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A novel and unusual method for C–N bond formation in 1-substituted-pyrrolidin-2-ones

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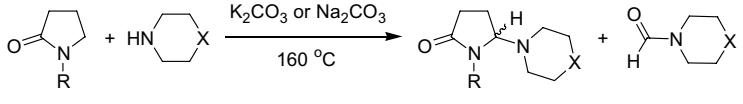
Abstract—A novel 5-C–N bond forming reaction is reported, which involves heating 1-substituted-pyrrolidin-2-ones with cyclic amines in the presence of a base. This reaction provides a convenient method for the synthesis of 1,5-disubstituted-pyrrolidin-2-ones.

N-Methylpyrrolidin-2-one (NMP) is commonly used as a solvent for difficult reactions on account of its stability and polarity, especially as it acts as an auxiliary catalyst and ensures that the reaction proceeds with rapidity and more smoothly than with other solvents. However, we have observed that under the conditions described in this letter NMP itself undergoes an unusual 5-C–N alkylation, and can also cause formylation of the amines used. Usually the formation of C–N bonds in 1-substituted-pyrrolidin-2-ones takes place either by replacement of halides[1,2] or through activated forms such as lactim ethers, lactam acetals,[3] etc., but nucleophilic substitution at the unsubstituted C-5 position of unactivated 1-substituted-pyrrolidin-2-ones has not yet been reported. We wish to report herein the interesting and synthetically useful observation that 1-alkyl- or 1-arylalkyl-pyrrolidin-2-ones react with aryl/alkyl-piperazines, piperidine and morpholine in the presence of sodium or potassium carbonate at 160 °C leading to the formation of 1-alkyl-5-[(4-alkyl/aryl-piperazin-1-yl)/piperidinyl/morpholinyl]-pyrrolidin-2-ones (**3**–**11a**)[4] in fair yields along with small quantities of the corresponding *N*-formyl derivatives of the cyclic amines used (**3**–**9b**) (Scheme 1, Table 1). This reaction provides a convenient method for the preparation of various synthetically and biologically important 1,5-disubstituted-pyrrolidin-2-ones.

In order to prove the structures of the products **3**–**11a**, compound **3a** was synthesized via an alternative route by reacting 1-phenylpiperazine **13** with 1-methyl-5-ethoxypyrrolidin-2-one **12** at 80 °C (Scheme 2).[5] The intermediate **12** was, in turn, synthesized via a literature method.[6] Compound **3a** was identical in all respects (IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analysis)[7] with that obtained according to Scheme 2. Compounds of type **3** are not well described in the literature except for **3a** in a Patent, which describes the generality of the reaction of compound **12** with various



Scheme 1.

