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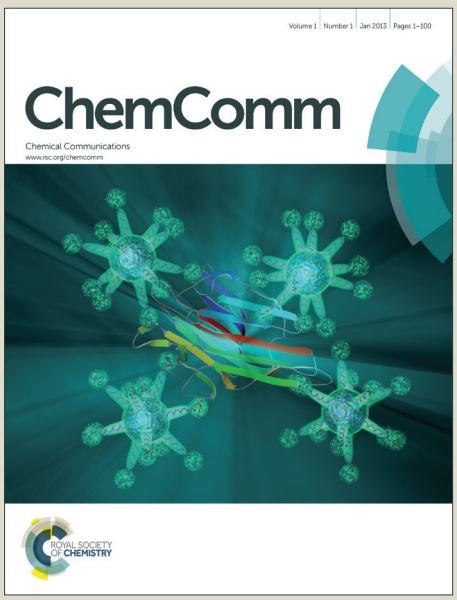

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5-component pyrroline synthesis

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Formal [3+2] cycloaddition of Ugi adducts towards pyrrolines.

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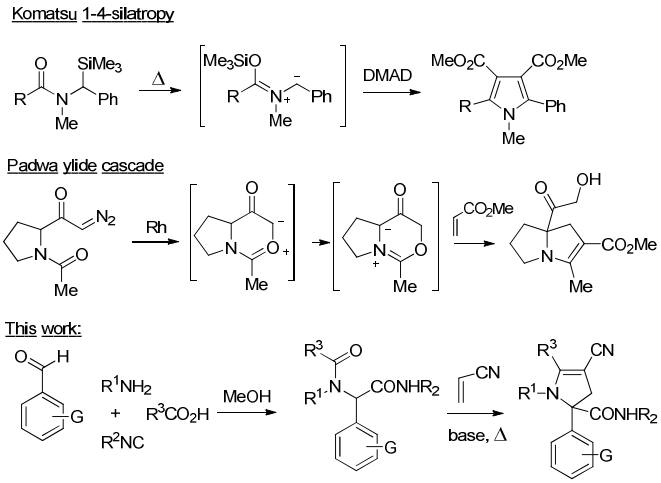
((Dedication----optional))

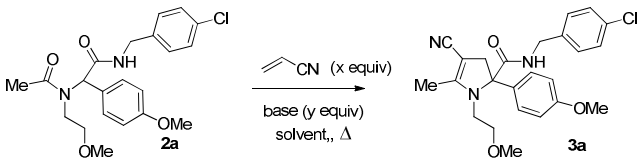
Pyrrolines and pyrroles heterocycles have found a wide range of applications in both medicinal chemistry and material sciences.[1] Their importance may be related to the numerous syntheses available starting from the early named reactions.[2] Among these methods, the [3+2] cycloadditions of azomethine ylides have shown particular usefulness in the fast assembly of the heterocyclic core.[3] The transient 1,3-dipolar species, easily obtained through deprotonation of intermediate iminiums or decarboxylation, readily add to olefines and alkynes. More recently important efforts have been made to report enantioselective versions of these cycloadditions.[4] Compared to reactive pathways involving iminium intermediates, the use of amides to generate the ylide is much less documented. Indeed, amides are poorly reactive and usually require an activation step with strong electrophiles to obtain activated imidates such as munchone derivatives[5] prone to undergo [3+2] cycloaddition. Besides the generation of the latter, an elegant 1,4 silyl transfer (Scheme 1, A),[6] a rhodium triggered generation of azomethine ylides from diazoamides (Scheme 1, B)[7] as well as a 1,3-dipole formation through Vilsmeeir-Haack cyclization[8] are worth to be mentioned. Herein we wish to present an unusual [3+2] type cycloaddition under microwave conditions without prior activation of the amide moiety (Scheme 1, C).

The field of multicomponent reactions is strongly associated with the Ugi reaction.[9] The use of the latter to generate libraries of heterocycles and to achieve the synthesis of highly complex derivatives within a limited number of steps has stimulated a rapid growth of the field. Besides these properties, mostly explored in medicinal chemistry, the Ugi reaction remains an underestimated tool to tackle new reactivity studies. Whenever amides possessing relatively acidic α-proton are searched for, using the Ugi reaction avoids tedious preparation of starting materials and an easy tuning of the acidity through proper choice of starting aldehydes.[10] With this properties in minds, we envisioned that Ugi adducts may be engaged in Michael type reaction and tried to figure out conditions allowing to cyclize the intermediate Michael adducts.[11]



Scheme 1. Pyrroles and pyrrolines formation from amides

Acrylonitrile **1a** and methyl acrylate **1b** were selected as potentially highly reactive Michael acceptors towards Ugi adduct **2a** prepared in 78% isolated yield from 4-methoxybenzaldehyde, methoxyethylamine, chlorobenzylisocyanide and acetic acid. Due to the volatility of **1a** and **1b**, the latter were heating under microwave with **2a** in various solvents together different amounts of triethylamine or diisopropylamine (DIPEA). All attempts at temperature up to 120°C failed to give any adduct either in toluene, methanol, acetonitrile or DMF. However, raising the temperature to 140°C in MeOH allowed us to observe traces of a new compound **3a** after 30 minutes heating (Scheme 2).



