acylated with chlorides **3** and **4** in benzene at a reactant molar ratio of 2 : 1. In the former case, (*S*,*S*)-amine **5a** (*de* ~80%) was obtained as the major product,[12] while acylation with chloride **4** under the same conditions resulted in the predominant formation of (*R*,*S*)-amine **6b** (*de* ~80%) (Scheme 1)[13].

Here we report the results of comparative studies of kinetic resolutions of amine **1a** under the action of chlorides **3** and **4** depending on the solvent and the auxiliary base.

Results and Discussion

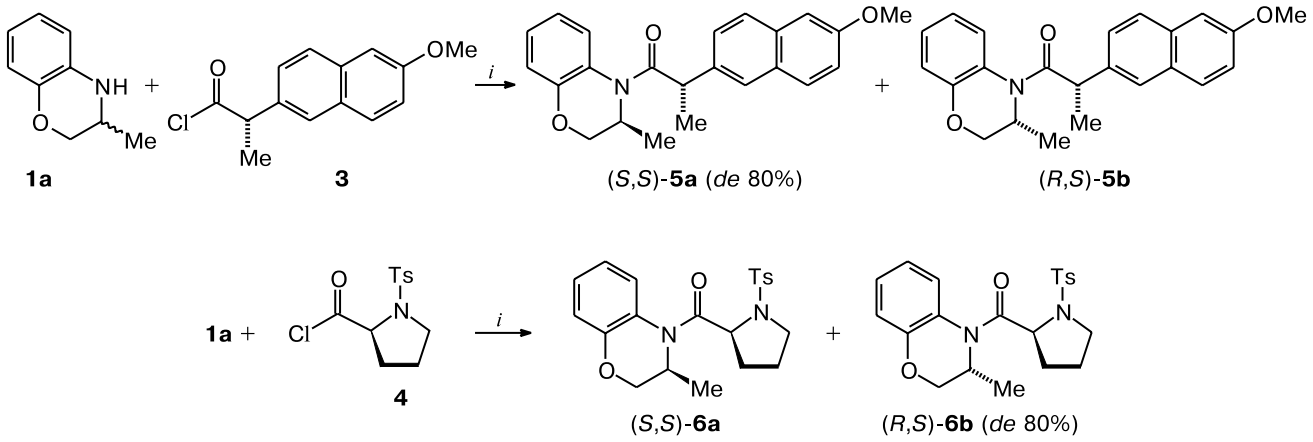
Benzene, CH_2Cl_2, and MeCN were used as solvents; acylation was carried out in the presence of tertiary amines with different structures and nucleophilicities, namely, triethylamine, *N*-methylmorpholine (NMM), *N*,*N*-diisopropyl-*N*-ethylamine (DPEA), Py, and DMAP.

The stereochemical outcome of the acylation is determined by the difference in the rates of reactions of the (*R*)- and (*S*)-enantiomers of amine **1a** with the chiral chloride. The reaction stereoselectivity was estimated

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1203—1206, June, 2004.

1066-5285/04/5306-1253

Scheme 1



i. C_6H_6, 20 °C.

based on the *de* value of the major diastereomer of the resulting amide determined by HPLC.

The reaction was carried out at an amine **1a** : chloride (:tertiary amine) molar ratio of 2 : 1 (: 1) at 20 °C for 24 h. The starting concentration of racemic amine **1a** was 0.1 mol L^{-1}. The mean *de* values (of 4—6 parallel measurements) for the major diastereomer in the reaction mixture are listed in Table 1.

In any of the solvents in both the presence and the absence of tertiary amines, (*S*)-enantiomer of amine **1a** reacts faster with chloride **3**, and (*S*,*S*)-amide **5a** predominates in the reaction products (see Table 1). *N*-Tosyl-(*S*)-proline chloride (**4**) acylates more rapidly the (*R*)-enantiomer of the amine, the product being enriched in (*R*,*S*)-amide **6b**. It is noteworthy that the diastereoselectivities observed in the reactions, under the same conditions, of chlorides **3** and **4** having different structures are similar.

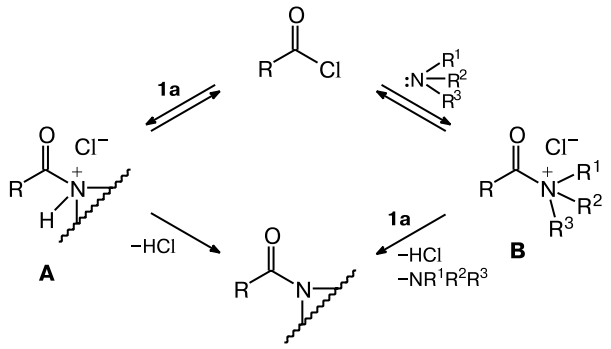
Table 1. Effects of the solvent and the base on the diastereoselectivity of acylation of amine **1a** with chlorides **3** and **4**

