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N-Acyl-4,5-dihydro-4,4-dimethyl-*N*-methyl-2-thiazolamine as a chemoselective acylating agent

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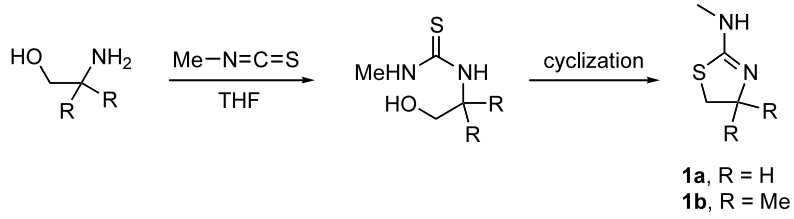
Abstract—2-Methylamino-2-thiazoline reacted with alkyl acyl halides to produce *N*-acyl-2-methylamino-2-thiazolines, *exo*-acylated product regioselectively, which were found to be highly chemoselective acylating agents for primary amine in the presence of secondary amine and for the less sterically hindered of two different primary amines. © 2002 Elsevier Science Ltd. All rights reserved.

Chemoselective acylation of amines is one of the most basic reactions for the protection or activation of functional groups in organic synthesis.[1] So far conventional reagents have been developed by devising an appropriate leaving group.[2] Each reagent, however, has its advantages and disadvantages and 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] Heterocycle system of 2-methylamino-2-thiazoline **1** is expected to be a good leaving group for acylating reagent of amines. In this paper we report that *N*-acyl-2-methylamino-2-thiazolines **2** serve as a new reagent for the selective acylation of a less hindered amines in the presence of a more hindered amines.

The synthesis of 2-methylamino-4,4-dimethyl-2-thiazoline was readily performed by the reaction of 1,2-aminoalcohol with methyl isothiocyanate to give the corresponding *N*-[(1,1-dimethylamino-2-hydroxy)ethyl]-*N*′-methylthiourea, followed by the S-cyclization to the 2-methylamino-2-thiazoline in 83% yield by a one-pot reaction using *p*-toluenesulfonyl chloride and NaOH (Scheme 1).[4] Acylation of the 2-methylamino-2-thiazolines can conceivably proceed through an attack upon acyl halide either by the *exo*-nitrogen to provide *N*-acylated-2-methylamino-2-thiazolines or by the *endo*-nitrogen to give *N*-acylated 2-methyliminothiazolidine.[5] Acylation of thiazolines **1** with acetic anhydride, propionyl chloride, and trimethylacetyl chloride in the presence of *tert*-BuOK gave only alkyl *N*-(4,5-dihydro-4,4-dimethyl-2-thiazolyl)-*N*-methylamide which were acylated to *exo*-nitrogen (Scheme 2). After column chromatography **2a**–**d** were obtained as air storable gel or solid in good yield.[6]

To test the *N*-acyl transfer potentiality of **2a**–**d**, acylation of various amines was examined at room temperature in CCl_4. The results were summarized in Table 1. At first to compare to the reactivity of **1a** and **1b** as a leaving group, acylation agent **2a** and **2c** was chosen to give propionyl amides with various amines. Compound **2c** showed a little more reactivity over **2a**



1a, R = H
1b, R = Me

Scheme 1.

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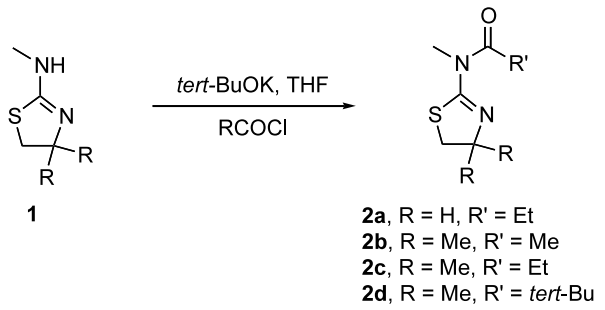
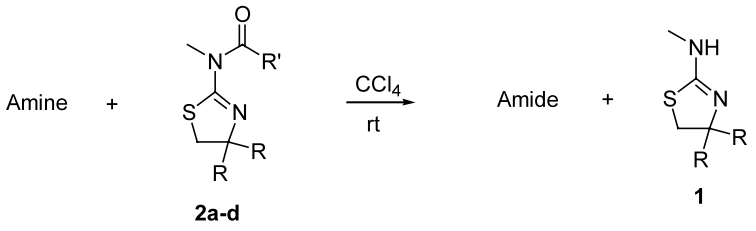


Scheme 2.