	3a
x = 1, DIPEA (y = 1), MeOH, 140°C (MW), 30 min :	traces
x = 3, DIPEA (y = 0.5), MeOH, 140°C (MW), 30 min:	45%
x = 3, DIPEA (y = 0.5), MeOH, 120°C (MW), 30 min:	-
x = 6, DIPEA (y = 0.5), MeOH, 140°C (MW), 30 min:	57%
x = 6, NEt_3 (y = 0.5), MeOH, 140°C (MW), 30 min:	56%
x = 6, DIPEA (y = 0.5), CF_3CO_2H, 140°C (MW), 30 min:	67%
x = 6, DIPEA (y = 1), CF_3CO_2H, 140°C (MW), 30 min:	46%

Scheme 2. Pyrroles and pyrrolines formation from amides

To our surprise the structure of **3a** revealed that a [3+2] type process was under the way with final elimination of water to form pyrrolines. The yield could be raised reasoning that at the high

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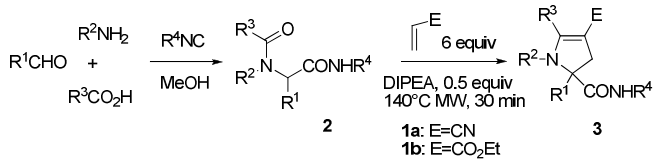
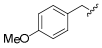
[**] Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

temperature required for the coupling, important loss of Michael acceptor was occurring through oligomerisation or solvolysis. With 3 equiv of **1a**, treating **2a** with 0.5 equiv of DIPEA in MeOH afforded **3a** in 45% isolated yield, whereas 6 equiv led to a better 57% yield. Under these conditions non protic solvents such as acetonitrile, toluene or DMF didn't give any adduct. Added lithium salts in methanol (LiCl, LiOTf) did not improve the reaction, however using a more acidic solvent such as trifluoroethanol gave the best yield in the absence of Lewis acid. Higher amount of base was detrimental and triethylamine remained slightly less efficient. The following reactions were thus performed in trifluorethanol with 0.5 equiv of DIPEA and 6 equiv of Michael acceptor and the results gathered in Table 1

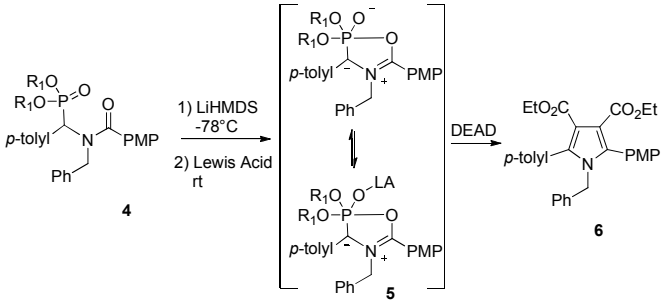
Table 1.Scope of the pyrroline synthesis



Entry	R^1	R^2	R^3	R^4	1	2 (Yield %)	3 (Yield %)
1	4-(MeO)C_6H_4	*n*-Pr	Me		**1a**	**2b** (74)	**3b** (60)
2	4-(MeO)C_6H_4	*n*-Pr	Me	Cy	**1a**	**2c** (73)	**3c** (17)
3	4-(MeO)C_6H_4	allyl	Me	Cy	**1a**	**2d** (84)	**3d** (26)
4	4-(MeO)C_6H_4	allyl	Me	*t*-Bu	**1a**	**2e** (66)	-
5	4-(NO_2)C_6H_4	*n*-Pr	Me		**1a**	**2f** (70)	**3f** (51)
6	4-(MeO)C_6H_4	*n*-Pr	Et		**1a**	**2g** (86)	**3g** (49)
7	4-(MeO)C_6H_4	allyl	Et		**1a**	**2h** (89)	**3h** (55)
8	4-ClC_6H_4	*n*-Pr	Et		**1a**	**2i** (61)	**3i** (64)
9	4-(MeO)C_6H_4	allyl	4-ClC_6H_4		**1a**	**2j** (88)	**3j** (54)
10	4-(MeO)C_6H_4	*n*-Pr	4-MeC_6H_4		**1a**	**2k** (65)	**3k** (42)
11	4-(MeO)C_6H_4	allyl	Me		**1a**	**2l** (70)	**3l** (57)
12	4-ClC_6H_4		Me		**1a**	**2m** (74)	**3m** (59)
13	4-ClC_6H_4		H		**1a**	**2n** (84)	**3n** (54)
14			Me		**1a**	**2o** (66)	**3o** (57)
15	4-(MeO)C_6H_4	allyl	Me		**1b**	**2p** (80)	**3p** (22)
16	4-(MeO)C_6H_4		Me		**1b**	**2a** (78)	**3q** (25)

