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Reaction of nonstabilized azomethine ylides with Mannich bases: an approach to 3-acylpyrrolidines

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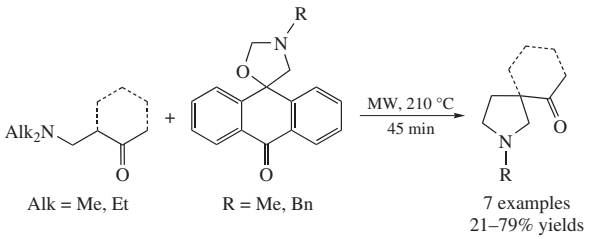
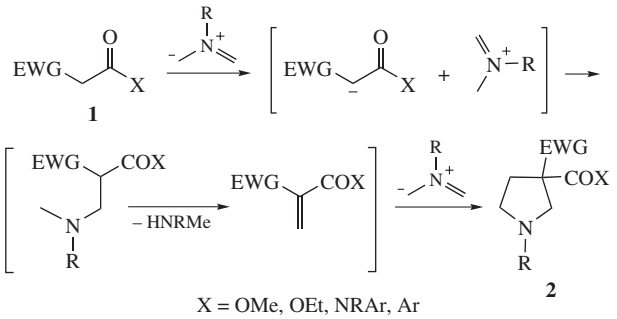
Mannich bases obtained from cycloalkanones and methylketones decompose on heating to give α,β-enones, which react *in situ* with nonstabilized azomethine ylides formed from spiro[anthracene-oxazolidines]. The final products, 3-acylpyrrolidines, were obtained in yields of 21–79% by heating the starting compounds in a microwave reactor in *o*-xylene at 210 °C for 45 min.



The pyrrolidine ring is an important structural moiety in many natural and synthetic biologically active compounds.[1] An efficient method for synthesizing pyrrolidines is the [3+2]-cycloaddition of azomethine ylides with electron-deficient alkenes. The advantages of this reaction include the simultaneous formation of two new C–C bonds in one stage, the availability of starting compounds and an easy reaction implementation.[2] In particular, synthesis of the spiro-fused pyrrolidines and their functionalized derivatives, which can subsequently be used as building blocks in organic and pharmaceutical chemistry, is of special interest since the formation of a quaternary carbon atom by alternative methods is a complicated synthetic challenge.

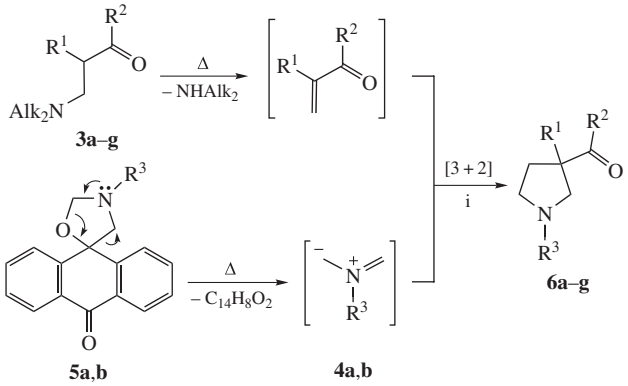
We have recently discovered a new domino reaction, comprising the Mannich reaction and [3+2]-cycloaddition, of methylene-active compounds **1** with nonstabilized azomethine ylides to give 3,3-disubstituted pyrrolidines **2** (Scheme 1).[3] Unfortunately, we failed to involve in this reaction the less reactive CH-acids, such as cycloalkanones and methylketones, so its synthetic value remained limited. Extending the scope of this approach was the subject of this work.



Scheme 1

We supposed that the basicity values of azomethine ylides are not sufficient for a successful reaction with aliphatic ketones. This lack of basicity makes difficult the deprotonation of α-C atoms and the following formation of iminium cations. For this reason, the Mannich reaction, which is the first step in the above mentioned domino process, does not occur. However, we expected that the replacement of ketones by Mannich bases obtained from them would allow us to develop a method for synthesizing hardly accessible 3-acylpyrrolidines.

