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

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Table S1 Optimization of the reaction conditions between Mannich bases **3** with azomethine ylides **4**.

№	Reactants	Solvent	Temperature	Time	Yield of **6a** (%)
1	sarcosine (1.5 equiv.), paraformaldehyde (2.0 equiv.)	DMF–*o*-xylene	reflux	3 h	traces
2	**3a** (1.0 equiv.), **5a** (1.1 equiv.)	*o*-xylene	reflux	4.5 h	–
3	**3a** (1.0 equiv.), **5a** (1.2 equiv.)	*o*-xylene	MW, 210 °C	45 min	31
4	**3b** (1.0 equiv.), **5a** (1.2 equiv.), 2 mmol scale	*o*-xylene	MW, 210 °C	45 min	26
5	**3b (1.0 equiv.), 5a (1.2 equiv.), 10 mmol scale**	***o*-xylene**	**MW, 210 °C**	**45 min**	**44**
6	**3a** (2.0 equiv.), **5a** (1.0 equiv.)	*o*-xylene	MW, 210 °C	45 min	–[a]
7	**3a** (1.0 equiv.), **5a** (1.2 equiv.)	*o*-xylene	MW, 190 °C	45 min	–[a]
8	**3a** (1.0 equiv.), $PhCH_2N(CH_2OMe)CH_2SiMe_3$ (1.2 equiv.), LiF (2.0 equiv.),	DMF	MW, 210 °C	45 min	–[b]
9	$PhCH_2N(CH_2OMe)CH_2SiMe_3$ (1.0 equiv.), **3a** (2.0 equiv.), LiF (2.0 equiv.)	DMF	MW, 210 °C	45 min	–[b]

[a] Crude product **6a** has many impurities.
[b] Attempts to synthesize *N*-benzylpyrrolidine.

General experimental details

All solvents were dried and distilled by standard procedures. Microwave syntheses were performed in a sealed tube in a Biotage Initiator+ instrument, and the temperature was monitored by an external surface sensor. Column chromatography was performed with silica gel (40−63 μm, ASTM), chloroform and ethanol were used as eluents. NMR spectra were recorded on Bruker DRX-400 (^{1}H, 400 MHz; ^{13}C, 101 MHz) and Bruker Avance III-500 (^{1}H, 500 MHz; ^{13}C, 126 MHz) spectrometers in DMSO-d_6 and $CDCl_3$. The chemical shifts (δ) are reported in ppm relative to the internal standard TMS (^{1}H NMR) and to residual signals of the solvents (^{13}C NMR). The HRMS spectra were obtained using an UHR-QqTOF maXis Impact HD Bruker Daltonics mass spectrometer. Electrospray ionization with a direct sample inlet (flow rate 240 μl h^{-1}) was used. The mass spectrometer operated in positive

mode in the mass range 50−1550 Da. Analytical studies were carried out using equipment of the Center for Joint Use «Spectroscopy and Analysis of Organic Compounds» at the I. Ya. Postovsky Institute of Organic Synthesis of the Russian Academy of Sciences (Ural Branch).

Characterization data of products 6b,d–g

2-Methyl-2-azaspiro[4.6]undecan-6-one (**6b)**. The product was synthesized from dimethylamino-Mannich base **3c** and purified by column chromatography (eluent: $CHCl_3$–EtOH, 100:12). R_f 0.16 (silica gel, $CHCl_3$–EtOH, 100:12). Dark-yellow oil, yield 21%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.22–1.35 (m, 1H), 1.52–1.59 (m, 2H), 1.68–1.76 (m, 2H), 1.80–1.95 (m, 2H), 1.83–1.90 (m, 1H), 2.06–2.12 (m, 1H), 2.16 (ddd, 1H, *J* 13.2, 6.9, 3.2 Hz), 2.52–2.57 (m, 1H), 2.59 (s, 3H, MeN), 2.65 (td, 1H, *J* 9.7, 7.5 Hz), 2.71 (td, 1H, *J* 11.2, 2.7 Hz), 2.84–2.92 (m, 1H), 3.05–3.16 (m, 1H), 3.13 (d, 1H, 1-CH*H*, *J* 10.1 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.4, 25.6, 29.3, 35.1, 37.7, 40.6, 41.6, 55.5, 58.2, 64.6, 214.1. HRMS (ESI), *m*/*z*: 182.1543 $[M+H]^+$ (calc. for $C_{11}H_{20}NO^+$, *m*/*z*: 182.1539).

