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Short Communication

Hydroamination of alkynes as a new source of Imines for Ugi MCRs - Scope and Limitations

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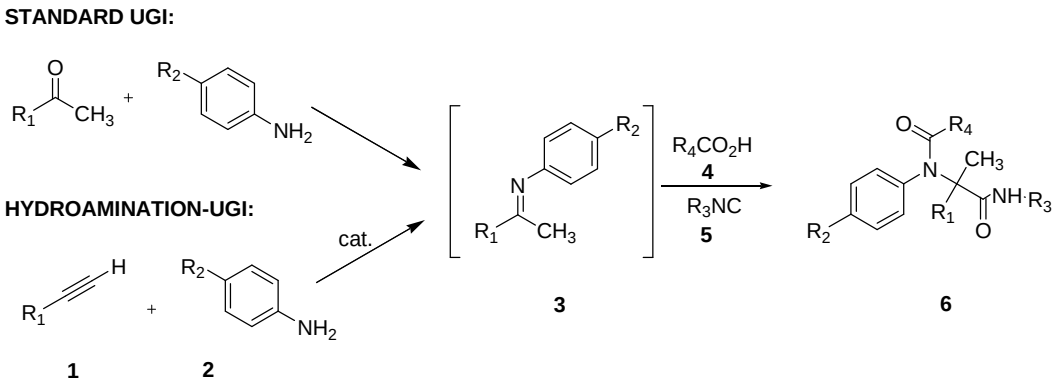
Abstract: The hydroamination of alkynes has been implemented to form imines which are involved in Ugi multicomponent reactions. The catalytic hydroamination (using $Zn(OTf)_2$, clays and Au catalysts) of anilines with terminal alkynes has furnished the corresponding imines with useful yields and these intermediates have been reacted in a tandem manner with isocyanides and carboxylic acids to yield the Ugi adducts. Although synthetically useful, as the process enables the use of alkynes as inputs in Ugi reactions, the main limitation deals with the low overall yields and the incompatibility of isocyanides with the metal catalysts which prevents the direct interaction of all four components. However, a one-pot process, separating both reactions, is feasible.

Keywords: Hydroamination, Alkynes, Amines, Imines, Multicomponent reactions

Introduction

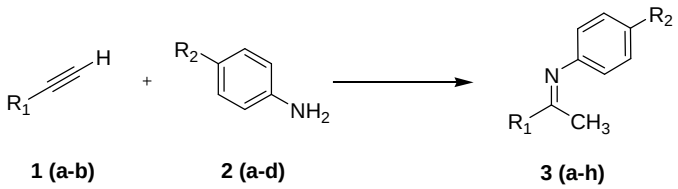
Multicomponent reactions (MCRs) display many features of the ideal synthesis, as they enable the formation of an adduct from three or more reactants with high atom economy and bond forming efficiency.[1] Therefore the development of new processes of this type may represent a significant improvement of the synthetic arsenal. One of the most useful transformations of this type is the Ugi MCR, which involves the interaction of an isocyanide, an amine, a carbonyl (aldehyde or ketone) and a carboxylic acid to yield an α-alkylamidomide adduct.[2] Usually, the intermediate imine is generated through the in situ condensation of the amine with the carbonyl component (Scheme 1), although recently Zhu described its formation by oxidation of amines.[3] We envisaged an alternative protocol which prepares such intermediates by the hydroamination of alkynes with anilines.[4] Such approach would rend alkynes as new inputs in Ugi reactions (Scheme 1).



Scheme 1

Results and Discussion

In order to find the optimal conditions for the hydroamination reaction, a number of aromatic amines were reacted with two representative terminal alkynes in the presence of different catalytic systems,[5-8] as shown in Table 1.



When *p*-anisidine (**2a**) and phenylacetylene (**1a**) were treated with various copper catalysts in different solvents, as well as in solvent-free conditions, no reaction occurred (Table 1, entry 1). The neat reaction with silver triflate allowed moderate conversion to the desired imine (Table 1, entry 2). Using zinc triflate in THF resulted in no conversion at all (Table 1, entry 3), while the neat reaction allowed 50% conversion (Table 1, entry 4); however, conversion did not improve by increasing the amount of catalyst (Table 1, entries 5, 6).

