N-Acyl-2-phenyliminooxazolidines as Chemoselective Monoacylating Agents

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Received April 11, 2005

Key Words : *N*-Acyl-2-phenyliminooxazolines, Acylating agents, Diamines, Chemoselectivity

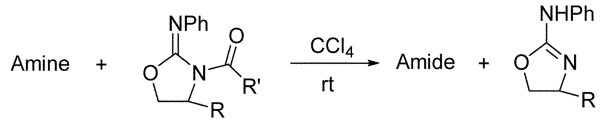
The selective monoacylation of amino groups in the presence of other functional groups has great practical utility.[1] *N*-Acylation is sometimes carried out using acyl transfer reagents developed by devising an appropriate leaving group. Several reagents have been developed for the above purpose,[2] however, some of the reagents available are unsatisfactory in terms of their usefulnesses and selectivities. Thus, satisfactory alternatives are required.

Recently we reported on the preparation of 2-phenylamino-2-oxazoline **2** based on the cyclization of *N*-(2-hydroxyethyl)-*N'*-phenylthiourea.[3] The 2-phenylamino-2-oxazoline heterocyclic system is believed to be a good leaving group for a chemoselective acylating reagent of amines.[4] Moreover, it is generally believed that reagents containing a bulky, electron accepting leaving group satisfy this requirement. Here we report that *N*-acyl-2-phenylimino-oxazolidine **3** may be used as a neutral reagent for the chemoselective acylation of primary amine in the presence of secondary amine or alcohol, and for the acylation of the less sterically hindered amine rather than other hindered primary amines.

2-Phenylamino-2-oxazoline was readily synthesized by reacting 1,2-aminoalcohol with phenyl isothiocyanate to give the corresponding *N*-(2-hydroxyethyl)-*N'*-methylthio-urea. This process was followed by the cyclo-desulfurization of the thiourea to 2-phenylamino-2-oxazoline in good yield using *p*-toluenesulfonyl chloride and NaOH in a one-pot reaction, as described previously.[3a] Acylation of the 2-phenylamino-2-oxazoline can conceivably proceed through an attack upon acyl halide either by the *exo*-nitrogen (to provide *N*-acylated-2-phenylamino-2-oxazolines) or by the *endo*-nitrogen (to give *N*-acylated 2-phenyliminooxazoli-dine). Acylation of 2-phenylamino-2-oxazolines **2** with acetic anhydride or benzoyl chloride in presence of *tert*-BuOK provided the acylated *endo*-nitrogen product.[4b,5] Column chromatography yielded **3a** and **3b** in good yields (70% and 77%, respectively), which are stable in air and easily handled.

We then evaluated the N-acyl transfer abilities of **3a-b**. The acylations of several amines, *i.e.*, benzylamine, α-methylbenzylamine, α,α-dimethylbenzylamine, and *N*-methylbenzylamine were examined at room temperature in CCl_4. Results were summarized in Table 1. Reaction times depended on amine bulkiness for **3a** and **3b**. The steric influences of substituents on the amino group were clearly

Table 1. N-Acylation of various amines using **3a-b**



3a, R = H R' = Me
3b, R = Me R' = Ph

2a-b

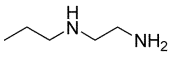
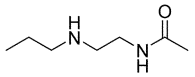
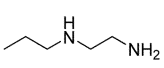
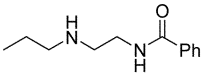
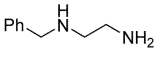
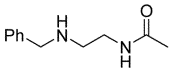
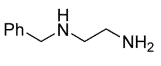
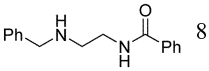
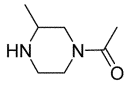
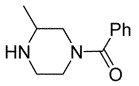
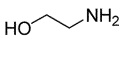
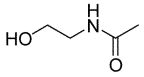
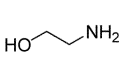
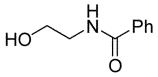
Entry	Reagent	Amine	Time (h)	Yield (%)[a,b]	Recovery Yield (%)[a] of **2**
1	**3a**	Ph, NH_2	1	92 (>99)	93
2	**3a**	Ph, NHMe	23	28 (30)	30
3	**3a**	Ph, NH_2	5	90 (92)	92
4	**3a**	Ph, NH_2	48	0	–[c]
4	**3b**	Ph, NH_2	3	76 (>99)	88
5	**3b**	Ph, NHMe	20	53 (62)	50
6	**3b**	Ph, NH_2	4	77 (85)	82

[a]Isolated yield. [b]Parenthesis yield as determined by ^{1}H NMR. [c]Not isolated.

