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A simple synthesis of 2-substituted oxazolines and oxazines

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Abstract—β-Aminoalcohols react with carboxylic acids in the presence of a zeolite, Ersorb-4, resulting in the formation of oxazoline derivatives in good yields. Similarly, 3-aminopropanol and benzoic acid gave the corresponding 2-phenyloxazine.

The oxazoline group is an important functionality in synthetic organic chemistry. The racemic 2-substituted oxazoline ring can be considered as a protected carboxylic acid group.[1] If this carboxylate group is incorporated in a pharmacologically active compound, this modification could change the absorption characteristics and pharmacokinetic properties of these drugs. Under physiological conditions the oxazoline ring will slowly hydrolyze liberating the free carboxylic acid moiety.[2] Some optically active oxazoline derivatives are valuable auxiliaries in asymmetric syntheses.[3]

Numerous methods have been developed for the preparation of 2-substituted oxazolines from carboxylic acids using high temperatures of up to 200–220°C,[4] repeated use of $SOCl_2$,[5] phosphines together with harmful halogenated hydrocarbons such as CCl_4 or hexachloroethane,[2] or under other drastic reaction conditions. Some other methods using carboxylic esters,[6] nitriles[7] or aldehydes[8] as starting materials have also been described but most of them utilize complex reagents, strongly acidic conditions or other stringent reaction parameters with occasional low yields of the reaction products.

The application of natural or artificial acidic or basic inorganic solid materials as efficient catalysts in organic synthesis has been studied.[9] Natural clays have several advantages as they are environmentally-friendly, non-toxic, recoverable, reusable and are inexpensive but efficient mild catalysts. Recently a detailed method was described for the preparation of 2-substituted oxazolines from nitriles in the presence of kaolinitic clay.[10]

Ersorb-4 is a weakly acidic zeolite-type adsorbent with 4 Å pore size. It can adsorb small molecules such as water, hydrochloric acid, ammonia, etc. Its use in the acylation of amines with carboxylic acids has been reported.[11] Based on the good results obtained in that acylation reaction, we examined the selective *N*-acylation of aminoalcohols with carboxylic acids. When 2-aminoethanol was reacted with benzoic acid in the presence of Ersorb-4 (E-4) in hot toluene or xylene the ring-closed oxazoline was obtained in good yield within

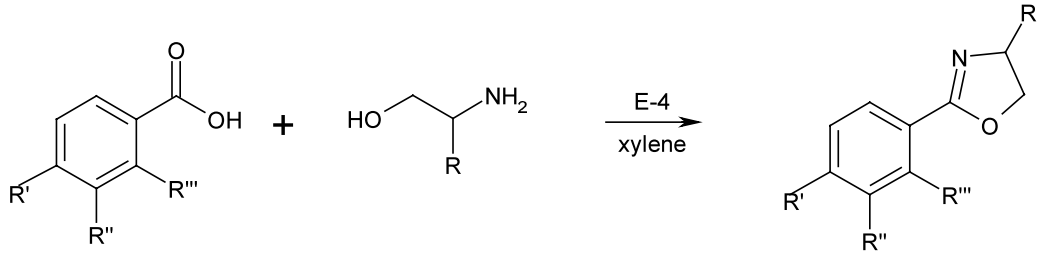

Figure 1.

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5 h (Fig. 1). Neither benzoic acid 2-hydroxyethyl amide—the known precursor of 2-phenyloxazoline[12]—nor benzoic acid 2-aminoethyl ester as the result of an *O*-acylation could be detected in the reaction mixture.

Examination of some aliphatic and aromatic carboxylic acids with different β-aminoalcohols gave the following results. The small aliphatic carboxylic acids, acetic and propionic acid, failed to give any product and completely destroyed the structure of E-4. Aromatic carboxylic acids gave good results.[13] The results are summarized in Table 1.[14]

In some cases (entries 4, 8 and 11) a small amount of the appropriate acid amide was identified but the formation of other byproducts was not observed. In these cases the product was purified by column chromatography. *ortho*-Substituted carboxylic acids gave poorer yields, probably due to steric hindrance. This is supported by the fact that the yield obtained with salicylic acid (entry 11) was better than that with both phthalic acid monoester (entry 12) and acetylsalicylic acid (entry 13). In the reaction of (−)-2-aminobutanol and *p*-chlorobenzoic acid (entry 9) the oxazoline was formed stereospecifically. Similarly, the optically active carboxylic acid Naproxen gave the oxazoline in 56% yield with no change in the stereochemistry (Fig. 2). Treatment of 3-aminopropanol with benzoic acid under similar reaction conditions gave the 2-phenyloxazine in 66% yield (Fig. 3).

The workup of the reaction mixture was very simple, After the evaporation of the solvent, the residue was triturated with acetone, E-4 was filtered off, the filtrate was evaporated and the residue characterized. The catalyst filtered out from the reaction mixture was reusable after 2 h thermal treatment at 120°C without significant loss of activity (Table 1, entry 2). Being a non-aggressive agent, E-4 can be used safely in the reaction of substances with different functional groups. (In other experiments we found that other functional groups, e.g. amines, nitriles, etc. remained intact even after heating for a long time in the presence of E-4.) In this way, a simple, cheap and environmentally-friendly synthesis of 2-substituted oxazolines was developed.