As a model experiment, we performed the reaction of α-[(dimethylamino)methyl]cyclohexanone **3a**, which was obtained from cyclohexanone, dimethylamine and formaldehyde, with *N*-methylazomethine ylide **4a** (Scheme 2) formed in the reaction medium from sarcosine and formaldehyde (Table S1, see Online Supplementary Materials). However, according to NMR data, the desired pyrrolidine **6a** was formed only in trace amounts in a complex mixture of non-basic products, indicating that the base **3a** had decomposed under the reaction conditions. Apparently, for



3a Alk = Me, $R^1 + R^2 = (CH_2)_4$
3b Alk = Et, $R^1 + R^2 = (CH_2)_4$
3c Alk = Me, $R^1 + R^2 = (CH_2)_5$
3d Alk = Et, R^1 = H, $R^2 = Bu^t$
3e Alk = Et, R^1 = H, R^2 = Ph
3f Alk = Et, R^1 = H, R^2 = 4-$MeOC_6H_4$
3g Alk = Et, R^1 = H, R^2 = 2-thienyl

4, **5**: **a** R^3 = Me
b R^3 = Bn

6a $R^1 + R^2 = (CH_2)_4$, R^3 = Me, 31% from **3a**, 44% from **3b**
6b $R^1 + R^2 = (CH_2)_5$, R^3 = Me, 21%
6c R^1 = H, $R^2 = Bu^t$, R^3 = Me, 76%
6d R^1 = H, $R^2 = Bu^t$, R^3 = Bn, 79%
6e R^1 = H, R^2 = Ph, R^3 = Me, 34%
6f R^1 = H, R^2 = 4-$MeOC_6H_4$, R^3 = Me, 65%
6g R^1 = H, R^2 = 2-thienyl, R^3 = Me, 61%

Scheme 2 *Reagents and conditions*: i, **3** (2 mmol), **5** (2.4 mmol), *o*-xylene, MW, 210 °C, 45 min.

a successful [3+2]-cycloaddition reaction between two unstable intermediates formed *in situ*, it is necessary for both moieties to be formed simultaneously and in sufficient concentrations.

Further, we tested the precursors of nonstabilized azomethine ylides, namely N-substituted spiro[anthracene-oxazolidines] **5a**,**b** that we reported previously.[4] Refluxing the Mannich base **3a** with compound **5a** in *o*-xylene for 4.5 h did not lead to the target spiropyrrolidine **6a**, the resulting crude mixture consisted of contaminated starting oxazolidine **5a**. However, the reaction did occur in the same solvent at much higher temperature of 210 °C and afforded the spiropyrrolidine **6a** in 31% yield. Replacement of Mannich dimethylamino base **3a** with diethylamino derivative **3b** also gave the spiropyrrolidine **6a** in 26% yield. The yield of this product reached 44% with five-fold increase of the amount of the starting compound **3b**. On the other hand, both the use of an excess of Mannich base and lowering the reaction temperature to 190 °C resulted in highly contaminated product in a poor yield. We also attempted to involve in this reaction a widely used precursor of *N*-benzylazomethine ylide **4b**, *i.e*. *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine, but the target product was not obtained (see Table S1). Thus, of the three methods we used to generate the azomethine ylides, only one proved to be suitable, namely the decomposition of spiro[anthracene-oxazolidine] **5a** at 210 °C.

Using the conditions found,[†] we obtained 2-methyl-2-azaspiro[4.6]undecan-6-one **6b** from (dimethylaminomethyl)cycloheptanone **3c** in 21% yield. 1-(Diethylamino)-4,4-dimethylpentan-3-one **3d** with a bulky *tert*-butyl group gave 1-methyl-3-pivaloylpyrrolidine **6c** in 76% yield. The related *N*-benzylpyrrolidine **6d** was obtained in 79% yield using oxazolidine **5b** as the precursor of *N*-benzylazomethine ylide **4b**. We succeeded in expanding the conditions found to the Mannich bases obtained from methyl(hetero)arylketones. Specifically, β-(diethylamino)-propiophenone **3e** and β-diethylamino-*p*-methoxypropiophenone **3f** afforded 3-aroylpyrrolidines **6e** and **6f** in 34 and 65% yields, respectively, while the reaction with the 2-thienyl compound **3g** gave the 3-(2-thenoyl)pyrrolidine **6g** in 61% yield. One can see that the increase in the product yield correlates with stability of the intermediate enone formed during the thermolysis of the Mannich base. This enone stability increases with removal of a moiety that undergoes enolization, with incorporation of a donor thienyl or anisyl substituent conjugated with C=O or with involvement of a bulky *tert*-butyl group.