demonstrated by reactions using various amines, in particular, primary amines were more reactive than secondary amines. These observed reactivity differences were attributed to differences in the steric demands of primary and secondary amines in accordance with aminolysis of esters.[6] The hindered primary amine, α-methylbenzylamine required more time than the less hindered primary amine. Sterically hindered α,α-dimethylbenzylamine with **3a** was not acylated at room temperature after 48 h (entry 4). Thus, reaction rates were greatly affected by steric bulkiness (in the environs) of the amine starting material and by that of the acylating reagent **3**. The leaving group, 2-phenylamino-2-oxazoline **2a-b** was almost quantitatively recovered for recycling by extracting the organic layer with acidified aqueous solution. Concentration of the organic layer provided the amide product, which was then purified by column chromatography or recrystallization.

The substantial observed difference between the reaction rates of hindered and less hindered amines encouraged us to examine the chemoselective acylation of amines. Thus the competitive acylations of mixtures (1 : 1 equiv) of benzyl-

Table 2. Chemoselective acylation of amines using **3a-b**

No	Reagent	Time (h)	Amine	Product	Yield (%)[a,b]
1	**3a**	4			83 (>99)
2	**3b**	3			83 (>99)
3	**3a**	4			85 (>99)
4	**3b**	3			81 (>99)
5	**3a**	20			67 (83)
6	**3b**	20			72
7	**3a**	3			96 (>99)
8	**3b**	3			75 (>99)

[a]Isolated yield by flash column chromatography. [b]Parenthesis shows ^{1}H NMR determined yields.

amine and *N*-methylbenzylamine by **3a-b** were investigated. The results have shown excellent chemoselectivity (>99%) for the primary amine, whereas direct acylation using acetic anhydride or benzoyl chloride afforded almost 1 : 1 mixtures with no evidence of selectivity. Chemoselective monoacylation was performed in diamine systems, *e.g.*, *N*-propylethylenediamine, *N*-benzylethylenediamine, and 2-methylpiperazine[7] (Table 2, entries 1-6). Monoacylated products at the less hindered nitrogen were selectively obtained in high yield. However, the acylation of these amines using acetic anhydride or benzoyl chloride afforded predominantly diacylated products. 2-Aminoethanol containing both amino and hydroxyl groups was selectively converted into the desired amides in high yields without blocking the hydroxyl group (Table 2, entries 7-8).[8]

In conclusion, *N*-acyl-2-phenyliminooxazolidines **3a-b** were found to be highly effective amine acylating agents due to their straightforward preparation, easy handling, excellent chemoselectivity, stability, and ability to react under neutral conditions.

Acknowledgment. This work was supported by the Basic Research Program of the Korean Science and Engineering Foundation (Grant No. R05-2004-000-11207-0) and the Regional Technology Innovation Program of the Ministry of Commerce, Industry and Energy (grant No. RTI04-03-03).

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5. Synthesis of *N*-acyl-2-phenyliminooxazolidine **3**. To a stirred solution of **2a** (4.79 mmol) and *tert*-BuOK (0.65 g, 120 M%) in dry tetrahydrofuran (10mL) under nitrogen was added acetic anhydride (140 M%) dropwise with a syringe. Then reaction mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with water (30 mL) and extracted with ether (3 × 50 mL). The organic layer was dried, filtered, evaporated, and purified by flash column chromatography to give the desired product **3a** (0.17 g, 70% yield). Oil; R_f = 0.6 (ethyl acetate/hexane, 5/5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.03 (m, 5H, Ph), 4.25 (t, 2H, OCH_2, J = 7.7 Hz), 3.96 (t, 2H, NCH_2, J = 7.7 Hz), 2.66 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 146.5, 145.7, 128.7, 123.5, 122.8, 64.0, 60.75, 43.3, 24.5; HRMS calcd for $C_{11}H_{12}N_2O_2$: 204.0899. Found 204.0897. **3b**: White solid, 77% yield; mp 72-73 °C; R_f = 0.6 (ethyl acetate/hexane, 3/7); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.70 (m, 5H, Ph), 6.81-7.18 (m, 5H, Ph), 4.66-4.73 (m, 1H), 4.49 (dd, 1H, OCH, J = 8.4, 7.0 Hz), 4.06 (dd, 1H, OCH, J = 8.4, 4.1 Hz), 1.55 (d, 3H, CH_3, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 145.8, 145.1, 134.8, 131.3, 128.8, 128.4, 127.5, 123.4, 122.8, 71.25, 52.1, 18.0; HRMS calcd for $C_{17}H_{16}N_2O_2$: 280.1212. Found 280.1214.
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