Shanbhag reported a method for the heterogeneous hydroamination of alkynes by using a Montmorillonite K-10 supported copper catalysts (Cu-K-10) in refluxing toluene.[9] Employing this method allowed a conversion of 60% with phenylacetylene (**1a**) and *p*-anisidine (**2a**) (Table 1, entry 7), and 50% using phenylacetylene (**1a**) and 4-bromo aniline (**2b**) (Table 1, entry 8).

Interesting results were described using titanium complexes by Bergman,[10-12] Doyle[13-15] and Odom and co-workers.[16] Moreover, Beller described the high selectivity in the formation of the anti-Markovnikov hydroamination product over the Markovnikov one using different phenol ligands in combination with $Ti(N_2Et)_4$.[7,17] However, when *p*-methylaniline (**2c**) and phenylacetylene (**1a**) were treated with $Ti(Et_2N)_4$ and 20% of diisopropylphenol in the conditions described, the reaction did not take place (Table 1, entry 9).

Table 1. Screening of catalysts for hydroamination of aromatic and aliphatic alkynes.

ENTRY	R_1	R_2	CATALYST	CONDITIONS	YIELD
1	C_6H_5	OCH_3	CuI[5]	THF, r.t.	No reaction
			CuI	DMF, reflux 48h	
			$Cu(OTf)_2$ 5% mol[8]	Solvent-free, r.t.	
			$Cu(OTf)_2$ 5% mol	Toluene, reflux 16h	
			$Cu(OAc)_2$	Toluene, reflux 16h	
2	C_6H_5	OCH_3	AgOTf	Solvent-free, 60 ºC, 3h	20%
3	C_6H_5	OCH_3	$Zn(OTf)_2$ 5% mol	THF	No reaction
4	C_6H_5	OCH_3	$Zn(OTf)_2$ 2.5% mol	60 ºC	50%
5	C_6H_5	OCH_3	$Zn(OTf)_2$ 10% mol	60 ºC	50%
6	C_6H_5	OCH_3	$Zn(OTf)_2$ 20% mol	60 ºC	50%
7	C_6H_5	OCH_3	Cu-K-10[6]	Toluene, reflux, 20h	60%
8	C_6H_5	Br	Cu-K-10	Toluene, reflux, 20h	50%
9	C_6H_5	CH_3	$Ti(Et_2N)_4$ 20%L[a 7]	Toluene, reflux, 24h	No reaction
10	C_6H_5	Br	$(PPh_3)AuCH_3$ 0.1% mol; TfOH, 1% mol	Solvent-free, 70 ºC, 16h	37%
11	C_6H_5	Br	$(PPh_3)AuCH_3$ 0.2% mol; $H_3PW_{12}O_{40}$ ·x H_2O, 0.1% mol	Solvent-free, 70 ºC, 16h	95%
12	C_6H_5	OCH_3	$(PPh_3)AuCH_3$ 0.2% mol; $H_3PW_{12}O_{40}$ · xH_2O, 0.5% mol	Solvent-free, 70 ºC, 16h	50%
13	C_6H_5	CH_3	$(PPh_3)AuCH_3$ 0.2% mol; $H_3PW_{12}O_{40}$ · xH_2O, 0.5% mol	Solvent-free, 70 ºC, 16h	40%
14	C_6H_5	NO_2	$(PPh_3)AuCH_3$ 0.2% mol; $H_3PW_{12}O_{40}$ · xH_2O, 0.5% mol	Solvent-free, 70 ºC, 16h	65%
15	$^nC_4H_9$	Br	$(PPh_3)AuCH_3$ 0.2% mol; $H_3PW_{12}O_{40}$ · xH_2O, 0.5% mol	Solvent-free, 70 ºC, 16h	60%
16	$^nC_4H_9$	OCH_3	$(PPh_3)AuCH_3$ 0.2% mol; $H_3PW_{12}O_{40}$ · xH_2O, 0.5% mol	Solvent-free, 70 ºC, 16h	33%
17	$^nC_4H_9$	CH_3	$(PPh_3)AuCH_3$ 0.2% mol; $H_3PW_{12}O_{40}$ · xH_2O, 0.5% mol	Solvent-free, 70 ºC, 16h	35%
18	$^nC_4H_9$	NO_2	$(PPh_3)AuCH_3$ 0.2% mol; $H_3PW_{12}O_{40}$ · xH_2O, 0.5% mol	Solvent-free, 70 ºC, 16h	85%