Keywords: 1-Substituted-pyrrolidin-2-ones; 5-C–N bond formation; 1,5-Disubstituted-pyrrolidin-2-ones; Formylation; 1,3-Disubstituted-pyrrolidin-2-ones.
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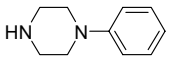
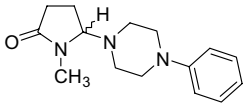
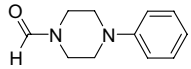
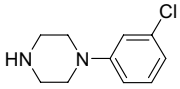
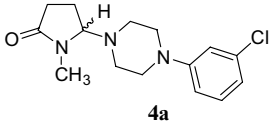
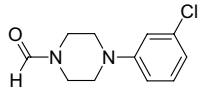
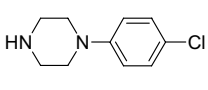
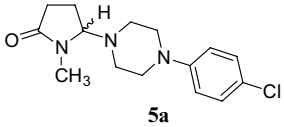
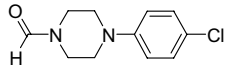
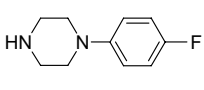
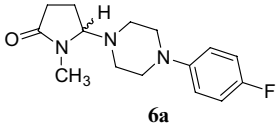
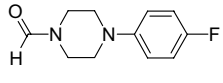
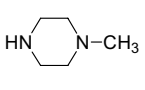
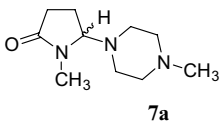
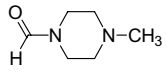
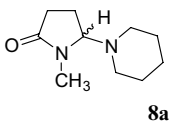
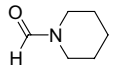
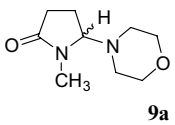
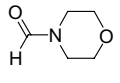
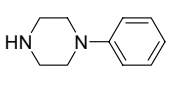
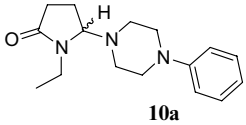
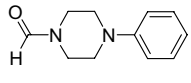
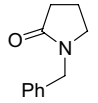
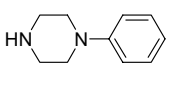
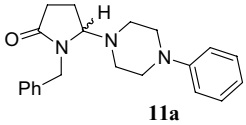
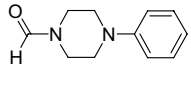
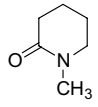
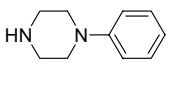
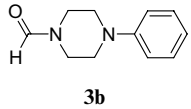
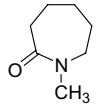
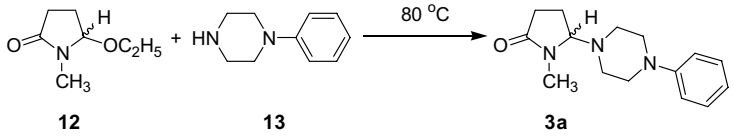
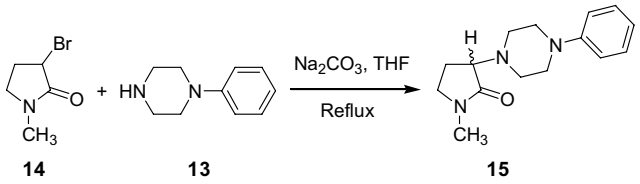
Table 1. Reaction of 1-substituted-pyrrolidin-2-ones with cyclic amines

Cyclic lactam (**1**)	Amine (**2**)	5-Substituted product[7] (**3**–**11a**)	Yield (%)[a]	1-Formyl product[13,14] (**3**–**9b**)[b]	Yield (%)[a]
		 **3a**	38	 **3b**	11
		 **4a**	32	 **4b**	15
		 **5a**	34	 **5b**	17
		 **6a**	41	 **6b**	14
		 **7a**	29	 **7b**	12
		 **8a**	37	 **8b**	9
		 **9a**	34	 **9b**	11
		 **10a**	28	 **3b**	10
		 **11a**	23	 **3b**	7
		—	—	 **3b**	19
		—	—	**3b**	16

[a] Yields of isolated products are based upon cyclic amines.
[b] Characterized on the basis of their IR, ^{1}H NMR and MS data.



Scheme 2.



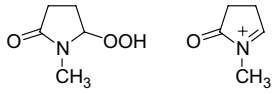
Scheme 3.

amines.[8] The present report provides a more direct approach to 1,5-disubstituted-pyrrolidin-2-ones (**3**–**11a**) (Scheme 1).

To confirm unambiguously the position of C–N bond formation (C-5 vs C-3), we synthesized 1-methyl-3-(4-phenylpiperazin-1-yl)-pyrolidin-2-one **15**[9] by reacting 1-phenylpiperazine **13** with 3-bromo-1-methyl-pyrrolidin-2-one **14**, prepared according to a literature method,[10] in the presence of Na_2CO_3, in THF at reflux (Scheme 3). The ^1H NMR spectrum of compound **3a** was different from that of compound **15** obtained according to the method shown in Scheme 3. In the ^1H NMR of compound **15**, the signal for 3-H (δ 3.30–3.50) merged with those of the $-NCH_2$ protons of the piperazine unlike that of **3a** in which the position of the 5-H signal appeared at δ 4.44. Compounds of type **15** are hitherto unknown in the literature.