(entries 1–3 and 7–10). A difference in reaction time depending on the bulkiness of amines occurred in both **2a** and **2c**. In addition, more convenient preparation and higher yield in acylation reaction were observed in reagent **1b**.[3,4] Thus reagent **1b** was chosen as a leaving group for chemoselective N-acylation. With **2b–d** prepared from **1b**, the steric influence of substituents on the amino group was clearly demonstrated by reaction using various amines such as benzylamine, α-methylbenzylamine, α,α-dimethylbenzylamine, and *N*-methylbenzylamine (Table 1). Primary amine was predominantly more reactive than secondary amine. With **2d** having a bulky acyl group, acylation of secondary amine did not occur at room temperature for 28 h (entry 12). The observed difference in 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. Sterically hindered α,α-dimethylbenzylamine was not acylated at room temperature for 48 h (entry 10). Thus, reaction rate was greatly affected by steric bulkiness in the vicinity of the starting amine and the acylating reagent. Treatment of **2a** and **2c** with hexylalcohol in refluxing CCl_4 did not provide the O-acylation product. The leaving group, 2-methylamino-2-thiazoline **1** was almost quantitatively recovered for recycling simply by the neutralization of acidic aqueous solution after extraction with $CHCl_3$. The concentration of $CHCl_3$ gave the amide product, which was purified by column chromatography or recrystallization.

Table 1. *N*-Acylation of various amines using **2a–d**



Entry	Reagent	R	R'	Amine	Time (h)	Yields (%)[a, b]	Recovery Yield (%)[a] of **1**
1	**2a**	H	Et	Ph, NH_2	6	93 (99)	88
2	**2a**	H	Et	Ph, NHMe	28	21 (39)	17
3	**2a**	H	Et	Ph, NH_2	24	88 (99)	83
4	**2b**	Me	Me	Ph, NH_2	2	95 (99)	92
5	**2b**	Me	Me	Ph, NHMe	28	81 (87)	75
6	**2b**	Me	Me	Ph, NH_2	16	93 (99)	90
7	**2c**	Me	Et	Ph, NH_2	4	96 (99)	92
8	**2c**	Me	Et	Ph, NHMe	28	43 (56)	40
9	**2c**	Me	Et	Ph, NH_2	20	90 (99)	85
10	**2c**	Me	Et	Ph, NH_2	48	0	-[c]
11	**2d**	Me	*tert*-Bu	Ph, NH_2	4	97 (99)	95
12	**2d**	Me	*tert*-Bu	Ph, NHMe	28	0	-[c]
13	**2d**	Me	*tert*-Bu	Ph, NH_2	24	92 (99)	88

[a] Isolated yield

[b] Parenthesis is the determined yield by ^{1}H NMR

[c] Not isolated

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 **2a–d** under neutral conditions at room temperature. Thus, we now have turned to the competitive acylation using **2a–d** in the presence of a 1:1 mixture of benzylamine and *N*-methylbenzylamine to examine selective acylation of amines. In comparison with acid halide or anhydride all reagents **2a–d** showed excellent chemoselectivity (Table 2). Also, with a 1:1 mixture of a benzyl amine and an α-methylbenzylamine the selectivity was investigated. The results are summarized in Table 3. All reagents **2a–d** gave high selectivity to a less hindered primary amine. The chemoselective acylation was performed with diamine system bearing structurally diverse amino group in a molecule such as *N*-propylethylene diamine and 2-methylpiperazine. Products acylated at the less hindered nitrogen with high regioselectivity were obtained in high yield (Table 4): acylation of these amines using acyl halide or acetic anhydride afforded predominantly diacylated products.