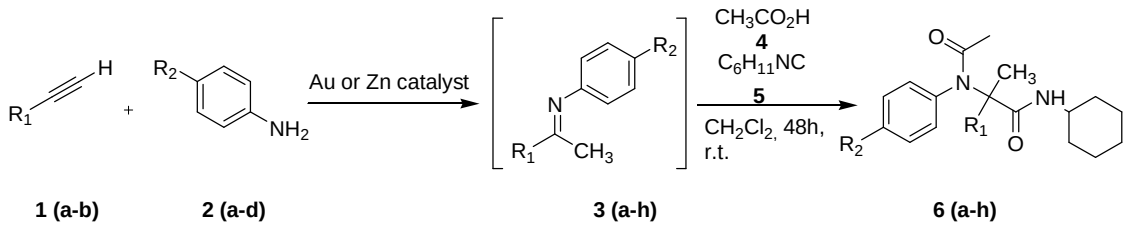
[a.] L= 2,6-Diisopropylphenol

Mizushima and co-workers have been studying extensively the homogeneous catalysis by gold complexes, and found that gold (I) complexes, in conjunction with acidic promoters, catalyze the hydroamination of alkynes in excellent yields.[18] Reacting phenylacetylene (**1a**) and 4-bromoaniline (**2b**) in the presence of $(PPh_3)AuCH_3$ (0.1% mol) and triflic acid (1% mol) in solvent-free conditions led to a conversion of 37% (Table 1, entry 10); when phosphotungstic acid hydrate was used as an

acidic promoter the conversion to the corresponding imines was 50% for *p*-anisidine (**2a**), 40% for *p*-methyl aniline (**2c**) and almost quantitative for 4-bromo aniline (**2b**) 95% (Table 1, entries 12, 13 and 11, respectively). 4-Bromoaniline (**2b**) was also reacted with 1-hexyne (**1b**), to give a conversion of 60% (Table 1, entry 15), and 4-nitroaniline (**2d**) was reacted with both phenylacetylene (**1a**) and 1-hexyne (**1b**), leading to 65% and 85%, respectively (Table 1, entries 14 and 18).

Having determined the conditions for converting the test alkynes and amines to the corresponding imines, a series of one-pot Ugi MCR reactions were performed, as described in the next section. It has to be remarked that some precedents deal with the Ugi processes with preformed imines, [19,20] and that the ketimines are considerably less reactive than the corresponding aldimines.

Remarkably, the Ugi-like 4CR with alkynes, anilines, isocyanides and carboxylic acids were not successful, and we were not able to detect any adduct neither the intermediate imines. Presumably the isocyanide was efficiently trapped by the metal cations through complexation and therefore no productive reactions were allowed. The tandem procedure for the Ugi MCR was carried out in the following manner: the selected amines and alkynes were reacted in the presence of either the zinc or gold catalysts (to achieve the best conversion yields) to the corresponding imines, and then the crude mixtures were treated then with cyclohexyl isocyanide (**5**) and acetic acid (**4**).



1 (a-b) **2 (a-d)** **3 (a-h)** **6 (a-h)**

Table 2. One-pot Ugi procedure for the synthesis of acylaminoamides structure **6**.

ENTRY	R_1	R_2	YIELD
1	C_6H_5	OCH_3	28%
2	C_6H_5	CH_3	12%
3	C_6H_5	Br	48%
4	C_6H_5	NO_2	10%
5	$^nC_4H_9$	OCH_3	15%
6	$^nC_4H_9$	CH_3	9%
7	$^nC_4H_9$	NO_2	15%
8	$^nC_4H_9$	Br	43%

Following the standard protocols for the Ugi MCR, the crude reaction mixtures containing the imines, synthesized from phenylacetylene and either *p*-anisidine or 4-bromo aniline were treated with cyclohexyl isocyanide and acetic acid in a variety of solvents, including toluene (at 70 ºC and at the

refluxing temperature) methanol and ethanol (at room temperature), furnishing the Ugi bis-amide adducts in yields between 2% and 25%.