1-(1-Benzylpyrrolidin-3-yl)-2,2-dimethylpropan-1-one (**6d**). The product was synthesized from diethylamino-Mannich base and was purified by column chromatography (eluent: $CHCl_3$–EtOH, 100:1). R_f 0.18 ($CHCl_3$–EtOH, 100:2). Dark-yellow oil, yield 79%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.12 (s, 9H, *t*-Bu), 1.87 (dddd, 1H, 4′-C*H*H, *J* 12.5, 8.5, 6.1, 3.8 Hz), 2.01 (ddt, 1H, 4′-CH*H*, *J* 12.5, 10.0, 7.9 Hz), 2.40 (t, 1H, 2′-C*H*H, *J* 8.8 Hz), 2.46 (q, 1H, 5′-C*H*H, *J* 8.4 Hz), 2.90 (td, 1H, 5′-CH*H*, *J* 8.4, 3.8 Hz), 2.95 (t, 1H, 2′-CH*H*, *J* 8.5 Hz), 3.57 (dtd, 1H, 3′-CH, *J* 10.0, 8.1, 6.2 Hz), 3.65 (AB-system, 2H, CH_2Ph, *J* 13.5 Hz), 7.23–7.27 (m, 1H, Ph), 7.29–7.34 (m, 4H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 26.2, 29.9, 43.5, 44.5, 54.3, 58.4, 60.3, 127.2, 128.4, 129.0, 138.9, 217.8. HRMS (ESI), *m*/*z*: 246.1853 $[M+H]^+$ (calc. for $C_{16}H_{24}NO^+$, *m*/*z*: 246.1852).

(1-Methylpyrrolidin-3-yl)(phenyl)methanone (**6e**). The product was synthesized from diethylamino-Mannich base and was purified by column chromatography (eluent: $CHCl_3$–EtOH, 10:1). R_f 0.2 ($CHCl_3$–EtOH, 100:16). Dark-yellow oil, yield 34%. ^{1}H NMR (500 MHz, DMSO-d_6, the hydrochloride) δ: 2.02–2.10 (m, 1H, 4′-C*H*H), 2.45 (ddt, 1H, 4′-CH*H*, *J* 13.2, 9.6, 7.3 Hz), 2.81 (s, 3H, MeN^+), 3.12–3.20 (m, 1H), 3.30–3.38 (m, 1H), 3.46–3.58 (m, 2H), 4.37 (quint, 1H, 3′-CH, *J* 8.0 Hz), 7.58 (t, 2H, Ph, *J* 7.7 Hz), 7.70 (t, 1H, Ph, *J* 7.4 Hz), 8.01 (d, 2H, Ph, *J* 8.0 Hz), 11.28 (br s, 1H, HN^+). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 27.7, 40.4, 44.0, 54.7, 55.8, 128.5, 128.9, 133.6, 135.3, 198.3. HRMS (ESI), *m*/*z*: 190.1228 $[M+H]^+$ (calc. for $C_{12}H_{16}NO^+$, *m*/*z*: 190.1226).

(4-Methoxyphenyl)(1-methylpyrrolidin-3-yl)methanone (**6f**). The product was synthesized from diethylamino-Mannich base and was purified by dissolution in a mixture of *n*-hexane (3 ml) and diethyl ether (3 ml). The solution was decanted from a viscous gum, was dried over Na_2SO_4 and was evaporated *in vacuo*. Dark-yellow oil, yield 65%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.13–2.23 (m, 2H, 4′-CH_2), 2.38 (s, 3H, MeN), 2.50 (q, 1H, 5′-C*H*H, *J* 8.0 Hz), 2.70 (dd, 1H, 2′-C*H*H, *J* 9.4, 7.1 Hz), 2.74 (ddd, 1H, 5′-CH*H*, *J* 8.8, 7.6, 5.1 Hz), 2.95 (t, 1H, 2′-CH*H*, *J* 8.8 Hz), 3.87 (s, 3H, MeO), 3.93 (dtd, 1H, 3′-CH, *J* 10.0, 8.1, 6.7 Hz), 6.94 (d, 2H, Ar, *J* 8.9 Hz), 7.94 (d, 2H, Ar, *J* 8.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.7, 29.5, 41.5, 43.2, 43.7, 56.0, 59.6, 216.5. HRMS (ESI), *m*/*z*: 220.1336 $[M+H]^+$ (calc. for $C_{13}H_{18}NO_2^+$, *m*/*z*: 220.1332).

(1-Methylpyrrolidin-3-yl)(thiophen-2-yl)methanone (**6g**). The product was synthesized from diethylamino-Mannich base and was purified by column chromatography (eluent: $CHCl_3$–EtOH, 10:1). R_f 0.25 ($CHCl_3$–EtOH,

100:12). Dark-yellow oil, yield 61%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.13–2.29 (m, 2H, 4′-CH_2), 2.40 (s, 3H, MeN), 2.53 (dt, 1H, 5′-C*H*H, *J* 9.2, 7.6 Hz), 2.72 (dd, 1H, 2′-C*H*H, *J* 9.4, 7.1 Hz), 2.79 (ddd, 1H, 5′-CH*H*, *J* 8.9, 7.6, 4.8 Hz), 3.01 (t, 1H, 2′-CH*H*, *J* 8.8 Hz), 3.86 (dddd, 1H, 3′-CH, *J* 10.1, 8.1, 7.1, 5.9 Hz), 7.14 (dd, 1H, 4″-CH, *J* 5.0, 3.8 Hz), 7.65 (dd, 1H, 5″-CH, *J* 5.0, 1.1 Hz), 7.72 (dd, 1H, 3″-CH, *J* 3.8, 1.1 Hz). HRMS (ESI), *m*/*z*: 196.0792 $[M+H]^+$ (calc. for $C_{10}H_{14}NOS^+$, *m*/*z*: 196.0791).