Ammonia in Ugi–Smiles and Ugi Couplings

Anaëlle Barthelon, Laurent El Kaim,* Marion Gizzi, Laurence Grimaud*

Laboratoire Chimie et Procédés, Ecole Nationale Supérieure de Techniques Avancées, 32 Bd Victor, 75739 Paris Cedex 15, France
Fax +33(1)45528322; E-mail: laurent.elkaim@ensta.fr; E-mail: laurence.grimaud@ensta.fr

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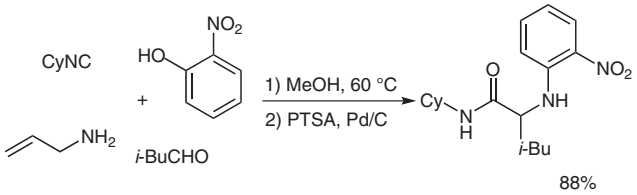
Abstract: Ammonia may be used in Ugi-type reactions, providing good yields of Ugi–Smiles and Ugi–Mumm adducts under microwave irradiation.

Key words: ammonia, Ugi–Smiles, isocyanide, multicomponent couplings

Among the tools available to chemists for the efficient synthesis of biologically relevant scaffolds, multicomponent reactions (MCRs) have been found to occupy a foremost position.[1] For instance, Ugi couplings have been widely used by medicinal chemists to synthesize peptidyl compounds as well as heterocyclic derivatives.[2] A few years ago, we disclosed a new Ugi-type reaction using an electron-deficient phenol as an acid surrogate, namely the Ugi–Smiles coupling.[3] Starting from primary amines, this reaction provides tertiary *N*-aryl amine derivatives that can be readily transformed into various heterocycles.[4] Though hydroxy pyridines and hydroxy pyrimidines are efficient partners in Ugi–Smiles reactions,[4] most of the *N*-aryl or *N*-heteroaryl derivatives of potential pharmacological interest include a free NH functionality. Indeed, a wide range of NH-pyridines and NH-pyrimidines have been described as potent drugs against asthma, rheumatoid arthritis,[5] psoriasis,[6] osteoporosis[7] and cancer.[8] An access to such compounds through an Ugi–Smiles coupling would logically imply the use of ammonia as the amine partner. Unfortunately, Ugi reactions with ammonia are rarely documented and good yields are only obtained with sterically hindered aldehydes.[9] Wishing to develop more efficient processes, chemists have chosen to develop alternatives to ammonia by using 'convertible primary amines' such as nitrobenzylamine,[10] that can be deprotected after the Ugi reaction. Herein, we wish to report new conditions that allow Ugi–Smiles and Ugi couplings to be performed with ammonia.

Since the discovery of the Ugi–Smiles reaction, we have been trying to perform Ugi–Smiles couplings with ammonia. Indeed, different sets of conditions have been surveyed, by varying both the ammonia sources and the solvents: ammonium acetate, ammonium chloride with a stoichiometric amount of base as additive, either triethylamine, potassium carbonate, DBU or potassium *tert*-butanolate, hexamethyldisilamine, or magnesium nitride, using methanol, acetonitrile or toluene. Unfortunately, the yields did not exceed 30%. These disappointing results, combined with the lack of reproducibility, have led us to design a sequence involving an Ugi–Smiles coupling combined with a deprotection, allylamine being used as an ammonia equivalent (Scheme 1).[11] However, this procedure was limited to *ortho*-nitrophenol as no NH-adducts could be obtained using other electron-deficient phenols.



Scheme 1 Allylamine as ammonia equivalent

Inspired by the results of Kazmaier et al. in Ugi couplings with ammonium salts,[9b,c] we recently reinvestigated the feasibility of a Ugi–Smiles coupling with ammonia using fluorinated solvents. Use of HFIP (hexafluoroisopropanol) or 2,2,2-trifluoroethanol did not result in the desired reaction taking place, but 2,2,2-trifluoroethanol helped to promote the reaction quite efficiently. Indeed, the coupling between *ortho*-nitro phenol, cyclohexylisocyanide, isovaleraldehyde and one equivalent of a 30% aqueous ammonia solution performed in 2,2,2-trifluoroethanol gave the desired adduct **1** in 53% yield, along with 15% of the *N*-aryl carboxamide **2** as by-product (Scheme 2).