The Ugi reaction was very efficient without much surprise and the following cyclizations with acrylonitrile gave pyrrolines in moderate to good yields for a variety of Ugi adducts prepared from aromatic aldehydes. On the latter, both electron-withdrawing and electron-donating groups afforded final products in comparable yields. The cyclization was observed with similar efficiency when performed on an Ugi adduct of cinnamaldehyde (Table 1, entry 14). The synthetic sequence was not limited to acetic acid (Table 1, entries 1-5, 11, 12, 14-16), as propionic (Table 1, entries 6-8), benzoic (Table 1 , entries 9, 10) an formic acid (Table 1, entry 13) lead to amides that cyclize equally well under these conditions. The main limitations concern the nature of the isocyanides and Michael acceptors involved. Benzylic isocyanides were the most efficient whereas cyclohexyl isocyanide led to pyrrolines in low yields (Table 1, entries 2, 3) and *t*-butyl Ugi adducts **2e** did not react at all under the same conditions (Table 1, entry 4). Acrylonitrile was the only electron-deficient alkene we could couple with reasonable yields under these conditions. Methyl acrylate in large excess afforded pyrrolines **3p** and **3q** in modest yields (Table 1, entry 15, 16) and **3a** failed to react with N-phenylmaleimide or dietylacetylene dicarboxylate under the same conditions (limiting the amount of these Michael acceptors to 2 equiv).

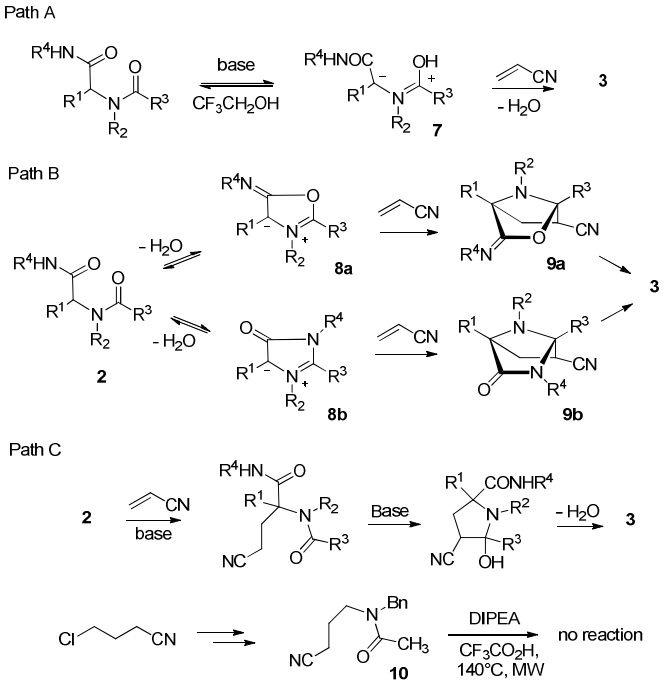
Among the numerous transformations of Ugi adducts disclosed in the literature the number of nucleophilic additions onto the amide moiety is rather limited. Most examples are associated to amine additions towards benzimidazole or quinazoline derivatives.[12] To the best of our knowledge the only amido to enamino group transformation involving Ugi adducts was observed in a pyrrole synthesis using cyclohexenyl isocyanide as a convertible isocyanide in the Ugi reaction. [13] The activation of the amide moiety is brought by the formation of an intermediate Munchnone which undergoes further cycloadditions with dimethylacetylene dicarboxylate. Besides the paucity of related transformations, this cyclization raises interesting mechanistic questions as the amide functionality is not expected to be activated for a [3+2] cycloaddition under these conditions. A further related cyclization towards pyrroles was observed under addition of phosphonoamide **4** to diethylacetylene dicarboxylate (Scheme 3).[14] The reaction performed under basic conditions is strongly activated with added Lewis acids. The intermediacy of a cyclic pentacoordinate phosphorus based dipole **5** was postulated. The latter may react with the alkyne to form pyrrole **6** after cleavage of the phosphorous group.



Scheme 3. Pyrrole formation from phosphonoamide 4.