In conclusion, *N*-acyl 2-methylamino-2-thiazoline is very effective in chemoselective acylation of amines. We believe that this novel acylating agent can be widely used for the selective protection of various polyamine compounds.

Acknowledgements

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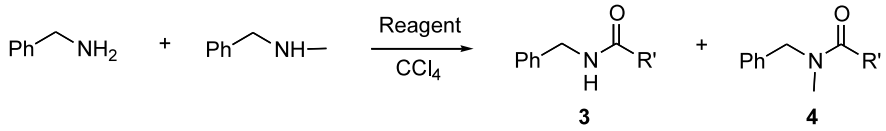
Table 2. Competitive acylation of a primary and secondary amine using **2a–d**

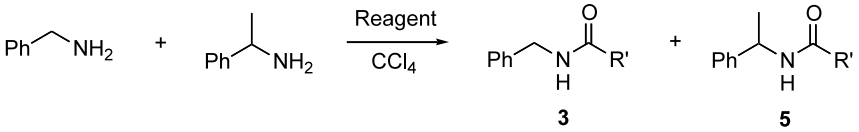


3 **4**

Entry	Reagent	R′	Conditions	Yield (%)[a] **3**+**4**	Selectivity[a] **3**:**4**
1	**2a**	Et	rt, 6 h	>99	100:0
2	**2c**	Et	rt, 4 h	>99	100:0
3	EtCOCl	Et	Et_3N, rt, 1 h	>99	46:54
4	**2b**	Me	rt, 2 h	>99	83:17
5	$(MeCO)_2O$	Me	Et_3N, rt, 1 h	>99	50:50
6	**2d**	*tert*-Bu	rt, 4 h	>99	100:0
7	*tert*-BuCOCl	*tert*-Bu	Et_3N, rt, 1 h	>99	66:34

[a] Determined by ^1H NMR.

Table 3. Competitive acylation of less hindered and more hindered primary amine using **2a–d**

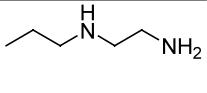
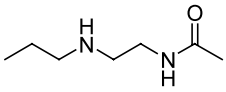
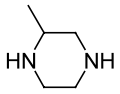
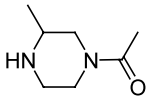
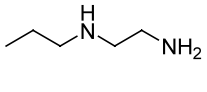
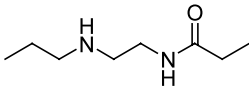
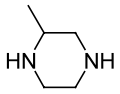
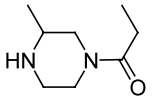
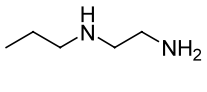
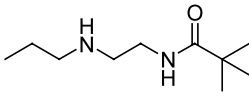
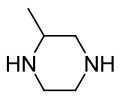
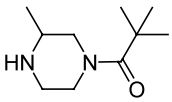


3 **5**

Entry	Reagent	R′	Conditions	Yield (%)[a] **3**+**5**	Selectivity[a] **3**:**5**
1	**2a**	Et	rt, 6 h	>99	88:12
2	**2c**	Et	rt, 4 h	>99	94:6
3	EtCOCl	Et	Et_3N, rt, 1 h	>99	63:37
4	**2b**	Me	rt, 2 h	>99	100:0
5	$(MeCO)_2O$	Me	Et_3N, rt, 1 h	>99	54:46
6	**2d**	*tert*-Bu	rt, 4 h	>99	96:4
7	*tert*-BuCOCl	*tert*-Bu	Et_3N, rt, 1 h	>99	60:40

[a] Determined by ^1H NMR.

Table 4. Chemoselective acylation of diamines using **2b–d**

Entry	Reagent	Amine	Product	Yields (%)[a, b]	Recovery Yield (%)[a] of **1**
1	**2b**			75 (>99)	85
2	**2b**			78 (>99)	84
3	**2c**			84 (>99)	86
4	**2c**			73 (>99)	80
5	**2d**			72 (>99)	81
6	**2d**			-[c] (15)[d]	-[c]

