



Y(OTf)₃-catalyzed novel Mannich reaction of *N*-alkoxycarbonylpyrroles, formaldehyde and primary amine hydrochlorides

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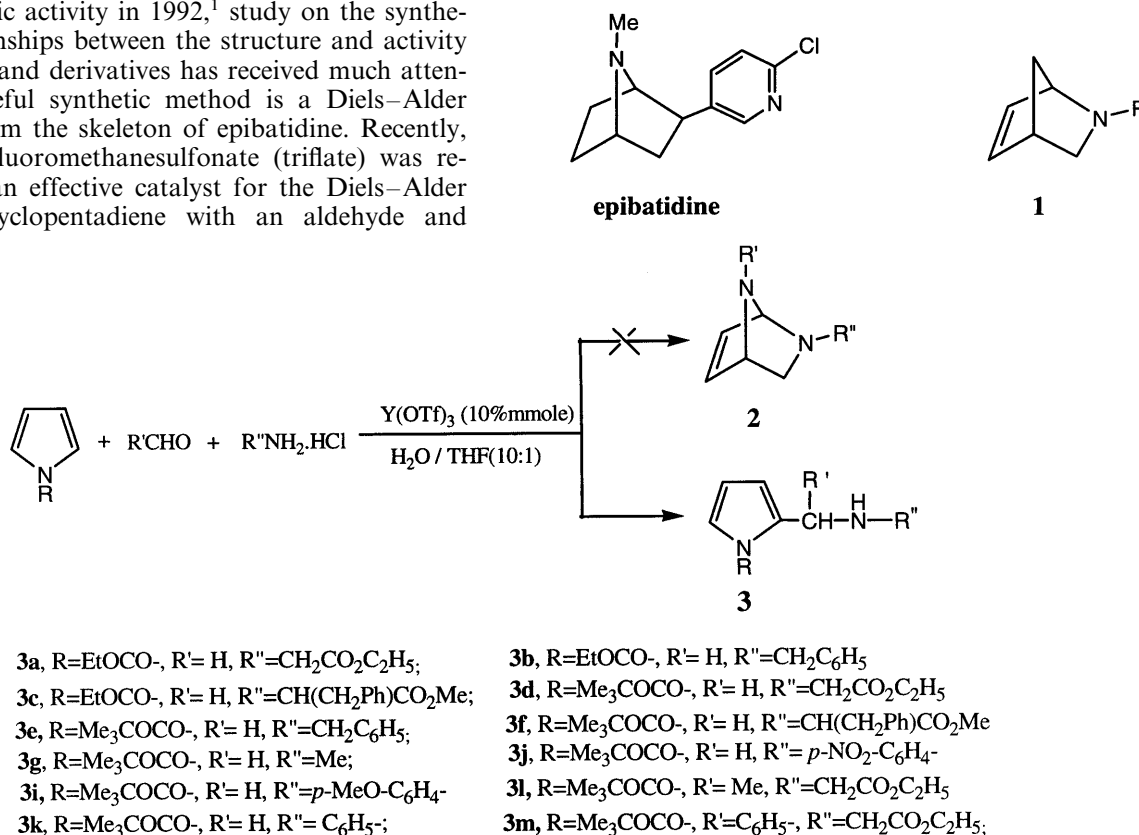
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Abstract—A novel Mannich reaction between *N*-alkoxycarbonylpyrroles, formaldehyde and primary amine hydrochlorides is catalyzed by Y(OTf)₃ to afford a monoaminoalkylation product in good yield in aqueous media. © 2001 Elsevier Science Ltd. All rights reserved.

Since Daly reported the structure of epibatidine and its potent analgesic activity in 1992,¹ study on the synthesis and relationships between the structure and activity of epibatidine and derivatives has received much attention.² One useful synthetic method is a Diels–Alder reaction to form the skeleton of epibatidine. Recently, lanthanide trifluoromethanesulfonate (triflate) was reported to be an effective catalyst for the Diels–Alder reaction of cyclopentadiene with an aldehyde and

amine salt to form 2-azabicyclic compounds **1**.³



Scheme 1.

Keywords: Mannich reaction; primary amine hydrochloride; Y(OTf)₃ catalyst.

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Table 1. Synthesis of monoaminoalkylation pyrrole derivatives **3**