Though the formation of a pentacoordianate phosphorous dipole is well suited to explain the former reaction, the analogous tetrahedral adduct from amides is unlikely to be the reactive intermediate in our reaction. However at the high temperature allowed by microwave conditions together with the use of a rather acidic solvent and a base, the existence of an equilibrium between **2** and a dipolar structure **7** could explain the following cycloaddition leading to **3** (Scheme 4, A). Alternatively munchnone type 1,3-dipoles **8a** and **8b** could give bicyclic intermediates **9a** or **9b** after cycloaddition with acrylonitrile (Scheme 4, B). Indeed, formation of dipole **8b** could fit with the strong dependence of the reaction to the nature of the starting isocyanide. A further possibility would be the

stepwise Michael addition followed by a knoevenagel type condensation (Scheme 4, C). To test this latter hypothesis, the cyanoamide **10** was prepared by a standard alkylation/acylation procedure from 4-chlorobutyronitrile (Scheme 4). When treated under our cyclization conditions, no pyrroline formation was observed and **10** was recovered unchanged. Aware that a Thorpe-Ingold effect could favor the cyclisation of our Ugi adducts, we tried to observe any potential Michael adduct performing the reaction at much lower temperature. When **2a** was heated at 60°C with 6 equiv of acrylonitrile and 0.5 equiv of DIPEA, a slow conversion was observed forming directly **3a** in 36 % isolated yield after three days. Though the two-step mechanism cannot be completely ruled out, these last two experiments are more in favor of a concerted process.



Scheme 4. Possible mechanisms for pyrroline formation.

In conclusion, we have disclosed a new pyrroline synthesis through addition of Ugi adducts to acrylonitrile. The reaction features a surprising activation of an amido residue probably brought by the use of a protic solvent under microwave conditions. The latter conditions avoid the use of added electrophilic reagents to remove water from the system et generate the reactive 1,3-dipole.

Experimental Section

Typical procedure given for **3a**: In a microwave vial, Ugi adduct **2a** (150 mg, 0.37 mmol) was dissolved in trifluoroethanol (1.5 mL). To this solution, *N*,*N*-diisopropylethylamine (32 µl, 0.5 equiv) and acrylonitrile (146 µl, 6.0 equiv) were subsequently added. The resulting mixture was subjected to microwave irradiation (140°C, 30 min, CEM Discover microwave, 150 W). After completion of the reaction, extraction with CH_2Cl_2 (3×10 mL) and purification by flash column chromatography (80:20 diethyl ether/ petroleum ether) afforded **3a** as an oil (110 mg, 67% yield). Rf: 0.6 (55:45 ethyl acetate/ petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.16 (t, *J*= 5.6 Hz, 1H, NH), 7.32-7.29 (m, 2H), 7.24-7.20 (m, 4H), 6.86-6.82 (m, 2H), 4.52-4.41 (m, 2H), 3.77 (s, 3H, OMe), 3.37 (s, 2H), 3.10-3.07 (m, 2H), 3.05-3.00 (m, 1H), 2.98 (s, 3H, OMe), 2.82-2.75 (m, 1H), 2.05 (s, 3H). ^{13}C NMR (CDCl3, 100.6 MHz): δ (ppm) 173.4, 161.8, 159.5, 136.7, 133.3, 131.4, 129.2, 128.9, 128.8, 119.4, 114.1, 77.4, 76.1, 70.1, 58.5, 55.3, 44.9, 44.3, 43.2, 14.1. I.R. (thin film): 3301, 3051, 2930, 2836, 2182, 1656, 1606, 1510, 1407, 1251, 1182, 1089, 728, 699 cm^{-1}. HRMS: Calcd. For $C_{24}H_{26}ClN_3O_3$: 439.1663, Found: 439.1653.

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5-component pyrroline synthesis

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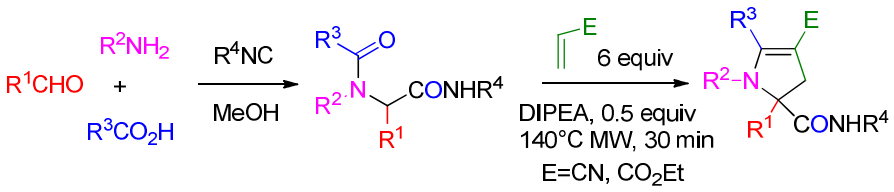
Formal [3+2] cycloaddition of Ugi adducts towards pyrrolines.



Ugi adducts derived from aromatic aldehydes may be converted to pyrrolines via addition of Michael acceptors under microwave irradiation. The reaction may proceed via an unusual fomation of azomethine ylide followed by a [3+2] cycloaddition with the Michael acceptor.