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Acylmethanesulfonamides as new acylating agents for primary amines

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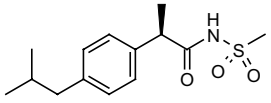
Abstract—A new, simple and efficient procedure for the preparation of secondary amides through internal condensation of acylmethanesulfonamides ammonium salts is described. The selective acylation of mixed primary–secondary amines could be an attractive application of the new method.

1. Introduction

Polyamines are frequently used intermediates in organic synthesis and selective derivatization of the amino groups generally requires complex multi-step protection/deprotection methods.[1] Monoacylation of mixed primary–secondary diamines poses considerable difficulties and, by consequence, a wide number of strategies have been proposed in order to approach this synthetic challenge.[2–5]

In this letter, we describe a novel method for the highly chemoselective acylation of primary amino groups in mixed primary–secondary diamines. This new method is based on the unusual property of alkyl ammonium salts of acylmethanesulfonamides to undergo internal condensation under thermal conditions. Our work has been inspired by the study of a novel class of IL-8 inhibitors belonging to the class of 2-phenylpropionylmethanesulfonamides.[6]

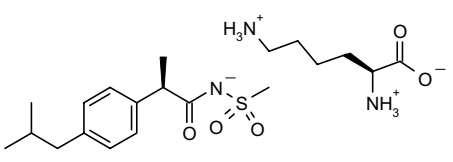


Repertaxin

2. Results and discussion

Repertaxin ((*R*)-4-isobutyl-α-methylphenylacetyl methanesulfonamide) is currently under clinical investigation for the prevention of delayed graft function during organ transplant and its L-lysine salt is actually under evaluation as a pharmaceutically acceptable salt for infusion administration.

Repertaxin L-lysine salt **1** is an amorphous, highly hygroscopic powder with melting point 85–90 °C. Stability studies on the 'raw material' have pointed out the time-dependent formation of traces (Table 1) of the amides **2** and **3** as the only degradation side products.



1

In stressed conditions, the amount of these products significantly enhanced and meaningful conversion of the

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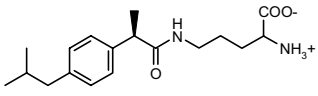
Table 1. Stability studies on repertaxin L-lysine salt

Entry	Starting material	Reaction conditions (T/time)	Recovered starting material (%)	**2** (%)	**3** (%)
1	**1**	Rt/24 h	>99.5	0.1	0.0
2	**1**	Rt/2 yr	95.2	0.7	0.2
3	**1**	50 °C/24 h	80.4	15.1	3.8
4	**1**	100 °C/24 h	32.7	51.3	13.5
5	Ibuprofen L-lysine salt	100 °C/24 h	95	3.1	0.8

starting material into the condensation by-products (**2** and **3**) occurred at $T = 100$ °C after 3 h.



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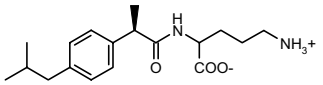

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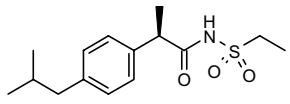
It has been observed that the formation of **2** and **3** is always accompanied by a proportional weight loss of the raw. This suggests the removal of methanesulfonamide by sublimation as the reaction driving force.

Compounds **2** and **3** seem to be directly obtained from internal condensation as in the solid state (Table 1, entry 3) as in the melted state (Table 1, entry 4). The relative ratio of the amides **2** and **3** is plausibly due to the different basicity, nucleophilicity and steric hindrance of the lysine amino groups. Internal condensation of carboxylate ammonium salts is a well known reaction[7] but its synthetic applications are actually limited by low yields. In agreement with this, in fact, only low amounts of **2** and **3** have been detected by heating the related carboxylic acid, ibuprofen L-lysine salt (Table 1, entry 5). The proposed reaction mechanism for the internal condensation of acylmethanesulfonamides ammonium salts is depicted in Scheme 1.

