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Three-component Ugi–Smiles couplings of cyclic imines

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ABSTRACT

Cyclic imines react with isocyanides and electron-deficient phenols to afford *N*-aryl piperidines and pyrrolidines in good yields (Ugi–Smiles couplings of cyclic imines). The starting imines were formed by oxidation with *N*-chlorosuccinimide followed by a base-induced dehydrochlorination.

The synthetic utility of the Ugi reaction has led to the use of isocyanide-based multicomponent reactions (IMCRs) to generate biologically relevant scaffolds with a high level of diversity.[1] Recent efforts in this field have mostly focused on the formation of heterocyclic derivatives through post-condensation transformations.[2] Alternatively, straightforward formation of heterocycles can be achieved when Ugi reactions are performed on difunctional starting components.

For example, the oxidation of cyclic amines to their related imines affords suitable substrates for a three-component Ugi reaction. This was first reported by Joullié two decades ago. This approach was later adopted by several groups to form pyrrolidine and piperidine derivatives.[3]

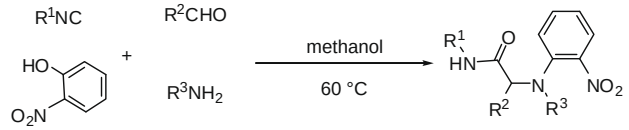
We recently reported a new Ugi-type coupling between an aldehyde, an amine, an isocyanide and an electron-deficient phenol leading to *N*-arylamino carboxamides (Scheme 1).[4] This coupling was further extended to different hydroxy- and mercapto-heterocycles, such as pyridines and pyrimidines.[5]

Ugi reactions involving carboxylic acids are traditionally performed at room temperature. The higher temperature required for phenol couplings, associated with the instability of cyclic imines,[6] may become an issue in obtaining *N*-aryl pyrrolidine or piperidine adducts in good yields.

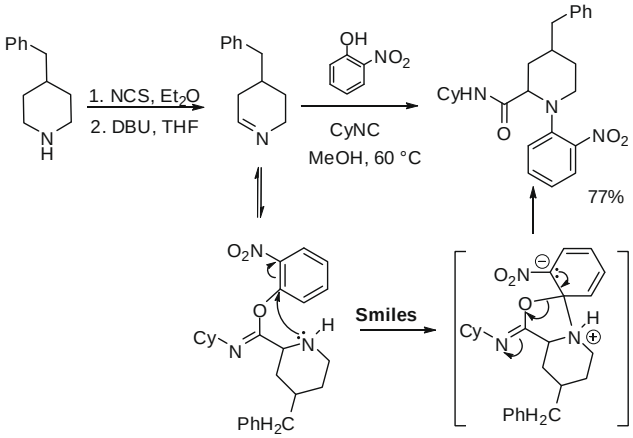
Herein, we present our results on the behavior of cyclic imines in Ugi–Smiles couplings.

We first started working with six-membered rings. Starting from 4-benzylpiperidine, oxidation with *N*-chlorosuccinimide (NCS) followed by treatment with diazabicycloundecene afforded, after filtration, the crude imine,[7] which was employed in the following Ugi–Smiles step. Upon addition of stoichiometric amounts of *para*-nitrophenol and cyclohexylisocyanide, the reaction did not reach completion under heating at 60 °C. However, the desired adduct was obtained in a moderate 34% yield. Degradation of the imine at such a temperature led us to perform the reaction with a two-fold excess of imine, and we were pleased to isolate the corresponding piperidine in 77% yield (Scheme 2).[8]

As reported in Table 1, various phenols and isocyanides behaved similarly. Indeed, *ortho*-nitrophenol gave the desired piperidines in good yields with different isocyanides (Table 1, entries 1 and 2). Hy-



Scheme 1.



Scheme 2.

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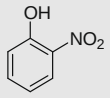
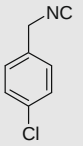
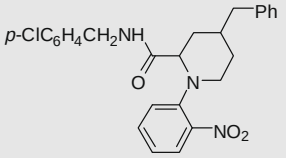
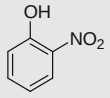
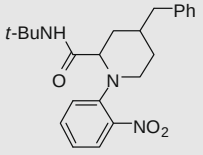
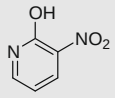
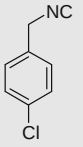
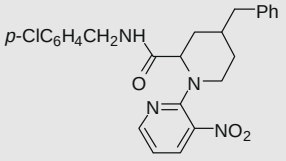
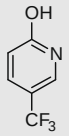
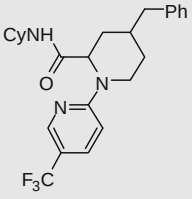
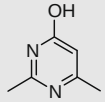
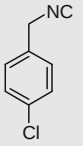
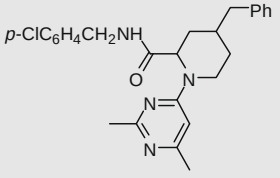
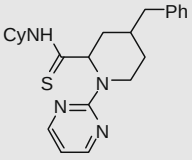
Table 1
Ugi–Smiles reaction of 4-benzylpiperidine

