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A Highly Regioselective Synthesis of α,α-Bis-Mannich Bases by Aminomethylation of Imines with Iminium Salts

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Abstract: The aminomethylation of imines $R(CH_3)C{=}NPr$ (R = alkyl, aryl) with iminium salts provides for the first time a mild, broadly applicable and highly regioselective route to bis-Mannich bases $RCOCH(CH_2NR'_2)_2$.

Keywords: *amino ketones; diamines; imines; Mannich reactions*

Bis-Mannich bases **3** are important as pro-drugs or precursors for $RCOC(=CH_2)CH_2NR'_2$ (the deamination of **3** is easily achieved, even under physiological conditions). These compounds have a variety of interesting properties (*e.g.*, they are known as antimicrotubular, antileukemic, antifungal or anticonvulsant agents, and as potent inhibitors for the epidermal growth factor tyrosine kinase).[1] However, Mannich-type reactions as the classical method for their preparation are fraught with serious drawbacks (*e.g.*, harsh reaction conditions, limited scope, formation of unwanted by-products, poor regioselectivity or low yields).[1-3] Hence, research has concentrated so far on the most simple bis-Mannich bases **3** (*i.e.*, generally R = aryl) and their derivatives.[1]

Recently, we disclosed that the aminoalkylation of imines with iminium salts is a mild and efficient method for the highly stereo- and regioselective synthesis of β-amino ketones.[4] This methodology is also well suited for the synthesis of **3**. The reaction between imines **1** and iminium salts **2** provides the desired bis-Mannich bases **3** in high yields under mild conditions (Table). The method is of broad scope, *i.e.*; good results are obtained for both, imines **1** derived from arylmethyl and alkylmethyl ketones. In addition, iminium salts **2** derived from cyclic as well as acyclic amines can be employed. Furthermore, in case of imines **1** with α-CH-groups the CH_3-moiety is attacked virtually exclusively (Table, Entries 3-8). In special cases even imines with an α-CH_2-group are highly regioselectively aminomethylated at the CH_3-group (Table, Entries 9, 10). However, imines with sterically less hindered α-CH_2-groups furnish complex reaction mixtures (Table, Entries 11, 12). Nevertheless, it turned out that these imines can be used for the synthesis of tris-Mannich bases such as **4** (Table, Entry 12[c]), which to the best of our knowledge constitute a novel class of β-amino ketones.

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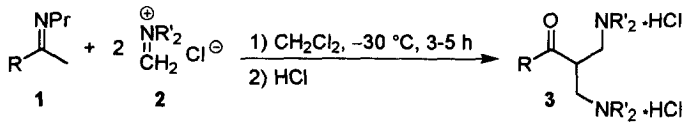
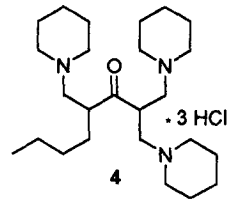
Table: Regioselective Synthesis of α,α-Bis-Mannich bases **3**.[5]





Entry	R	NR'$_2$	Yield (%)[a]	Entry	R	NR'$_2$	Yield (%)[a]
1	Phenyl	NMe_2	70	7	*i*-Propyl	NMe_2	68
2	Phenyl	$N(CH_2)_4$	81	8	*i*-Propyl	$N(CH_2)_4$	74
3	Cyclopropyl	NMe_2	55	9	*i*-Butyl	NMe_2	64
4	Cyclopropyl	$N(CH_2)_4$	62	10	*i*-Butyl	$N(CH_2)_4$	71
5	Cyclohexyl	NMe_2	69	11	*n*-Pentyl	NMe_2	-[b]
6	Cyclohexyl	$N(CH_2)_4$	76	12	*n*-Pentyl	$N(CH_2)_4$	-[b,c]

[a]Isolated yields after recrystallization. The products are regioisomerically pure (≥ 96% rs) according to NMR spectroscopy. [b]A complex mixture was obtained. [c]After modification of the reaction conditions (using 4 eq of the iminium salt **2** and prolonging the reaction time to 18 h) the tris-Mannich base **4** was obtained in 31% yield.

In summary, our methodology is distinguished by its unique scope, excellent regioselectivity, and mild reaction conditions. It can even be used for tris-aminomethylations.

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References and Notes

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4. a) Arend, M.; Risch, N. *Angew. Chem.* **1995**, *107*, 2861; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2639; b) Arend, M.; Risch, N. *Synlett* **1997**, 974.
5. General procedure: The reactions were conducted in dry apparatus under argon. A solution of imine **1**[6a] (5 mmol) in anhydrous CH_2Cl_2 (5 mL) was cooled to –30 °C. The iminium salt **2**[6b] (10.5 mmol) was added and the reaction mixture was stirred vigorously for 3-5 h, during which the temperature was kept between –30 °C and –25 °C. Then HCl (6 N, 10 mL) was added and the mixture was stirred at 25 °C for 3-4 h. The organic phase was decanted and the aqueous phase washed with Et_2O (2 x 100 mL). Subsequently, the aqueous phase was treated with dilute NH_3 (25% NH_3 : H_2O = 1 :4, 50 mL) with vigorous stirring and extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4 and the solvent removed on a rotary evaporator without heating. Then the residue was dissolved in Et_2O (100 mL) and ethereal HCl solution (1 N, 22 mL) was added with stirring. Recrystallization of the resulting precipitate furnished analytically pure **3**.
6. For their synthesis, see: a) Carlson, R.; Larsson, U.; Hansson, L. *Acta Chem. Scand.* **1992**, *46*, 1211; b) Kinast, G.; Tietze, L. F. *Angew. Chem.* **1976**, *88*, 261; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 239.