We examined the generality of the 5-C–N bond forming reaction and our results are shown in Table 1. 1-Ethyl- and 1-benzyl-pyrrolidin-2-one also gave the amination products along with 1-formyl-4-phenylpiperazine. However, with 1-methylpiperidin-2-one and 1-methylazepan-2-one, only 1-formyl-4-phenylpiperazine was obtained. No reaction took place with *N*,*N*-diethylpropionamide and 1-methylpyrrolidin-2-thione. This reaction thus seems specific for pyrrolidin-2-ones. Pyrrolidin-2-ones are known to have special reactivity as they undergo autoxidation and peroxide formation at the C-5 position.[11]

The above experiments confirm that nucleophilic substitution takes place at C-5 position of 1-substituted-pyrrolidin-2-ones and not at C-3 position. No mechanistic study was carried out to investigate the pathway of nucleophilic displacement at the unactivated C-5 centre, however, this must involve the generation of the immonium species **17**, which would readily undergo nucleophilic addition with cyclic amines. The immonium species could be formed through the known propensity of 1-methylpyrrolidin-2-one to undergo hydroperoxidation[11] at C-5 to form **16**, which could lose hydroperoxide under thermal conditions, or through intermolecular hydride transfer at high temperature. The mechanism of formylation may involve the breakdown of the pyrrolidin-2-one and would be related to the oxidative potential of the pyrrolidin-2-one to form succinimide.[11] This is also reminiscent of the so-called tertiary amine effect where a position next to the nitrogen in an enamine is activated for substitution.[12]



In conclusion, we have demonstrated an unusual, but direct and useful method for the synthesis of 1,5-disubstituted-pyrrolidin-2-ones from 1-substituted-pyrrolidin-2-ones and cyclic amines using potassium or sodium carbonate under heating. This unusual and facile C–N bond formation has allowed the synthesis of various synthetically as well as biologically important 1,5-disubstituted-pyrrolidines very conveniently in multigram quantities. We also describe a convenient method for the synthesis of 1-substituted-3-amino-pyrrolidin-2-ones.

Acknowledgements

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References and notes

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3. Anand, N.; Singh, J. *Tetrahedron* **1988**, *44*, 5975–5999.
4. *Typical procedure*: Initially, the reaction was carried out by taking 1-substituted-pyrrolidin-2-ones as solvent (in excess) but later on we used 1.2 molar equivalents. We observed that the yields were very similar using either method. Both procedures are described below.
Method A: A mixture of 1-phenylpiperazine (**13**, 1.0 g, 6.17 mmol), oven-dried Na_2CO_3 (0.327 g, 3.09 mmol) in 1-methylpyrrolidin-2-one (5 mL, 52.17 mmol) was heated at 160 °C with stirring for 24 h. 1-Methylpyrrolidin-2-one was evaporated at reduced pressure; the residue was suspended in water (30 mL) and extracted with diethyl ether (3×30 mL). The combined organic layers were washed with water (3×30 mL), dried over anhydrous Na_2SO_4 and

filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by column chromatography over silica gel (230–400 mesh) using 1% methanol–chloroform as eluent to afford 0.61 g (38%) of **3a** and **3b** (0.13 g, 11%).

Method B: A mixture of compound **13** (1.0 g, 6.17 mmol), oven-dried Na_2CO_3 (0.327 g, 3.09 mmol) in 1-methylpyrrolidin-2-one (0.71 mL, 7.40 mmol, 1.2 equiv) was heated at 160 °C with stirring for 24 h. Water (30 mL) was added and the reaction mixture extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with water (3 × 30 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (230–400 mesh silica gel, 1% methanol–chloroform) provided 0.59 g (37%) of **3a** and **3b** (0.12 g, 11%).

The other compounds given in Table 1 were synthesized by the same procedures described above.