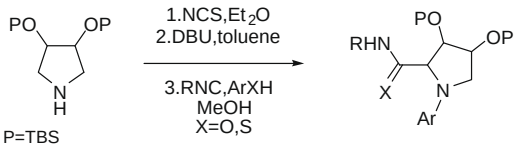
Entry	ArXH	RNC	Product	Yield (%)
1				88
2				50
3				48
4				45
5				67
6				65

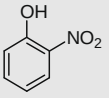
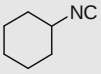
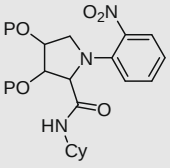
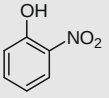
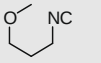
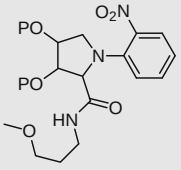
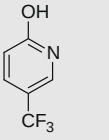
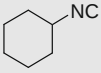
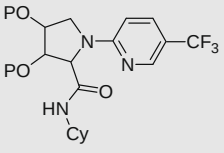
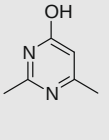
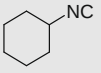
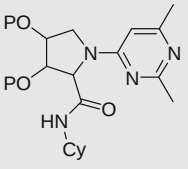
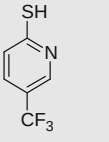
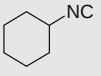
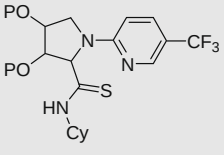
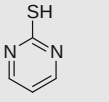
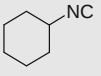
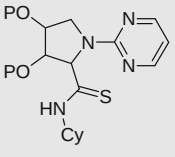
droxy-containing heterocycles, such as hydroxy-pyridines and pyrimidines (Table 1, entries 3–5) reacted efficiently, as did 2-mercaptopyrimidine (Table 1, entry 6). In all these reactions, a single diastereomer was isolated (>95:5 by ^{1}H NMR), which is probably due to an axial attack of the nucleophilic isocyanide on the cyclic iminium.

In order to investigate five-membered ring imines, L-tartaric acid was condensed with benzylamine. Then reduction, protection of the two hydroxy groups, and debenzylation gave the starting pyrrolidine which was utilized in the same oxidation–dehydrochlorination sequence.[9]

The results summarized in Table 2[10] show that this imine behaved just as efficiently toward phenols (Table 2, entries 1 and 2), hydroxy and mercapto-heterocycles (Table 2, entries 3–6). In contrast to six-membered ring imines, poor diastereoselectivity was observed (1:1 to 1.2:1), probably due to the higher conformational flexibility of these imines.[11]

Table 2
Ugi–Smiles reaction of five-membered ring imines



Entry	ArXH	Isocyanide	Product	Yield (%)
1				78
2				82
3				53
4				77
5				65
6				63

In conclusion, we have developed a new route to *N*-aryl pyrrolidines and piperidines. This constitutes the first example of a three-component Ugi–Smiles coupling involving cyclic imines. These couplings will be further studied with aromatic imines such as pyridines and quinolines.[12]