In order to limit the formation of **2**, two equivalents of ammonia were introduced in the reaction mixture. We were then able to isolate the desired four-component adduct in a 58% yield after 36 hours at 60 °C. Most noteworthy, the reaction time can be dramatically decreased under microwave irradiation (Scheme 3) at 130 °C (100 W, 90 min), giving the product in similar yields (65%) even with a decreased amount of ammonia (1.5 equiv). Under this new set of conditions, protic polar solvents were screened again and methanol gave the best yields.

With these conditions in hand, the reaction proceeded smoothly to completion, as shown in Table 1. The desired NH-adducts were isolated in good yields with various *ortho*- (entries 1–4, Table 1) and *para*-nitro phenols (entries 5–7, Table 1) and with several different isocyanides. However, concerning the carbonyl substrate, this method failed with aromatic aldehydes and is therefore limited to aliphatic derivatives for the moment.

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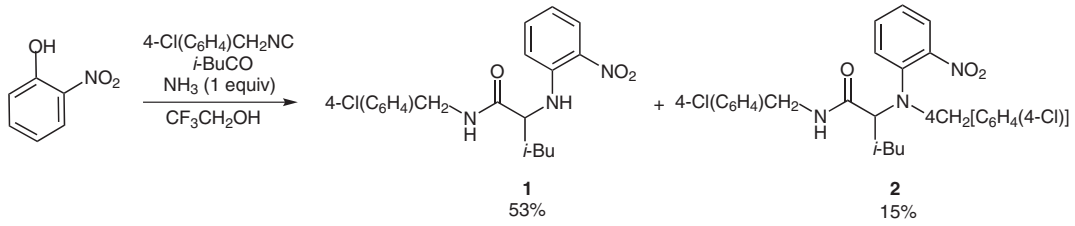


Scheme 2 Ammonia couplings in CF_3CH_2OH

Scheme 3 Ammonia couplings under microwave irradiation

Table 1 Ammonia Couplings with Nitro Phenols

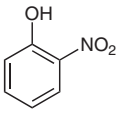
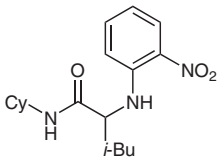
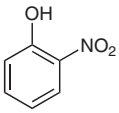
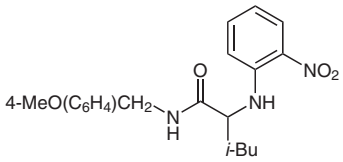
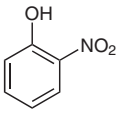
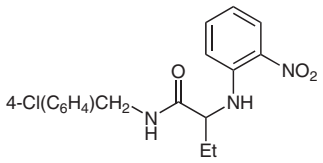
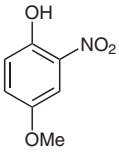
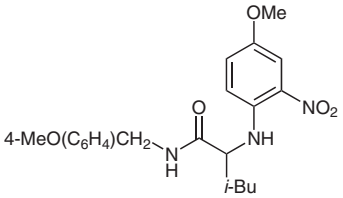
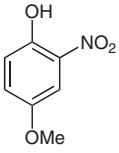
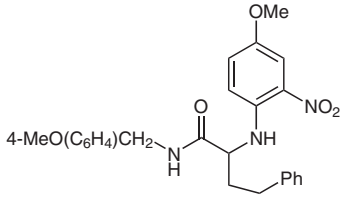
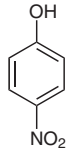
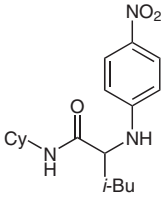
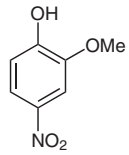
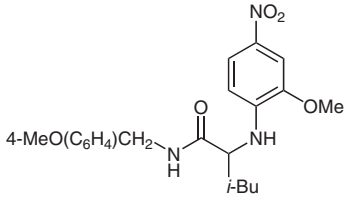
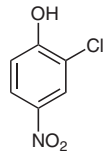
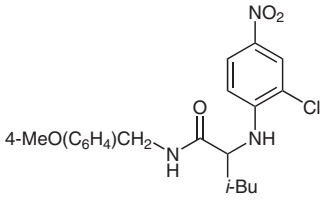
Entry	Phenol	RCHO	RNC	Product	Yield (%)
1		*i*-BuCHO	CyNC		44
2		*i*-BuCHO	4-MeO(C_6H_4)CH_2NC		89
3		EtCHO	4-Cl(C_6H_4)CH_2NC		55
4		*i*-BuCHO	4-MeO(C_6H_4)CH_2NC		69
4		$Ph(CH_2)_2CHO$	4-MeO(C_6H_4)CH_2NC		23

