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Ugi–Smiles couplings in water

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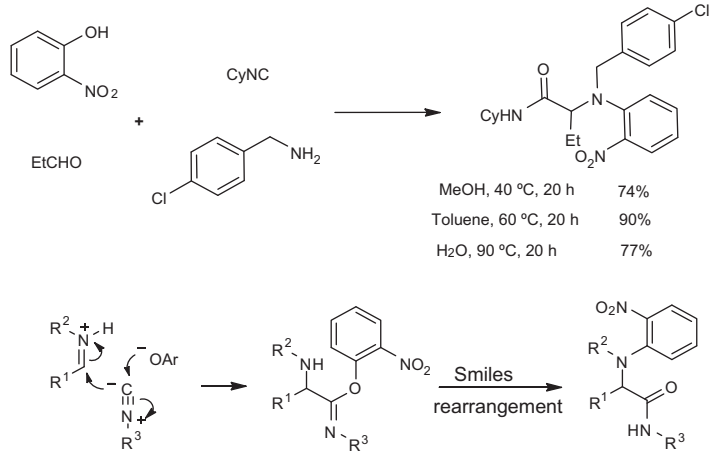
ABSTRACT

The four-component couplings of isocyanides with amines, aldehydes and phenols (Ugi–Smiles reactions) can be performed in water as the solvent instead of methanol or toluene.

Discovered in the late 50s, the Ugi reaction[1] has seen its popularity enhanced dramatically by new trends in organic chemistry. Following the emergence of combinatorial chemistry and the need for efficient library preparation of bioactive compounds, medicinal chemists have used the Ugi reaction extensively in combination with post-condensation processes to prepare various heterocyclic scaffolds.[2] More recently, growing environmental concern in chemistry has further turned the spotlight on this reaction. Indeed, the Ugi reaction achieves complex product formation within one step, without any added reagents and with the sole formation of water as a side product. As such, this reaction probably embodies perfectly both the concepts of step and atom economy in chemistry.

We recently proposed an extension of the Ugi reaction by introducing electron-deficient phenols in place of the traditional carboxylic acids.[3] This reaction was termed an Ugi–Smiles coupling in relation to the Smiles rearrangement occurring in the final irreversible step of the process (Scheme 1). We have shown in several studies the utility of this new coupling for the synthesis of complex-fused heterocycles.[4] The coupling is usually performed in methanol or toluene in rather high concentration. In order to further comply with the requirements of 'green chemistry', we wished to perform this four-component coupling in water as the solvent.

The reaction was tested using a 2 M aqueous solution of propanal and adding a stoichiometric amount of *ortho*-nitrophenol, *para*-chlorobenzylamine and cyclohexyl isocyanide. The resulting heterogenous mixture was heated at 90 °C and stirred for 20 h. After completion of the reaction, the desired adduct was isolated in 77% yield (Scheme 1). This result can be compared with the 74% yield obtained using methanol at 40 °C and with the 90% yield in toluene at 60 °C.



Scheme 1. Comparison of various solvents in Ugi–Smiles couplings.

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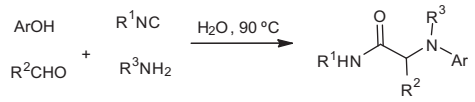
Table 1
Ugi–Smiles couplings with nitrophenols in water



Entry	Ar	R^1	R^2	R^3	Yield (%)
1	2-$NO_2C_6H_4$	Cy	Ph	$MeO(CH_2)_2$	60
2	2-$NO_2C_6H_4$	Cy	4-ClC_6H_4	4-ClBn	72 (80)[a]
3	2-$NO_2C_6H_4$	Cy	3,4-$MeO_2C_6H_3CH_2$	4-ClBn	80 (90)[a]
4	2-$NO_2C_6H_4$	Cy	4-$NO_2C_6H_4$	4-ClBn	39
5	2-$NO_2C_6H_4$	Cy	2-NCC_6H_4	4-ClBn	30
6	2-$NO_2C_6H_4$	Cy	Et	$MeO(CH_2)_2$	90 (71)[a]
7	2-$NO_2C_6H_4$	Cy	H	Allyl	81 (72)[a]
8	2-$NO_2C_6H_4$	Cy	*i*-Bu	Furyl	68
9	2-$NO_2C_6H_4$	4-Cl $C_6H_4CH_2$	Ph	Allyl	58
10	2-$NO_2C_6H_4$	4-Cl $C_6H_4CH_2$	Et	Allyl	77
11	2-$NO_2C_6H_4$	4-Cl $C_6H_4CH_2$	$(CH_2)_4$	Allyl	51
12	2-$NO_2C_6H_4$	*t*-Bu	Ph	4-MeO $C_6H_4CH_2$	74
13	4-$NO_2C_6H_4$	Cy	Et	4-$ClC_6H_4CH_2$	70
14	4-$NO_2C_6H_4$	Cy	H	Allyl	68
15	2,4-$(NO_2)_2C_6H_3$	Cy	Et	4-$ClC_6H_4CH_2$	70 (73)[a]
16	4-MeO-2-$NO_2C_6H_3$	Cy	Et	4-$ClC_6H_4CH_2$	92 (98)[a]
17	2-Cl-4-$NO_2C_6H_3$	Cy	Et	4-$ClC_6H_4CH_2$	70 (95)[a]
18	2-F-4-$NO_2C_6H_3$	Cy	Et	4-$ClC_6H_4CH_2$	58
19	4-Me-2-$NO_2C_6H_3$	Cy	Et	4-$ClC_6H_4CH_2$	90 (96)[a]