Solvent	Base	*de* (%)	
		Amide **5a**	Amide **6b**
PhH	—	80.4	80.2
	Et_3N	83.6	82.6
	NMM	85.8	73.2
	DPEA	80.2	—
	Py	75.4	73.5
	DMAP	20.0	14.2
CH_2Cl_2	—	55.8	56.4
	Et_3N	73.8	69.0
	NMM	63.6	62.0
	Py	54.8	48.8
	DMAP	77.6	11.6
MeCN	—	46.0	43.0
	Et_3N	—	45.4
	NMM	50.2	23.8
	Py	50.0	21.6
	DMAP	70.2	*

* Numerous by-products.

According to current views, acylation of a nucleophilic reagent (in our case, secondary amine **1a**) with an acyl chloride leading to the amide occurs *via* intermediate acylammonium salt **A** (Scheme 2),[2,15,16] which then eliminates HCl under the action of a base. In the presence of a tertiary amine as the catalyst, the reaction first gives acylammonium salt (**B**), which is then converted into the amide under the action of the secondary amine with simultaneous elimination of HCl.

Scheme 2



In the absence of tertiary amine, the highest diastereoselectivity (*de* ~80%) was observed with benzene as the solvent. On passing to more polar solvents, CH_2Cl_2 and MeCN, the diastereoselectivity decreased. Apparently, without tertiary amines, direct replacement of chlorine

takes place to give a tetrahedral intermediate whose polarity is higher than that of the initial molecule, *i.e.*, acylation occurs with charge separation. In more polar solvents, it proceeds *via* relatively loose transition states in which the steric requirements are less stringent, which results in leveling out of the acylation rates of the enantiomers.

The influence of the structure and properties of the tertiary amine on the diastereoselectivity of acylation of amine **1a** with chlorides **3** and **4** is most pronounced when the reaction is carried out in benzene (see Table 1). The highest diastereoselectivity was found in the presence of aliphatic amines, *N*-methylmorpholine (in the case of acylation with chloride **3**) and Et_3N (in the case of **4**). In the presence of tertiary amine, the process is appreciably complicated, because several competing reactions can occur simultaneously in both the formation of the acylammonium salt and HCl elimination. These processes involve, to a certain extent, both the molecules of the auxiliary base and secondary amine enantiomers. Therefore, elucidation of the fine mechanisms determining the predominant formation of one amide diastereomer requires further investigations. However, the fact that the *de* values of the products obtained in different solvents in the presence of aliphatic tertiary amines differ substantially from those for the products obtained without tertiary amines suggests that the reaction involves the intermediate formation of salt **A** and, to a lesser extent, salt **B**. The role of the tertiary amine is mainly reduced to the abstraction of HCl from the acylammonium salt.

In the presence of DMAP, the diastereoselectivity of acylation is markedly lower (**5a**, *de* 20%; **6b**, *de* 14%) than that observed in reactions in benzene in the presence of other bases. Apparently, this is due to the fact that DMAP is a hypernucleophile and forms stable salt **B** much faster than other amines.

In a more polar solvent, CH_2Cl_2, the content of amide **6b** (*de* 11.6%) is also lower with DMAP than with other bases. In MeCN, the reaction of chloride **4** with amine **1a** gives numerous by-products, and the diastereomeric composition could not be determined by HPLC.

The predominant formation of amide **5a** in CH_2Cl_2 and MeCN in the presence of DMAP (*de* 77.6% and *de* 70.2%, respectively), compared to the reactions in the presence of other bases in the same solvents, was unexpected.

Generally, the results of the study on the influence of various factors on the diastereoselectivity of the kinetic resolution of racemic amine **1a** under the action of (*S*)-naproxen and *N*-tosyl-(*S*)-proline chlorides indicate that the stereochemical outcome depends not only on the structure of the acylating agent but also on the solvent and the auxiliary base.

This dependence is probably due to the involvement of several acylation mechanisms (both in direct substitution and in the reaction with the acylammonium salt), each being characterized by its own diastereodifferentiation pattern.

Our studies showed that the efficiency of kinetic resolution of compound **1a** can be somewhat increased compared to that observed under conditions employed previously[12,13] by using *N*-methylmorpholine for chloride **3** and Et_3N for chloride **4** and with benzene as the solvent.

Experimental

^1H NMR spectra were recorded on a Bruker DRX-400 instrument (400 MHz) in $CDCl_3$ with tetramethylsilane as the internal standard. HPLC analysis was carried out on a 4-UV Milikhrom chromatograph using a 80×2 mm column, Silasorb 600, and UV detection at 230 nm. The rate of elution was 200 μL min^{-1}; a hexane—Pr^iOH mixture (120 : 1) was used as the mobile phase to analyze the diastereomeric composition of **5a,b**, τ_R = 7.4 (**5a**), 5.5 min (**5b**) and a hexane—Pr^iOH mixture (15 : 1) was used to analyze the diastereomeric composition of **6a,b**, τ_R = 3.6 (**6a**), 5.7 min (**6b**).