Methanesulfonamide displacement is highly favored by the proximity of the reactive centers in the constrained salified form. Ions solvation disfavors internal condensation step; in fact the heating of solutions of repertaxin L-lysine salt in water or in dipolar solvents does not afford **2** and **3**. As previously mentioned, harvesting of methanesulfonamide by sublimation has been supposed strongly to contribute to drive the reaction equilibrium. In agreement with this, homologues **4** and **5** show only poor reactivity in the reaction conditions.



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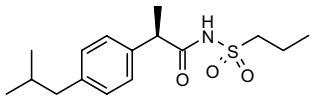

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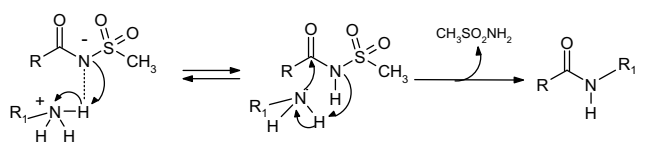
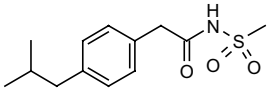


Scheme 1.

Based on these preliminary observations, more experiments have been performed in order to explore further applications of this reaction. Ammonium salts have been prepared simply by mixing acylmethanesulfonamides with the desired amine in dichloromethane; after solvent evaporation the crude has been heated at $T = 120$ °C for 3 h in a drying oven. Standard conditions have been selected in order to compare the reactivity of representative substrates (Table 2). Linear and branched amines (entries 1–5) react in high yield to give the corresponding amides. The wide applicability of the reaction is supported by the high reactivity of methanesulfonamides derived from alkyl, benzyl (**6**) and benzoic acids.



6

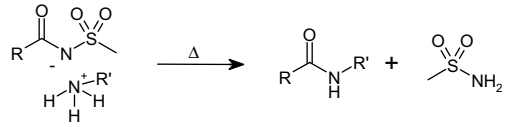
The reaction has been also successfully applied to the acylation of aminoalcohols (entries 6 and 7).

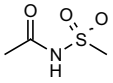
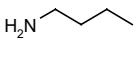
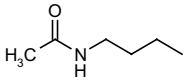
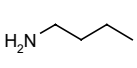
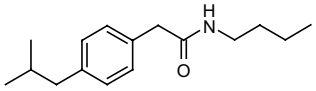
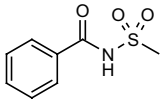
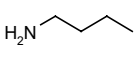
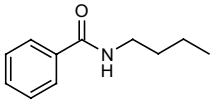
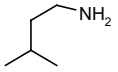
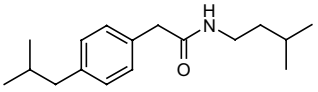
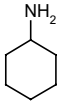
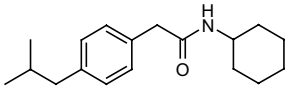
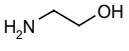
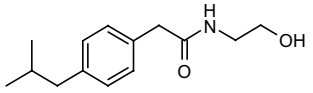
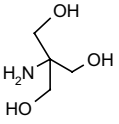
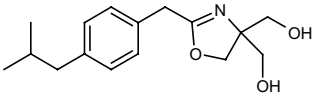
The most interesting application of this procedure, still under evaluation, is the selective acylation of mixed primary–secondary amines. As shown in Table 3, probably due to the additional steric hindrance, secondary ammonium salts (entries 1 and 2) do not react in the reaction conditions. The reaction sensitivity to steric factors allows the discrimination between primary and secondary amino groups in mixed diamines.

When N-propylaminoethylamine has been reacted with 1 equimolar amount of **6** (entry 3) only traces of the condensation product have been isolated. This result is in agreement with the higher basicity of the secondary amino group. By contrast, when both the amino groups were salified (entries 4 and 5), due to the steric hindrance of the secondary amino groups, the selective acylation of the primary group occurred in a quantitative manner.

N-Acyl-N-arylmethanesulfonamides have been previously reported[5] as highly reactive N-acylating reagents. These reagents show good chemoselectivity in the acylation of hindered amines mainly in force of the bulkiness of the leaving group. We have herein described for the first time the internal condensation of N-acylmethanesulfonamides ammonium salts. This reaction, although requiring relatively harsh conditions, is still extremely sensitive to the steric effects. The ionic interaction between the reagents has been proposed as the crucial factor in determining the observed selectivity.

