단 신

화학선택적인 Benzoylation 시약으로서 *N*-Benzoyl-4,4-dimethyl-2-methylamino-2-thiazoline

양갑열 · 김택천*

전남대학교 공과대학 응용화학공학부 및 촉매연구소
 (2003. 8. 19 접수)

N-Benzoyl-4,4-dimethyl-2-methylamino-2-thiazoline as a Chemoselective Benzoylating Reagent

Garp-Yeol Yang and Taek Hyeon Kim*

Department of Applied Chemistry and The Research Institute for Catalysis, Chonnam National University,
 Gwangju 500-757, Korea
 (Received August 19, 2003)

주제어: 4,4-디메틸-2-메틸아미노-2-티아졸린, *N*-벤조일레이션, 화학선택성

Keywords: 4,4-Dimethyl-2-methylamino-2-thiazoline, *N*-Benzoylation, Chemoselectivity

Chemoselective benzoylation of amines is one of the most basic reactions for the protection of functional groups in organic synthesis.¹ So far conventional reagents have been developed by devising an appropriate leaving group.² Each reagent, however, is still unsatisfactory in the limited usefulness and selectivity. Thus continuing efforts have been made to develop an efficient chemoselective reagent. Recently we reported synthetic route to 2-methylamino-2-thiazolines by the selective S-cyclization of *N*-(2-hydroxyethyl)-*N*-methylthioureas.³ Heterocyclic system of 2-methylamino-2-thiazoline **1** was used as a good leaving group for acylating reagent of amines.⁴ In this paper, we report that *N*-benzoyl-2-methylamino-2-thiazolines **2** serve as reagent for the selective benzoylation of a less hindered amines in the presence of a more hindered amines.

The synthesis of 2-methylamino-4,4-dimethyl-2-thiazoline **1** was readily performed by the S-cyclization of the *N*-[(1,1-dimethylamino-2-hydroxy)ethyl]-*N*-methylthiourea according to our previous work (Scheme 1).⁴ Benzoylation of the 2-methylamino-2-thiazolines may proceed through the reaction of

benzoyl chloride either with the *exo*-nitrogen to provide *N*-benzoyl-2-methylamino-2-thiazolines or with the *endo*-nitrogen to give *N*-benzoyl-2-methyliminothiazolidine.⁵ Benzoylation of our thiazo-

Scheme 1.

Scheme 2.

Table 1. N-Benzoylation of various amines

entry	reagent	amines	time (h)	yields (%) ^{a, b}	recovery yields (%) ^a of 1
1	2	$\text{Ph}-\text{CH}_2-\text{NH}_2$	4	94 (99)	91
2	2	$\text{Ph}-\text{CH}_2-\text{NHMe}$	28	56 (78)	48
3	2	$\text{Ph}-\text{CH}(\text{Me})-\text{NH}_2$	24	88 (92)	81

^aIsolated yield^bParenthesis is the determined yield by ¹H NMR

line **1** with benzoyl chloride in the presence of *tert*-BuOK gave *exo*-regiocontrolled *N*-benzoyl-2-methylamino-2-thiazolines **2**.⁶

To test the *N*-benzoyl transfer potentiality of **2**, reaction of various amines was examined at room temperature in CCl_4 . The results were summarized in Table 1. The steric influence of substituents on the amino group was clearly demonstrated by reaction using various amines such as benzylamine, *N*-methylbenzylamine, and *N*-methylbenzylamine (Table 1). Primary amine was predominantly more reactive than secondary amine (entry 1). The observed different reactivity is attributed to the differences in steric demand of primary and secondary amines in accordance with aminolysis of esters.⁷ Hindered primary amine needed more reaction time than less hindered primary amine. Thus, reaction rate was greatly affected by steric bulkiness in the vicinity of the starting amine and the acylating reagent. The leaving group, 2-methylamino-2-thiazoline was very soluble to acidic aqueous solution (pH=2), which

almost quantitatively recovered simply by the neutralization and extraction.

From the substantial difference in reaction rate between hindered and less hindered amines we expected that chemoselective acylation of amine can be conveniently achieved by simple mixing of the amine and a stoichiometric amount of **2** under neutral conditions at room temperature. Thus we now have turned to the competitive benzoylation in the presence of 1:1 mixture of benzylamine and *N*-methylbenzylamine to examine selective acylation of amines. Comparing with benzoyl chloride, reagent **2** showed excellent chemoselectivity (Table 2). Also with a 1:1 mixture of a benzyl amine and a *N*-methylbenzylamine the selectivity was investigated. The results are summarized in Table 3. Reagent **2** also gives high selectivity to a less hindered primary amine. The chemoselective benzoylation was applied to the diamine system bearing structurally diverse amino group in a molecule such as *N*-propylethylenediamine and 2-methylpiperazine. Product acy-

Table 2. Competitive benzoylation of a primary and secondary amine

entry	reagent	conditions	yields (%) ^a 3 + 4	selectivity ^a 3 : 4
1	2	rt, 4 h	> 99	100:0
2	PhCOCl	Et_3N , rt, 1 h	> 99	41:59

^aDetermined by ¹H NMR

Table 3. Competitive benzoylation of less hindered and more hindered primary amine

entry	reagent	conditions	yields (%) ^a 3 + 5	selectivity ^a 3 : 5
1	2	rt, 4 h	> 99	92:8
2	PhCOCl	Et ₃ N, rt, 1 h	> 99	64:36

^aDetermined by ¹H NMR

Table 4. Chemoselective benzoylation of diamines

entry	reagent	amine	product	yields (%) ^{a, b}	recovery yields (%) ^a of 1
1	2			91 (>99)	88
2	2			75 (>99)	82

^aIsolated yield by flash column chromatography

^bParenthesis is the determined yield by ¹H NMR

lated at the less hindered nitrogen with high regioselectivity were obtained in high yield (Table 4).

In summary, *N*-acyl 2-methylamino-2-thiazoline is very effective in chemoselective benzoylation of amines. This reagent should be widely used for the selective benzoylation of various polyamine compounds.

Acknowledgment. This work was supported by the grant No. (R05-2002-000-00043-0) from the Basic Research Program of the Korea Science and Engineering Foundation.

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- N*-(4, 5-Dihydro-4, 4-dimethyl-2-thiazolyl)-*N*-methylbenzamide **2**. To a stirred solution of **1** (0.5 g, 3.45 mmol) and *tert*-BuOK (0.46 g, 4.14 mmol, 120 M%) in dry THF (20 mL) under nitrogen was added benzoyl chloride (0.56 mL, 4.83 mmol, 140 M%) dropwise with a syringe. After 30 min the reaction mixture was quenched with water (30 mL) and extracted with ether

(50 mL×3). The organic layer was dried, filtered, evaporated. The crude product was purified by flash column chromatography to give the desired product **2**, yield 88%; mp 55 °C; R_f =0.6 (ethyl acetate/hexane 5/5); ^1H NMR (300 MHz, CDCl_3) δ 7.41-7.55 (5H, m), 3.37 (3H, s), 3.08 (2H, s), 1.32 (6H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 174.9, 157.7, 135.3, 131.0, 128.5, 127.8,

71.5, 45.7, 38.1, 27.7; HRMS calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}$: 252.1263. Found 252.1262.

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