5. *Experimental procedure* (Scheme 2): A mixture of compounds **12** (0.715 g, 5 mmol) and **13** (0.810 g, 5 mmol) was heated at 80 °C with stirring for 3 h. Water (25 mL) was added and the reaction mixture extracted with diethyl ether (2 × 25 mL). The combined organic layers were washed with water (1 × 20 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to yield the crude product. Purification by column chromatography over silica gel (230–400 mesh) using chloroform–methanol (99:1) as eluent yielded 0.66 g (51%) of compound **3a** as a white solid.
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7. All new compounds reported here were fully characterized on the basis of complementary spectroscopic (IR, ^{1}H NMR, ^{13}C NMR and MS) and analytical data. Analytical data for the compounds **3**–**11a**.

Compound **3a**: mp 94–95 °C (lit.[8] mp 96–97 °C). IR (KBr) cm^{-1}: 2960, 2820, 1670, 1600, 1240, 1140, 750. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92–2.14 (m, 2H), 2.38 (t, J = 6.0 Hz, 2H), 2.55–2.78 (m, 4H), 2.89 (s, 3H), 3.10–3.30 (m, 4H), 4.44 (dd, J = 6.0 Hz, J = 3.0 Hz, 1H), 6.84–7.35 (m, 5H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 17.65, 29.82, 48.23, 49.38, 27.79, 79.83, 117.45, 128.92, 124.79, 149.85, 174.53. MS: *m/z* 259 (M^+). Anal. Calcd for $C_{15}H_{21}N_3O$: C, 69.47; H, 8.16; N, 16.20%. Found: C, 69.23; H, 8.23; N, 15.97%. Compound **4a**: mp 98–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93–2.10 (m, 2H), 2.39 (t, J = 6.0 Hz, 2H), 2.62 (t, J = 6.0 Hz, 4H), 2.89 (s, 3H), 3.10–3.32 (m, 4H), 4.44 (dd, J = 6.0 Hz, J = 3.0 Hz, 1H), 6.70–6.90 (m, 4H). MS: *m/z* 293 (M^+), 295 (M+2). Anal. Calcd for $C_{15}H_{20}ClN_3O$: C, 61.32; H, 6.86; N, 14.30%. Found: C, 61.08; H, 6.54; N, 13.92%. Compound **5a**: mp 149–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90–2.10 (m, 2H), 2.40 (t, J = 6.0 Hz, 2H), 2.62 (t, J = 6.0 Hz, 4H), 2.88 (s, 3H), 3.10–3.28 (m, 4H), 4.42 (dd, J = 6.0 Hz, J = 3.0 Hz, 1H), 6.82 (d, J = 9.0 Hz, 2H), 7.20 (d, J = 9.0 Hz, 2H). MS: *m/z* 293 (M^+), 295 (M+2). Anal. Calcd for $C_{15}H_{20}ClN_3O$: C, 61.32; H, 6.86; N, 14.30%. Found: C, 61.53; H, 6.47; N, 13.93%. Compound **6a**: mp 161–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95–2.12 (m, 2H), 2.38 (t, J = 6.0 Hz, 2H), 2.65 (t, J = 6.0 Hz, 4H), 2.90 (s, 3H), 3.11–3.30 (m, 4H), 4.44 (dd, J = 6.0 Hz, J = 3.0 Hz, 1H), 6.80–7.25 (m, 4H). MS: *m/z* 277 (M^+). Anal. Calcd for $C_{15}H_{20}FN_3O$: C, 64.96; H, 7.27; N, 15.15%. Found: C, 65.31; H, 7.59; N, 15.50%. Compound **7a**: thick oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80–2.10 (m, 2H), 2.28 (s, 3H), 2.35 (t, J = 6.0 Hz, 2H), 2.41–2.60 (m, 8H), 2.85 (s, 3H), 4.35 (dd, J = 6.0 Hz, J = 3.0 Hz, 1H). MS: *m/z* 197 (M^+). Anal. Calcd for $C_{10}H_{19}N_3O$: C, 60.88; H, 9.71; N, 21.30%. Found: C, 61.19; H, 10.04; N, 21.59%. Compound **8a**: thick oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30–1.60 (m, 6H), 1.70–2.05 (m, 2H), 2.20–2.50 (m, 6H), 2.78 (s, 3H), 4.25 (dd, J = 6.0 Hz, J = 3.0 Hz, 1H). MS: *m/z* 182 (M^+). Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.90; H, 9.95; N, 15.37%. Found: C, 66.17; H, 10.27; N, 15.52%. Compound **9a**: thick oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30–1.50 (m, 2H), 1.70–2.05 (m, 2H), 2.50–2.70 (m, 6H), 2.78 (s, 3H), 3.10–3.30 (m, 2H), 4.25 (dd, J = 6.0 Hz, J = 3.0 Hz, 1H). MS: *m/z* 184 (M^+). Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21%. Found: C, 58.44; H, 8.93; N, 15.33%. Compound **10a**: thick oil. IR (neat) cm^{-1}: 3010, 2960, 1660, 1600, 1470, 1200, 1000, 730. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, J = 6.0 Hz, 3H), 1.93–2.09 (m, 4H), 2.31–2.45 (m, 4H), 2.58–2.70 (m, 4H), 3.43 (q, J = 6.0 Hz, 2H), 4.55 (dd, J = 6.0 Hz, J = 3.0 Hz, 1H), 5.89–6.95 (m, 3H), 7.22–7.31 (m, 2H). MS: *m/z* 273 (M^+). Anal. Calcd for $C_{16}H_{23}N_3O$: C, 70.29; H, 8.48; N, 15.37%. Found: C, 70.02; H, 8.53; N, 15.59%. Compound **11a**: thick oil. IR (neat) cm^{-1}: 3000, 2960, 1660, 1590, 1480, 1430, 1200, 990, 720. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89–2.11 (m, 4H), 2.66–2.70 (m, 4H), 2.95–3.03 (m, 4H), 4.31 (d, J = 6.0 Hz, 1H), 4.62–4.70 (m, 2H), 6.77–6.82 (m, 3H), 7.22–7.50 (m, 7H). MS: *m/z* 335 (M^+). Anal. Calcd for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.51; N, 12.53%. Found: C, 75.44; H, 7.42; N, 12.87%.
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9. *Experimental procedure* (Scheme 3): A mixture of compounds **14** (0.730 g, 4 mmol), **13** (0.66 g, 4 mmol) and oven-dried Na_2CO_3 (0.212 g, 2 mmol) in tetrahydrofuran (25 mL) was heated at reflux with stirring for 3 h. The solvent was removed under reduced pressure and water (25 mL) was added to the residue. The reaction mixture was extracted with diethyl ether (2 × 20 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by column chromatography over silica gel (230–400 mesh) using chloroform–methanol (99:1) as eluent to afford 0.32 g (31%) of **15** as a dense oil. IR (neat) cm^{-1}: 3025, 2940, 1670, 1440, 1220. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05–2.20 (m, 2H), 2.65–2.80 (m, 2H), 2.85 (s, 3H), 2.90–3.05 (m, 2H), 3.10–3.40 (m, 6H), 3.55 (t, J = 6.0 Hz, 1H), 6.80–7.00 (m, 3H), 7.20–7.40 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.70, 29.36, 45.96, 48.69, 64.05, 115.58, 119.06, 128.56, 150.90, 171.96. MS: *m/z* 259 (M^+). Anal. Calcd for $C_{15}H_{21}N_3O$: C, 69.47; H, 8.16; N, 16.20%. Found: C, 69.31; H, 8.57; N, 16.32%.
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14. All the 1-formyl products reported here, were fully characterized on the basis of their IR, ^{1}H NMR and MS data and were consistent with reported data. Analytical data for the compound **3b**: mp 80–81 °C (lit.[13c] mp 83.5 °C). IR (KBr) cm^{-1}: 3500, 2820, 1670, 1600, 1400, 1230, 1000, 910, 750, 670. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.12 (t, J = 6.0 Hz, 2H), 3.20 (t, J = 6.0 Hz, 2H), 3.54 (t, J = 6.0 Hz, 2H), 3.74 (t, J = 6.0 Hz, 2H), 6.84–7.40 (m, 5H), 8.12 (s, 1H). MS: *m/z* 190 (M^+).