Table 1 Ammonia Couplings with Nitro Phenols (continued)

Entry	Phenol	RCHO	RNC	Product	Yield (%)
5		*i*-BuCHO	CyNC		42
6		*i*-BuCHO	4-MeO(C_6H_4)CH_2NC		53
7		*i*-BuCHO	4-MeO(C_6H_4)CH_2NC		68

More interestingly, these conditions can be efficiently applied to 2-hydroxypyridine (Table 2, entry 1) or 4-hydroxypyrimidines (Table 2, entries 2–4), as these compounds yield the expected NH-heteroaryl substrates. As the previous MCR-deprotection sequence failed with heteroaromatic phenols, this procedure is thus far the sole pathway for the synthesis of such products via Ugi–Smiles couplings.

The possibility to form Ugi–Smiles adducts between ammonia and simple aldehydes such as propionaldehyde (Table 1, entry 3) is noteworthy when considering the low efficiency of these aldehydes in related Ugi–Mumm reactions (couplings with carboxylic acids).[9] This might be due to the higher temperature used, which allows a reversible formation of all the aminal side products easily formed with ammonia.[9b,c] Therefore, microwave irradia-

Table 2 Ammonia Couplings with Hydroxy Heteroaromatic

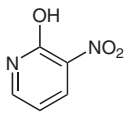
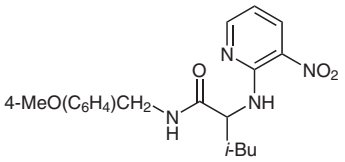
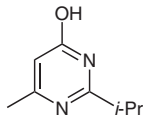
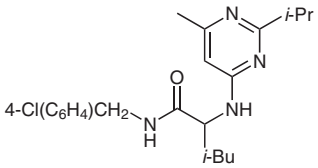
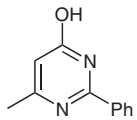
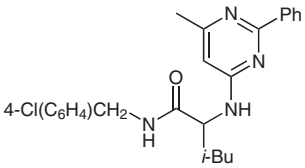
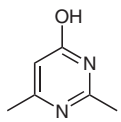
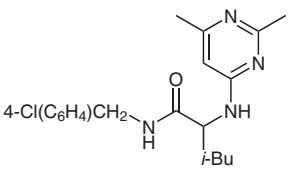
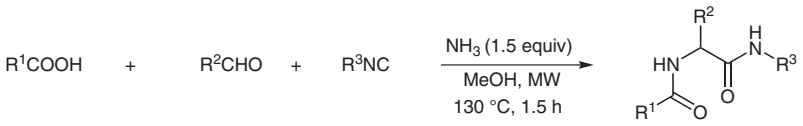
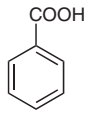
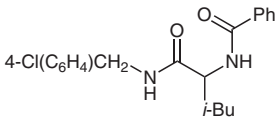
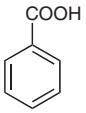
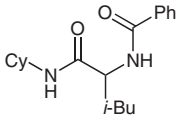
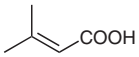
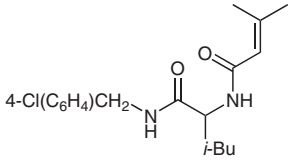
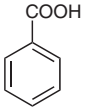
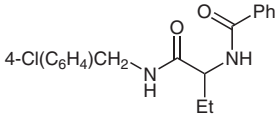
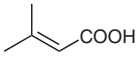
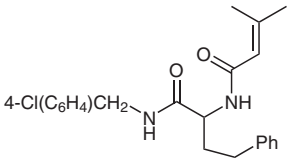
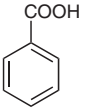
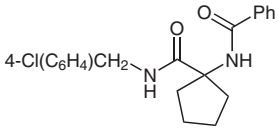
Entry	HetOH	RCHO	RNC	Product	Yield(%)
1		*i*-BuCHO	4-MeO(C_6H_4)CH_2NC		47
2		*i*-BuCHO	4-Cl(C_6H_4)CH_2NC		42
3		*i*-BuCHO	4-Cl(C_6H_4)CH_2NC		74
4		*i*-BuCHO	4-Cl(C_6H_4)CH_2NC		57