Entry	Condition (°C/h)	Catalyst	Yield (%) ^a	Bp (°C/mmHg)	Formula	HRMS(FAB) calcd/found
3a	35/22	Sc(OTf) ₃	37	130–131/2	C ₁₂ H ₁₉ N ₂ O ₄ (MH ⁺)	255.1343/255.1339
	30/4	Y(OTf) ₃	81			
3b	35/12	Sc(OTf) ₃	34	122–123/2	C ₁₅ H ₁₉ N ₂ O ₂ (MH ⁺)	259.1438/259.1441
	30/12	Y(OTf) ₃	65			
3c	35/12	Sc(OTf) ₃	33	172–174/2	C ₁₈ H ₂₃ N ₂ O ₄ (MH ⁺)	331.1648/331.1652
	30/6	Y(OTf) ₃	77			
3d	35/22	Sc(OTf) ₃	47	103–104/2	C ₁₄ H ₂₃ N ₂ O ₄ (MH ⁺)	283.1648/283.1652
	30/4	Y(OTf) ₃	80			
3e	35/24	Sc(OTf) ₃	35	117–119/2	C ₁₇ H ₂₃ N ₂ O ₂ (MH ⁺)	287.1755/287.1754
	30/12	Y(OTf) ₃	55			
	35/5	–	20			
3f	35/5	Sc(OTf) ₃	48	140–142/2	C ₂₀ H ₂₇ N ₂ O ₄ (MH ⁺)	359.1962/359.1965
	30/4	Y(OTf) ₃	61			
	30/4	Ln(OTf) ₃	43			
3g	25/20	Y(OTf) ₃	14	58–60/2	C ₁₂ H ₁₉ N ₂ O ₂ (M ⁺)	210.1363/210.1359
3i	25/5	Y(OTf) ₃	35	148–149/760	C ₁₇ H ₂₂ N ₂ O ₃ (M ⁺)	302.1624/302.1625
3j	35/30	Y(OTf) ₃	No			
3k	35/30	Y(OTf) ₃	No			
3l	35/30	Y(OTf) ₃	No			
3m	35/30	Y(OTf) ₃	No			

^a Yield of isolated material.

Based on this work, we hoped to obtain the 2,7-diazabicyclic derivative **2** through the aza Diels–Alder reaction of an *N*-protected pyrrole with an aldehyde and amine salts by catalysis with triflate. However, we only obtained the Mannich reaction product **3** rather than the Diels–Alder reaction product **2** (Scheme 1).

It has been reported that the Mannich reaction of pyrrole compounds with primary amine hydrochlorides gave yields that were significantly lower than those obtained with secondary amine hydrochlorides.^{4,5} Increasing the steric bulk of the group on the nitrogen of the primary amine and the excess of amine hydrochloride enabled a higher yield of the monoaminoalkylation product.⁶ Heaney^{7–9} found chlorosilane or sulfur dioxide could catalyze the Mannich reaction of pyrrole with aminals or aminol ethers. However, only *N*-alkyl substituted pyrroles were investigated. Recently, Kobayashi¹⁰ reported that the Mannich reaction of aldehydes, amines and vinyl ethers proceeded smoothly by the catalysis of lanthanide triflate. To the best of our knowledge, the Ln(OTf)₃ catalyzed Mannich reaction of *N*-alkoxycarbonylpyrroles, formaldehyde and primary amine hydrochloride has not been reported.

The effect of different catalysts, primary amine salts, aldehydes and *N*-alkoxycarbonylpyrroles on the Mannich reaction was investigated (Table 1). The results showed that rare earth metal triflate M(OTf)₃ exhibited catalytic action and Y(OTf)₃ was the best one among three kinds of M(OTf)₃ **3a–f** tried. The reactivity of α -amino acid ester salts (**3a**, **3c**, **3d**, **3f**) and benzylamine salt (**3b**, **3e**) is higher than aliphatic amine salt **3g** and aromatic amine salt **3i**. When formaldehyde was replaced by acetaldehyde **3l** or benzaldehyde **3m**, no reaction occurred.

In conclusion, Y(OTf)₃ is an effective catalyst for the Mannich reaction between *N*-alkoxycarbonylpyrrole, formaldehyde and primary amine hydrochloride. The reaction is mild and the yields are good.

Typical procedure for the preparation of 3: To 40% formaldehyde (10 ml) was added the amine hydrochloride (2 mmol) and Y(OTf)₃ (0.2 mmol) at room temperature under N₂. After stirring for 0.5 h, the solution of *N*-alkoxycarbonyl pyrrole (1.5 mmol) in THF (1 ml) was added and the stirring was continued under the same conditions until completion of the reaction (monitored via TLC). The reaction mixture was extracted with chloroform (3 × 10 ml), the combined organic layer was washed with brine until pH 7, and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum and the residue chromatographed on silica, eluting with a mixture of ethyl acetate and petroleum ether, to give the corresponding product (yellow oil). **3a:** ¹H NMR (500 MHz, CD₃COCD₃), δ (ppm), 1.21 (t, 3H, *J* = 7 Hz), 1.43 (t, 3H, *J* = 7 Hz), 2.88 (br, 1H), 3.35 (s, 2H), 3.98 (s, 2H), 4.06 (q, 2H, *J* = 7 Hz), 4.44 (q, 2H, *J* = 7 Hz), 6.16 (m, 2H), 7.28 (q, 1H); ¹³C NMR (300 MHz, CDCl₃), δ (ppm), 14.38, 14.44, 46.66, 49.90, 60.71, 64.00, 110.96, 114.48, 122.23, 134.34, 151.39, 172.83. HRMS (FAB, MH⁺), calcd for C₁₂H₁₈N₂O₄ 255.1343; found 255.1339.

Acknowledgements

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