Despite the simplicity of their structures, 3-substituted pyrrolidines **6a–g** cannot be regarded as readily available compounds, since only the syntheses of compounds **6d** and **6e** were reported.[6,7] At the same time, the obtained pyrrolidine derivatives are of interest as convenient building blocks in organic and medicinal chemistry.[8]

Thus, we were the first to find the conditions for implementing a domino reaction between Mannich bases and spiro[anthracene-oxazolidines]. The suggested approach expands the applicability scope of nonstabilized azomethine ylides and allows one to carry out their [3+2]-cycloaddition to unstable α-methyleneketones without the necessity to synthesize and purify the latter compounds.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.03.008.

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[†] *General procedure*. A 10 ml microwave reaction tube was charged with a stir bar, the Mannich base **3** (2.0 mmol),[5] 3′-substituted 10*H*-spiro[anthracene-9,5′-oxazolidin]-10-one **5** (2.4 mmol),[4] dry *o*-xylene (4 ml) and was sealed with a cap. After prestirring for 3 min, the mixture was heated in a microwave reactor at 210 °C for 45 min with stirring. After cooling with a compressed air flow, the resulting mixture was diluted with toluene (10 ml). The precipitate was filtered off and washed with toluene (4 ml). The solution was extracted with cold 0.35 M HCl (20 ml) and the aqueous phase was washed with toluene (2×12 ml). Then the separated aqueous layer was basified with Na_2CO_3 to pH 9–10 and extracted with toluene (2×10 ml). The combined organic phase was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo* to give the product. The latter was purified by column chromatography on silica gel with $CHCl_3$–EtOH as eluent.

2-Methyl-2-azaspiro[4.5]decan-6-one **6a**. The product was synthesized from dimethylamino-Mannich base **3a** and purified by column chromatography (eluent: $CHCl_3$–EtOH, 100:12). R_f 0.35 (silica gel, $CHCl_3$–EtOH, 100:15). Dark-yellow oil, yield 31%.

Pyrrolidine **6a** was also synthesized from diethylamino-Mannich base **3b** as a dark-yellow oil in 44% yield (10 mmol scale synthesis).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.43 (ddd, 1H, *J* 12.5, 7.5, 6.1 Hz), 1.6–1.8 (m, 6H), 2.17 (s, 3H, MeN), 2.23 (ddd, 1H, *J* 13.2, 7.6, 5.7 Hz), 2.29–2.36 (m, 4H), 2.43 (td, 1H, 3-CH*H*, *J* 8.0, 5.8 Hz), 2.74 (d, 1H, 1-CH*H*, *J* 9.4 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 22.2, 26.8, 33.3, 39.2, 39.4, 41.7, 55.2, 55.9, 63.7, 211.2. HRMS (ESI), *m*/*z*: 168.1385 $[M+H]^+$ (calc. for $C_{10}H_{18}NO^+$, *m*/*z*: 168.1383).

2,2-Dimethyl-1-(1-methylpyrrolidin-3-yl)propan-1-one **6c**. The product was synthesized from diethylamino-Mannich base **3d** and purified by column chromatography (eluent: $CHCl_3$–EtOH, 100:9). R_f 0.18 (silica gel, $CHCl_3$–EtOH, 100:9). Dark-yellow oil, yield 76%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.07 (s, 9H, Bu^t), 1.73 (dddd, 1H, 4′-C*H*H, *J* 12.0, 7.9, 6.0, 4.9 Hz), 1.88 (ddt, 1H, 4′-CH*H*, *J* 12.0, 9.9, 7.2 Hz), 2.20–2.25 (m, 1H, 2′-C*H*H), 2.22 (s, MeN), 2.30 (q, 1H, 5′-C*H*H, *J* 7.9 Hz), 2.61 (ddd, 1H, 5′-CH*H*, *J* 8.7, 7.4, 4.9 Hz), 2.75 (t, 1H, 2′-CH*H*, *J* 8.5 Hz), 3.57 (dtd, 1H, 3′-CH, *J* 9.8, 7.8, 6.3 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.7, 29.5, 41.5, 43.2, 43.7, 56.0, 59.6, 216.5. HRMS (ESI), *m*/*z*: 170.1542 $[M+H]^+$ (calc. for $C_{10}H_{20}NO^+$, *m*/*z*: 170.1539).

For characteristics of products **6b,d–g**, see Online Supplementary Materials.