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7. Davis, B.; Maughan, M.; Chapman, T.; Villard, R.; Courtney, S. *Org. Lett.* **2002**, *4*, 103.
8. *Typical procedure for six-membered ring Joullié-Ugi adducts*: To a 2 M solution of imine (1.6 mmol) in methanol were added successively 0.5 equiv of *o*-nitrophenol (111 mg, 0.8 mmol) and 0.5 equiv of cyclohexyl isocyanide (100 μL, 0.8 mmol). The resulting mixture was stirred at 60 °C overnight. The solvent was then removed under reduced pressure and the crude reaction mixture was purified by flash column chromatography on silica gel (petroleum ether–diethyl ether, 90:10) to give 260 mg of 4-benzyl-1-(2-nitrophenyl)-piperidine-2-carboxylic acid cyclohexylamide (77%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (dd, J = 8.2, 1.6 Hz, 1H), 7.63 (d, J = 7.4 Hz, 1H), 7.50 (ddd, J = 8.5, 7.3, 1.6 Hz, 1H), 7.29 (t, J = 8.5 Hz, 2H), 7.23–7.13 (m, 4H), 7.02 (ddd, J = 8.2, 7.3, 1.1 Hz, 1H), 4.38–4.34 (m, 1H), 3.82–3.71 (m, 1H), 3.15 (ddd, J = 13.8, 12.7, 2.9 Hz, 1H), 2.80 (d, J = 13.8 Hz, 1H), 2.75 (dd, J = 13.6, 5.8 Hz, 1H), 2.67 (br d, J = 13.1 Hz, 1H), 2.45 (dd, J = 13.6, 8.5 Hz, 1H), 1.88–1.56 (m, 5H), 1.55–1.09 (m, 9H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 169.7, 146.1, 141.6, 139.8, 134.5, 129.6, 128.7, 127.4, 126.5, 122.1, 121.2, 60.5, 51.0, 48.9, 43.4, 33.8, 33.7, 33.2, 32.2, 30.6, 25.9, 25.4, 22.8. IR (thin film) 3363, 3027, 2929, 1668, 1602, 1513, 1481, 1447, 1340 cm^{-1}. HRMS: Calcd for $C_{25}H_{31}N_3O_3$ 421.2365. Found: 421.2369.
9. For the use of this imine in an Ugi reaction see: Chapman, T. M.; Davies, I. G.; Gu, B.; Block, T. M.; Scopes, D. I. C.; Hay, P. A.; Courtney, S. M.; McNeill, L. A.; Schofield, C. J.; Davis, B. G. *J. Am. Chem. Soc.* **2005**, *127*, 506.
10. *Typical procedure for five-membered ring Joullié-Ugi adducts*: To 1.6 mmol of imine were added successively 0.5 equiv of 2-mercaptopyrimidine (90 mg, 0.8 mmol) and 0.5 equiv of cyclohexylisocyanide (100 μL, 0.8 mmol). The resulting mixture was stirred at 80 °C for 2 d without any solvent. The crude reaction mixture was purified by flash column chromatography on silica gel (cyclohexane–diethyl ether, 90:10) to give 278 mg of 4-bis-(*tert*-butyl-dimethyl-silyloxy)-1-pyrimidin-2-yl-pyrrolidine-2-carbothioic acid cyclohexylamide (63%) as a 1:1.2 mixture of two diastereomers. *Major diastereomer*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (d, J = 4.8 Hz, 2H), 7.68 (br d, J = 8.2 Hz, 1H), 6.64 (t, J = 4.8 Hz, 1H), 5.08 (d, J = 4.0 Hz, 1H), 4.49 (d, J = 4.0 Hz, 1H), 4.43–4.35 (m, 1H), 4.14 (d, J = 11.3 Hz, 1H), 4.03 (s, 1H), 3.86 (dd, J = 11.3, 2.8 Hz, 1H), 2.01–1.89 (m, 2H), 1.70–1.49 (m, 4H), 1.39–1.23 (m, 2H), 0.93–0.85 (m, 2H), 0.87 (s, 9H), 0.73 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), 0.05 (s, 3H), 0.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 196.7, 163.2, 158.1, 112.2, 79.9, 75.8, 75.7, 56.1, 53.6, 32.2, 31.2, 26.2, 25.9, 25.1, 24.8, 18.4, 18.2, −4.0, −4.2, −4.5, −4.6. *Minor diastereomer*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.38 (d, J = 4.8 Hz, 2H), 7.84 (br d, J = 7.7 Hz, 1H), 6.67 (t, J = 4.8 Hz, 1H), 4.80 (s, 1H), 4.71 (s, 1H), 4.35–4.27 (m, 1H), 4.07 (d, J = 3.8 Hz, 1H), 3.88 (dd, J = 8.0, 3.8 Hz, 1H), 3.70 (d, J = 11.3 Hz, 1H), 2.01–1.89 (m, 2H), 1.70–1.49 (m, 4H), 1.39–1.23 (m, 2H), 1.21–1.00 (m, 2H), 0.87 (s, 9H), 0.82 (s, 9H), 0.22 (s, 3H), 0.19 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 197.3, 162.4, 158.3, 112.3, 83.4, 79.1, 77.7, 56.3, 53.5, 31.7, 31.2, 26.3, 26.1, 25.9, 24.8, 24.7, 18.8, 18.4, −3.8, −4.3, −4.4, −4.5. IR (thin film) 2931, 2857, 1584, 1555, 1527, 1471, 1452, 1104 cm^{-1}. HRMS: Calcd for $C_{27}H_{50}N_4O_2SSi_2$ Calcd: 550.3193. Found: 550.3181.
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12. (a) Williams, N. A. O.; Masdeu, C.; Diaz, J. L.; Lavilla, R. *Org. Lett.* **2006**, *8*, 5789; (b) Diaz, J. L.; Miguel, M.; Lavilla, R. *J. Org. Chem.* **2004**, *69*, 3550.