[a] Isolated yield by flash column chromatography

[b] Parenthesis is the determined yield by ^{1}H NMR

[c] Not isolated

[d] Low conversion yield without another acylated product

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3. Kim, T. H.; Cha, M.-H. *Tetrahedron Lett.* **1999**, *40*, 3125–3128.
4. Synthesis of 4,5-dihydro-4,4-dimethyl-*N*-methyl-2-thiazolamine **1**. To a stirred solution of *N*-[(1,1-dimethyl-2-hydroxy)ethyl]-*N*-methylthiourea (3.01 g, 19 mmol) in THF (20 mL) under nitrogen at room temperature was added a solution of NaOH (0.76 g, 2.2 mmol, 250 M%) in water (5 mL) and TsCl (3.89 g, mmol, 110 M%) in THF (5 mL) dropwise for 5 min with a syringe. The reaction mixture was stirred for 30 min at room temperature, quenched with water (30 mL), and extracted with ether (3×30 mL). The organic layer was dried, filtered, evaporated, and purified by flash column chromatography to give the cyclized product **1** (2.3 g, 83% yield). White solid, mp 105–107°C; R_f=0.1 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 2H, SCH_2), 2.94 (s, 3H, NCH_3), 1.42 (s, 6H, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 158.5, 70.6, 45.2, 40.5, 37.1, 28.1, 27.9. Anal calcd for $C_6H_{12}N_2S$: C, 49.96; H, 8.39; N, 19.42; S, 22.23. Found: C, 51.29; H, 8.12; N, 19.23; S, 22.00%. This method was more efficient in purification than our previous work using Mitsunobu reaction (DEAD and triphenyl phosphine).[3]

5. Argay, G.; Kalman, A.; Toth, G.; Toldy, L. *Tetrahedron Lett*. **1972**, 3179–3182.
6. Synthesis of alkyl *N*-(4,5-dihydro-4,4-dimethyl-2-thiazolyl)-*N*-methylamide **2**. To a stirred solution of **1** (3.45 mmol) and *tert*-BuOK (0.46 g, 120 M%) in dry THF (20 mL) under nitrogen was added acyl halide or acetic anhydride (140 M%) dropwise with a syringe. After 30 min 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 **2**. **Compound 2a**. Yield 67%; mp 55°C; R_f=0.8 (ethyl acetate/hexane, 5/5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (2H, t, J=8.2 Hz), 3.42 (3H, s), 3.23 (2H, t, J=8.2 Hz), 2.59–2.56 (2H, q, J=7.3 Hz), 1.18 (3H, t, J=7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 160.5, 57.5, 35.0, 34.1, 28.8, 8.8. Anal. calcd for $C_7H_{12}N_2OS$: C, 48.81; H, 7.02; N, 16.26; S, 18.62. Found: C, 49.17; H, 7.35; N, 16.54; S, 18.44%. **Compound 2b**. Yield 84%; R_f=0.3–0.4 (ethyl acetate/hexane, 5/5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.37 (3H, s), 3.07 (2H, s), 2.29 (3H, s), 1.36 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 156.6, 71.2, 45.5, 35.6, 27.8, 23.9. **Compound 2c**. Yield 75%; R_f=0.5–0.7 (ethyl acetate/hexane, 5/5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.37 (3H, s), 3.05(2H, s), 2.54–2.56 (2H, q, J=7.3 Hz), 1.35 (6H, s), 1.17 (3H, t, J=7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 156.7, 70.9, 45.4, 34.9, 28.8, 27.9, 8.8. **Compound 2d**. Yield 75%; mp 65°C; R_f=0.6 (ethyl acetate/hexane, 5/5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44 (3H, s), 3.01 (2H, s), 1.36 (15H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 158.5, 70.6, 45.2, 40.5, 37.1, 28.1, 27.9. Anal. calcd for $C_{11}H_{20}N_2OS$: C, 57.86; H, 8.83; N, 12.27; S, 14.04. Found: C, 57.58; H, 9.07; N, 12.18; S, 13.86%.
7. (a) Mc Arnett, E.; Miller, J. G.; Day, A. R. *J. Am. Chem. Soc*. **1950**, *72*, 5635–5638; (b) Mc Arnett, E.; Miller, J. G.; Day, A. R. *J. Am. Chem. Soc*. **1951**, *73*, 5393–5395.