Chlorides **3** and **4** obtained from the corresponding acids and $(COCl)_2$ in dry benzene were used in the acylation without additional purification. According to ^1H NMR data, freshly prepared chlorides **3** and **4** contained 97 to 100% of the major compound.

Prior to use, benzene was purified and dehydrated by refluxing and distillation over metallic Na; CH_2Cl_2 was washed with concentrated H_2SO_4 and water and distilled over anhydrous $CaCl_2$; MeCN was purified and dehydrated by two distillations over P_2O_5 with subsequent distillation over K_2CO_3. Tertiary amines, Et_3N, Py and *N*-methylmorpholine, were refluxed and distilled over KOH; commercial DPEA and DMAP (Lancaster) were used as received. (±)-3-Methyl-2,3-dihydro-4*H*-1,4-benzoxazine was prepared by a known procedure.[17]

Kinetic resolution of racemic amine 1a (general procedure). A solution of chloride **3** or **4** (0.1 mmol) in 1 mL of the appropriate solvent was added to a solution of amine **1a** (0.030 g, 0.2 mmol) and tertiary amine (0.1 mmol) (or without it) in 1 mL of the same solvent. The reaction mixture was kept in a thermostat at 20 °C for 24 h and passed through a silica gel layer. The filtrate (0.2 mL) was diluted with 0.5 mL of CH_2Cl_2, 0.2 mL of the resulting solution was diluted with 0.5 mL of the corresponding mobile phase, and the solution was analyzed by HPLC.

This work was financially supported by the Russian Foundation for Basic Research (Projects No. 03-03-33091 and No. 04-03-32344) and President of the Russian Federation (Program for the Support of Leading Scientific Schools, NSh 1766.2003.3).

References

1. H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, 1988, **18**, 249.
2. E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic compounds*, J. Wiley and Sons, Inc., New York, 1994, 1267 pp.
3. J. M. Keith, J. F. Larrow, and E. N. Jacobsen, *Adv. Synth. Cat.*, 2001, **343**, 5.

4. F. Haeffner and T. Norin, *Chem. Pharm. Bull.*, 1999, **47**, 591.
5. A. C. Spivey, A. Maddaford, and A. J. Redgrave, *Org. Prep. Proced. Int.*, 2000, **32**, 331.
6. P. Somfai, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2731.
7. C. Fu, *Acc. Chem. Res.*, 2000, **33**, 412.
8. E. Vedejs, O. Daugulis, and S. T. Diver, *J. Am. Chem. Soc.*, 1999, **121**, 5813.
9. T. Kawabata, M. Nagato, K. Takasu, and K. Fuji, *J. Am. Chem. Soc.*, 1997, **119**, 3169.
10. S. J. Miller, G. T. Copeland, N. Papaioannou, T. E. Horstmann, and E. M. Ruel, *J. Am. Chem. Soc.*, 1998, **120**, 1629.
11. D. E. J. E. Robinson and S. D. Bull, *Tetrahedron: Asymmetry*, 2003, **14**, 1407.
12. V. N. Charushin, V. P. Krasnov, G. L. Levit, M. A. Korolyova, M. I. Kodess, O. N. Chupakhin, M. H. Kim, H. S. Lee, Y. J. Park, and K.-Ch. Kim, *Tetrahedron: Asymmetry*, 1999, **10**, 2691.
13. V. P. Krasnov, G. L. Levit, I. M. Bukrina, I. N. Andreeva, L. Sh. Sadretdinova, M. A. Korolyova, M. I. Kodess, V. N. Charushin, and O. N. Chupakhin, *Tetrahedron: Asymmetry*, 2003, **14**, 1985.
14. L. A. Mitscher, P. N. Sharma, D. T. W. Chu, L.-L. Shen, and A. G.Pernet, *J. Med. Chem.*, 1987, **30**, 2283.
15. L. M. Litvinenko, and N. M. Oleinik, *Organicheskie katalizatory i gomogennyi kataliz* [*Organic Catalysts and Homogeneous Catalysis*], Naukova dumka, Kiev, 1981, 259 pp. (in Russian).
16. P. Hubbard and W. J. Brittain, *J. Org. Chem.*, 1998, **63**, 677.
17. I. Hayakawa, T. Hiramitsu, and Y. Tanaka, *Chem. Pharm. Bull.*, 1984, **32**, 4907.

Received December 29, 2003;
in revised form April 9, 2004