Table 1. Reaction of β-aminoalcohols with aromatic carboxylic acids

Entry	R	R′	R″	R‴	Yield[a] (%)	Mp (°C) (lit.)
1	H	H	H	H	90	138–139 (135–136[15])
2	H	H	H	H	79[b]	138–139 (135–136[15])
3	H	H	H	H	52[c]	138–139 (135–136[15])
4	H	CH_3	H	H	35[d]	144–145
5	H	Cl	H	H	88	118–119
6	H	$(CH_3)_3C$	H	H	75	153–154
7	C_2H_5 (±)	H	H	H	73	–[e]
8	C_2H_5 (±)	Cl	H	H	55[d]	–[e] (25[16])
9	C_2H_5 (*S*)	Cl	H	H	88	101–102
10	H	CH_3O	NO_2	H	78	104–105 (122–123[17])
11	H	H	H	OH	30[d]	40 (42–43[18])
12	H	H	H	$COOCH_3$	32	124
13	H	H	H	$OCOCH_3$	30	104
14	H	$COOCH_3$	H	H	85	134 (130–132[8])
15	H	CH_2Cl	H	OH	45	89–90

[a] Isolated yield.
[b] Recycled E-4.
[c] 0.5 g E-4/mmol acid, see Ref. 13.
[d] Product purified by column chromatography (Kieselgel, acetone eluent).
[e] Oil.

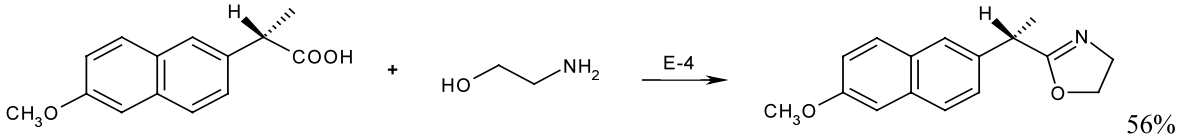

Figure 2.

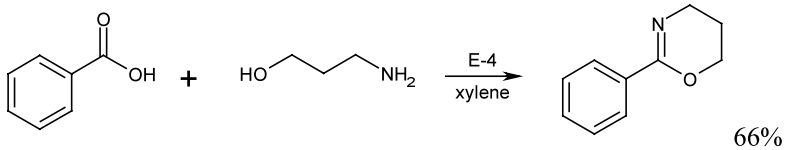

Figure 3.

Acknowledgements

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References

1. (a) Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, 2nd ed.; J. Wiley: New York, 1991; (b) Kocienski, P. J. In *Protecting Groups*; Enders, D.; Noyori, R.; Trost, B. M., Eds.; George Thieme: New York, 1994.
2. Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9353.
3. (a) Lutomski, K. A.; Meyers, A. I. In *Asymmetric Synthesis*; Morisson, J. D., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3, p. 213; (b) Wipf, P.; Miller, Ch. P. *Tetrahedron Lett*. **1992**, *33*, 907.
4. See e.g. (a) Frump, J. A. *Chem. Rev*. **1971**, *71*, 483; (b) Meyers, A. I.; Michelich, E. D. *Angew. Chem*. **1976**, 321.
5. Wenker, H. *J. Am. Chem. Soc*. **1935**, *57*, 1079.
6. (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett*. **1990**, *31*, 6005; (b) Corey, E. J.; Wang, Z. *Tetrahedron Lett*. **1993**, *34*, 4001.
7. Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber*. **1991**, *124*, 1173.
8. Badiang, J. G.; Aube, J. *J. Org. Chem*. **1996**, *61*, 2484.
9. (a) Laszlo, P. *Science* **1987**, *235*, 1473; (b) Laszlo, P. *Pure Appl. Chem*. **1990**, *62*, 2027.
10. Jnaneswara, G. K.; Deshpande, V. H.; Lalithambika, M.; Ravindranathan, T.; Bedekar, A. V. *Tetrahedron Lett*. **1998**, *39*, 459.
11. Hell, Z.; Cwik, A.; Finta, Z.; Horváth, Z. *J. Mol. Catal. A (Chem.)* **2002**, *184*, 191.
12. Seeliger, W.; Thier, W. *Liebigs Ann. Chem*. **1966**, *698*, 158.
13. A typical protocol for the cyclization is as follows: a mixture of 5 mmol acid, 5 mmol amine and 0.8 g E-4 in 10 ml xylene was heated at 130°C for 5 h. The solvent was evaporated, the residue was triturated with acetone, E-4 was filtered off, the filtrate was evaporated and the residue characterized.
14. All products have satisfactory spectral data (IR, ^{1}H NMR). Selected data of (*S*)-2-(4-chlorophenyl)-4-ethyl-oxazoline (entry 9): IR (KBr): 1612, 1591 cm^{-1}, ^{1}H NMR (250 MHz, methanol-d_4): 1.01 (t, 3H, $J=7.3$ Hz), 1.65 (m, 2H), 3.1 (m, 1H), 3.54 (dd, 1H, $J_1=6.3$ Hz, $J_2=11.2$ Hz), 3.75 (dd, 1H, $J_1=3.4$ Hz, $J_2=11.2$ Hz), 7.38 (m, 2H), 7.92 (m, 2H).
15. Cassebaum, H.; Uhlig, K. Ger (East) Patent 107262, 1974; *Chem. Abstr*. **1974**, *82*, 155879.
16. Boyd, R. N.; Rittner, R. C. *J. Am. Chem. Soc*. **1960**, *82*, 2032–2034.
17. Leffler, A. *J. Am. Chem. Soc*. **1937**, *59*, 2252–2257.
18. Black, D. S. C.; Wade, M. J. *Aust. J. Chem*. **1972**, *25*, 1797–1810.