[a] Same reaction performed in MeOH at 60 °C.

Table 2
Ugi–Smiles couplings with heterocyclic phenols in water

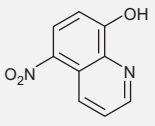
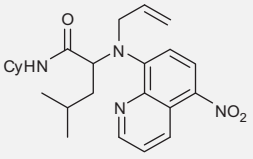
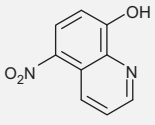
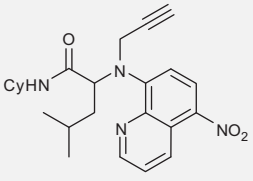
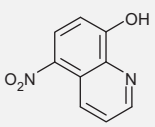
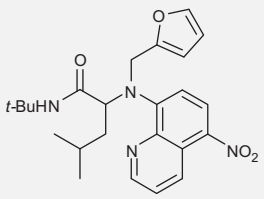
Entry	ArOH	Product	Time (h)	Yield (%)
1			48	70
2			36	47
3			30	38

Table 2 (*continued*)

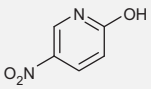
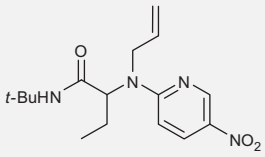
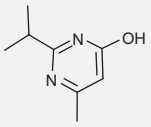
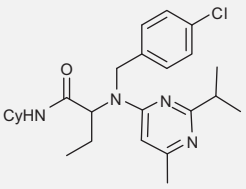
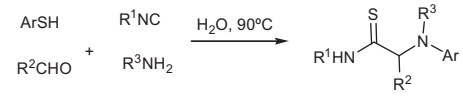
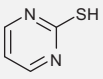
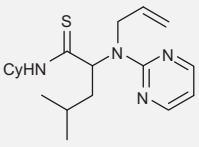
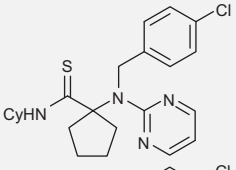
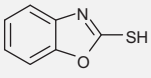
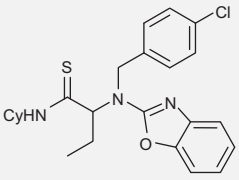
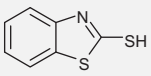
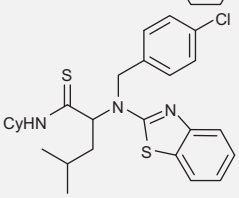
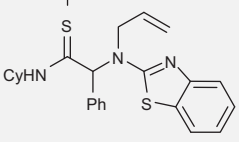
Entry	ArOH	Product	Time (h)	Yield (%)
4			14	56
5			40	35

Table 3
Ugi–Smiles couplings with mercapto derivatives in water



Entry	ArSH	Product	Reaction time (h)	Yields (%)
1			48	69
2			36	47
3			30	38
4			14	66
5			40	41

Under such conditions, the reaction proved to be quite general and a wide range of isocyanides, aldehydes and amines were coupled successfully with *ortho*- and *para*-nitrophenols (Table 1).[5]

We further extended the aqueous Ugi–Smiles coupling to heterocyclic phenols.[6] Hydroxy nitroquinolines reacted in water in similar yields to those reported with methanol (Table 2, entries 1–3). However, the reactions involving the 2-hydroxypyridine

(Table 2, entry 4) or 4-hydroxypyrimidines (Table 2, entry 5) were less efficient in water when compared to the results obtained in methanol.