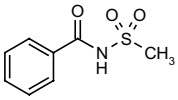
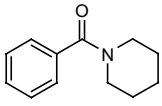
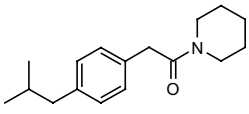
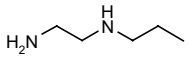
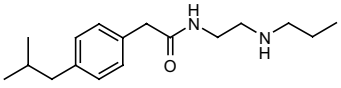
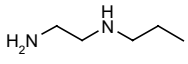
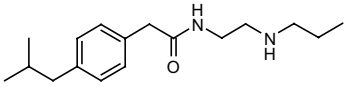
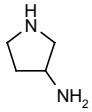
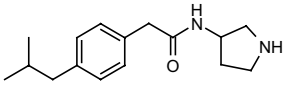
Table 2. Internal condensation of acylmethanesulfonamides with primary amines[a]



Entry	Reagent	Amine	Product	Yield (%)
1				90
2	**6**			85
3				91
4	**6**			88
5	**6**			75
6[b]	**6**			85
7[c]	**6**			70

[a] All the internal salts at $T = 120\,^{\circ}C$ are in the melted state.
[b] In the reaction conditions a small amount of the cyclization product, oxazole, has been isolated.
[c] After 3 h a 1:1 mixture of amide and oxazole derivative was observed. Prolonging the reaction time the oxazole derivative is obtained as main product.

Table 3. Internal condensation of acylmethanesulfonamides with secondary and mixed primary–secondary amines[a]

Entry	Reagent	Reagent/Amine ratio	Amine	Product	Yield (%)
1[b]		1:1			0
2[b]	**6**	1:1			0
3[c]	**6**	1:1			<5
4[c]	**6**	2:1			98
5[c]	**6**	2:1			90

[a] All the internal salts at $T = 120\,^{\circ}C$ are in the melted state.
[b] General procedure (Method A).
[c] General procedure (Method B).

Summarizing, this new procedure can be considered a new alternative to classical methods for acylation of primary amino groups. The full scope of the reaction remains to be exploited but the high reaction chemoselectivity with mixed primary–secondary amines suggests interesting potential synthetic applications.

3. Experimental section

3.1. General procedure

3.1.1. Method A (reaction with primary amines)

3.1.1.1. 2-[(4-Isobutyl)phenyl]-N-butyl acetamide (Table 2, entry 2). Butylamine (73 μL, 0.74 mmol) was added to a stirring solution of **6** (0.2 g, 0.74 mmol) in CH_2Cl_2 at rt. After 1 h, the solvent was distilled off and the residue, 2-[(4′-isobutyl)phenyl]acetyl methanesulfonamide butylammonium salt, was heated for 3 h at $T = 120$ °C in a drying oven. After cooling at room temperature, the reaction mixture was dissolved in CH_2Cl_2 (10 mL) and washed with water (2×5 mL), dried over Na_2SO_4. After solvent evaporation under reduced pressure pure 2-[(4-isobutyl)phenyl]-N-butyl acetamide was obtained as a yellow oil (0.154 g, 0.629 mmol) in 85% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.16 (d, 2H, $J = 7$ Hz), 7.04 (d, 2H, $J = 7$ Hz), 5.22 (br s, 1H, CONH), 3.82 (s, 2H), 3.18 (m, 2H), 2.50 (d, 2H, $J = 7$ Hz), 1.85 (m, 1H), 1.38 (m, 2H), 1.22 (m, 2H), 0.97–0.86 (m, 9H).

3.1.1.2. N-Butylbenzamide (Table 2, entry 3). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.90 (d, 2H, $J = 7$ Hz), 7.45–7.30 (m, 3H, $J = 7$ Hz), 6.05 (br s, 1H, CONH), 3.45 (m, 2H), 1.60 (m, 2H), 1.25 (m, 2H), 0.91 (t, 3H, $J = 7$ Hz).