Table 3 Ammonia Couplings in Ugi Reaction



Entry	RCO_2H	RR′CO	RNC	Product	Yield (%)
1		*i*-BuCHO	4-Cl(C_6H_4)CH_2NC		93
2		*i*-BuCHO	CyNC		92
3		*i*-BuCHO	4-Cl(C_6H_4)CH_2NC		quant
4		EtCHO	4-Cl(C_6H_4)CH_2NC		64
5		$Ph(CH_2)_2CHO$	4-Cl(C_6H_4)CH_2NC		45
6			4-Cl(C_6H_4)CH_2NC		60

tion in Ugi reactions with ammonia should bring similar improvements. Indeed, when various Ugi reactions were attempted with ammonia under microwave irradiation, good yields were obtained with aliphatic aldehydes as well as ketones (Table 3).

To conclude, we have developed a straightforward Ugi–Smiles access to NH-aryl and NH-heteroaryl derivatives via a four-component coupling involving ammonia.[12] This method allows the direct formation of medicinally relevant heterocyclic scaffolds. It can be furthermore applied to Ugi couplings with ammonia and carboxylic acids.

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(12) **Typical Procedure for 1**: In a microwave tube were introduced MeOH (1.0 mL), 2-nitrophenol (140 mg, 1.0 mmol), a 30% aq solution of NH_3 (120 μL, 1.5 equiv), isovaleraldehyde (108 μL, 1.0 equiv), and *p*-chlorobenzyl-isocyanide (150 μL, 1.0 equiv). The reaction mixture was stirred for 90 min under microwave irradiation (100 W, 130 °C). The solvent was then removed under reduced pressure to afford the Ugi–Smiles product after purification by flash column chromatography on silica gel (244 mg, 65% yield); mp 91–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (dd, 1 H, *J* = 8.6, 1.4 Hz), 8.07 (d, 1 H, *J* = 4.5 Hz), 7.48 (ddd, 1 H, *J* = 8.4, 7.1, 1.4 Hz), 7.24 (dt, 2 H, *J* = 8.6, 2.3 Hz), 7.09 (d, 2 H, *J* = 8.6 Hz), 6.84 (ddd, 1 H, *J* = 8.6, 7.1, 1.3 Hz), 6.76 (d, 1 H, *J* = 8.4 Hz), 6.72 (t, 1 H, *J* = 5.9 Hz), 4.43 (dd, 1 H, *J* = 15.3, 5.9 Hz), 4.38 (dd, 1 H, *J* = 15.3, 5.9 Hz), 4.01 (dt, 1 H, *J* = 9.3, 4.5 Hz), 1.98–1.75 (m, 3 H), 1.05 (d, 3 H, *J* = 6.2 Hz), 0.95 (d, 3 H, *J* = 6.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.1, 144.3, 137.1, 136.8, 133.8, 133.6, 129.3, 129.2, 127.4, 118.0, 115.0, 58.1, 43.0, 42.7, 25.6, 23.6, 21.8. HRMS: *m/z* calcd for $C_{19}H_{22}ClN_3O_3$: 375.1350; found: 375.1352.