We next investigated the behaviour of mercapto derivatives[6a,7] in Ugi–Smiles reactions under this new set of conditions in order to form functionalized thioamides in one step (Table 3). Surprisingly, 2-mercaptopyrimidine which was poorly reactive in various organic solvents (the best results were obtained without solvent) gave some good results in water (Table 3, entries 1 and 2). Benzo-fused mercapto derivatives such as benzoxazol-2-yl and benzothiazol-2-yl[7a] reacted under these conditions to afford similar yields to those previously reported (Table 3, entries 3–5).[8]

Ugi reactions are mostly performed in methanol but good yields are also observed in aprotic solvents such as dichloromethane or acetonitrile. The use of water as solvent, as reported by Pirrung and Das Sarma, leads to an acceleration of the reaction without any decrease in the yields.[9] Further results from Mironov's group indicate a more pronounced beneficial effect of water on the Passerini reaction.[10] In the case of the Ugi–Smiles reaction, the resulting reactivity is close to that observed in organic solvents using either nonpolar solvents such as toluene or polar ones such as methanol or acetonitrile. These results expand further the range of solvents that can be employed in Ugi–Smiles couplings. Further work is in progress in order to examine the analogous Passerini–Smiles couplings in water.

Acknowledgement

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5. Typical procedure for Ugi–Smiles coupling in H_2O for 2-[allyl(2-nitrophenyl)amino]-*N*-(4-chlorobenzyl)butanamide (Table 1, entry 10). To an aqueous 1 M solution of propanal (70 mL, 1.0 mmol) was added allylamine (120 mL, 1.0 mmol) followed by *para*-chlorobenzyl isocyanide (160 mL, 1.0 mmol) and phenol (140 mg, 1.0 mmol). The reaction mixture was stirred at 90 °C for 20 h and extracted with EtOAc (2 × 15 mL). The combined organic layers were dried ($MgSO_4$), concentrated and the residue was purified by flash chromatography on silica gel (EtOAc/PE, 1:2) to give the desired adduct (300 mg, 77%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (dd, 1H, J = 1.5, 8.1 Hz), 7.48 (dt, 1H, J = 1.5, 8.1 Hz), 7.38 (t, 1H, J = 5.3 Hz), 7.27–7.22 (m, 3H), 7.18–7.10 (m, 3H), 5.65–5.55 (m, 1H), 5.08–5.01 (m, 2H), 4.44 (dd, 1H, J = 6.1, 14.9 Hz), 4.36 (dd, 1H, J = 6.1, 14.9 Hz), 3.82–3.77 (m, 1H), 3.74 (d, 1H, J = 6.1 Hz), 3.51 (dd, 1H, J = 6.3, 15.4 Hz), 2.05–1.94 (m, 1H), 1.83–1.72 (m, 1H), 0.95 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 172.0, 146.3, 143.0, 137.3, 133.4, 133.3, 132.9, 129.5, 129.0, 125.6, 125.5, 124.2, 119.6, 68.5, 53.6, 43.1, 23.4, 11.5; IR (thin film) 3307, 2925, 1662, 1603, 1520, 1491, 1349, 1276, 1091 cm^{-1}; HRMS calcd for $C_{20}H_{22}ClN_3O_3$: 387.1350, found 387.1329.
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8. Typical procedure for the synthesis of 2-[allyl(benzo[*d*]thiazol-2-yl)amino]-*N*-cyclohexyl-2-phenyl-ethanethioamide (Table 3, entry 5). To an aqueous 1 M solution of benzaldehyde (100 μL, 1.0 mmol) was added allylamine (70 μL, 1.0 mmol) followed by cyclohexyl isocyanide (120 μL, 1.0 mmol) and 2-mercaptobenzothiazole (150 mg, 1.0 mmol). The reaction mixture was stirred at 90 °C for 40 h and extracted with EtOAc (2 × 15 mL). The combined organic layer was dried ($MgSO_4$), concentrated in vacuo and the residue was purified by flash chromatography on silica gel (EtOAc/PE, 1:9) to give the desired adduct (170 mg, 41%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.78 (br s, 1H), 7.64 (d, 1H, J = 7.8 Hz), 7.43 (d, 1H, J = 8.0 Hz), 7.39–7.27 (m, 6H), 7.13 (t, 1H, J = 7.4 Hz), 6.17 (s, 1H), 5.95–5.85 (m, 1H), 5.32 (dd, 1H, J = 1.3, 17.2 Hz), 5.26 (dd, 1H, J = 1.0, 10.1 Hz), 4.50–4.40 (m, 1H), 4.29 (dd, 1H, J = 5.4, 16.3 Hz), 4.21 (dd, 1H, J = 5.4, 16.3 Hz), 2.20–2.12 (m, 1H), 2.01–1.93 (m, 1H), 1.79–1.70 (m, 1H), 1.66–1.57 (m, 2H), 1.52–1.33 (m, 3H), 1.28–1.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 198.1, 168.1, 151.6, 136.1, 132.5, 131.2, 128.9, 128.6, 128.5, 126.4, 122.3, 121.2, 120.1, 119.5, 77.1, 56.6, 54.7, 31.4, 31.3, 25.9, 24.74, 24.67; IR (thin film) 2930, 1519, 1445, 1285, 1214, 1123, 1068 cm^{-1}; HRMS calcd for $C_{24}H_{27}N_3S_2$: 421.1646, found 421.1658.
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