3.1.1.3. 2-[(4-Isobutyl)phenyl]-N-isoamylacetamide (Table 2, entry 4). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.15 (d, 2H, $J = 7$ Hz), 7.06 (d, 2H, $J = 7$ Hz), 5.31 (br s, 1H, CONH), 3.80 (s, 2H), 2.95 (m, 2H), 2.55 (d, 2H, $J = 7$ Hz), 1.90–1.80 (m, 2H), 1.36 (m, 2H, $J = 7$ Hz), 1.01–0.90 (m, 12H, $J = 7$ Hz).

3.1.1.4. 2-[(4-Isobutyl)phenyl]-N-cyclohexylacetamide (Table 2, entry 5). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20 (d, 2H, $J = 7$ Hz), 7.09 (d, 2H, $J = 7$ Hz), 5.25 (br s, 1H, CONH), 3.20 (m, 1H), 3.76 (s, 2H), 2.55 (d, 2H, $J = 7$ Hz), 1.90–1.65 (m, 5H), 1.40–0.90 (m, 12H).

3.1.1.5. 2-[(4-Isobutyl)phenyl]-N-(2-hydroxyethyl)acetamide (Table 2, entry 6). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.15 (d, 2H, $J = 7$ Hz), 7.05 (d, 2H, $J = 7$ Hz), 5.70 (br s, 1H, CONH), 3.81 (s, 2H), 3.58 (m, 2H), 3.28 (m, 2H), 2.35 (d, 2H, $J = 7$ Hz), 1.75 (m, 1H), 0.82 (d, 6H, $J = 7$ Hz).

3.1.1.6. [4-(Hydroxymethyl)-2-(4-isobutylbenzyl)-4,5-dihydro-1,3-oxazol-4- yl]methanol (Table 2, entry 7). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.21 (d, 2H, $J = 7$ Hz), 7.10 (d, 2H, $J = 7$ Hz), 4.2 (d, 2H, $J = 2$ Hz), 3.82 (s, 2H), 3.62 (dd, 2H, $J_1 = 11$ Hz, $J_2 = 2$ Hz), 3.48 (d, 2H, $J = 11$ Hz), 2.44 (d, 2H, $J = 7$ Hz), 1.79 (m, 1H), 1.59 (br s, 2H, OH), 0.89 (d, 6H, $J = 7$ Hz).

3.1.2. Method B (reaction with mixed primary–secondary amines)

3.1.2.1. 2-[(4-Isobutyl)phenyl]-N-[2-N-propylaminoethyl]acetamide (Table 3, entry 4). N-Propylethylenediamine (0.1 mL, 0.81 mmol) was added to a stirred solution of **6** (0.44 g, 1.62 mmol) in CH_2Cl_2 at rt. After 1 h the solvent was evaporated and the residue heated for 3 h at $T = 120$ °C in a drying oven. After cooling at room temperature, the reaction mixture was dissolved in CH_2Cl_2 (10 mL) and washed with 0.5 M NaOH (2×5 mL) and then with water (2×10 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give pure 2-[(4-isobutyl)phenyl]-N-[2-N-propylaminoethyl]acetamide as a yellow oil (0.21 g, 0.79 mmol) in 98% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.14 (d, 2H, $J = 7$ Hz), 7.03 (d, 2H, $J = 7$ Hz), 5.90 (br s, 1H, CON*H*), 4.20 (br s, 1H, N*H*), 3.50 (s, 2H), 3.35 (m, 2H), 2.65 (d, 2H, $J = 7$ Hz), 2.45 (m, 4H), 1.79 (m, 1H), 1.35 (m, 2H), 0.97–0.86 (m, 9H).

3.1.2.2. 2-[(4-Isobutyl)phenyl]-N-pyrrolidin-3-yl acetamide (Table 3, entry 5). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.10 (d, 2H, $J = 7$ Hz), 7.01 (d, 2H, $J = 7$ Hz), 5.50 (br s, 1H, CON*H*), 4.2 (br s, 1H, N*H*), 3.85 (m, 1H), 3.80 (s, 2H), 2.85 (m, 2H), 2.75 (m, 2H), 2.35 (d, 2H, $J = 7$ Hz), 1.75 (m, 1H), 1.55 (m, 2H), 0.89 (d, 6H, $J = 7$ Hz).

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