By performing the reactions in dichloromethane at room temperature it was possible, in some cases, to increase the overall yields, as shown in Table 2. Both electron rich and electron deficient anilines were used, as well as aromatic and aliphatic alkynes, in order to assess the reactivity of the intermediate imines in the Ugi MCR. The preliminary results show the yields to be varying in the range of 9%-48% conversion (Table 2).

In conclusion, we have developed a tandem sequence involving the hydroamination of alkynes with anilines followed by the interaction of the resulting imine with isocyanides and carboxylic acids. The process could be conveniently carried out without isolation of the intermediate imine and, although in moderate yields, leads to the corresponding Ugi adduct using alkynes as carbonyl surrogates.

Experimental Section

Typical procedure for Cu-K-10 catalyzed hydroamination reaction.[9] Synthesis of 4-methoxy-*N*-*(*1-phenylethylidene)benzenamine (**3a**) (entry 7, Table 1): phenylacetelene (**1a**, 241 mg, 2.0 mmol) and *p*-anisidine (**2a**, 200 mg, 2.0 mmol) were added to suspension of Cu-K-10 (73 mg) in toluene (1.5 mL). The resulting mixture was heated to reflux for 16 h under an atmosphere of nitrogen in a sealed tube. The reaction mixture was then cooled, filtered through Celite® to remove the Cu-K-10 catalysts and the filtrate concentrated under reduced pressure. The resulting material was then purified by crystallization from a mixture of *n*-pentane/ethyl acetate, furnishing the desired product (**3a**) as red crystals in 60% yield; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.98-7.94 (m, 2H), 7.46-7.40 (m, 2H), 6.91 (d (AB system), 2H, ^{3}J= 8.8), 6.75 (d (AB system), 2H, ^{3}J= 8.8), 3.82 (s, 3H), 2.25 (s, 3H). These data are in good agreement with literature values.[21]

Typical procedure for $Zn(OTf)_2$ or $(Ph_3P)AuCH_3$ catalyzed hydroamination reaction.[8] Synthesis of 4-methoxy-*N*-(1-phenylethylidene)benzenamine (**3a**) (entry 4-6 and 12, Table 1). Phenylacetylene (**1a**) (120 mg, 0.98 mmol) and *p*-anisidine (**2a**) (210 mg, 0.98 mmol) were mixed under an atmosphere of nitrogen in a reaction tube, and the catalyst immediately added. The tube was sealed and the resulting mixture was stirred at 60 ºC for 16 h. The reaction mixture was then cooled to room temperature, diluted with diethyl ether and filtered through a plug of silica gel. The solvent was removed under reduced pressure and the residue used in next step without any further purification.

Typical procedure for Ugi MCR reaction: Synthesis of *N*-cyclohexyl-2-(*N*-(4-methoxyphenyl)acetamido)-2-phenylpropanamide (**6a**) (entry 1, Table 2). The crude mixture obtained in the previous step (**3a**) was dissolved in dry dichloromethane under an atmosphere of nitrogen. Acetic acid (**4**, 59 mg, 0.98 mmol) and cyclohexylisocyanide (**5**, 89 mg, 0.81 mmol) were added and the resulting mixture was stirred at room temperature under nitrogen for 48 h. The solvent was then the removed under reduced pressure and the resulting material purified by column chromatography, eluting

with hexane/ethylacetate (80/20), to furnish the desired product *N*-cyclohexyl-2-(*N*-(4-methoxyphenyl)acetamido)-2-phenylpropanamide (**6a**) as a brown oil in 28% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.45-7.41 (m, 2H), 7.39-7.33 (m, 2H), 7.31-7.26 (m, 2H), 7.00 (dd, 1H, $^{2,3}J$= 2.6, 8.6), 6.92 (dd, 1H, $^{2,3}J$= 2.9, 8.6), 6.82 (dd, 1H, $^{2,3}J$= 2.9, 8.6), 6.61-6.54 (m, 1H), 3.91-3.83 (m, 1H), 3.81 (s, 3H), 1.98-1.86 (m, 2H), 1.85 (s, 3H), 1.70-1.50 (m, 4H), 1.42-1-30 (m, 5H), 1.22-1.08 (m, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz) 172.4, 172.2, 159.5, 142.1, 134.0, 131.7, 130.6, 128.6, 127.5, 126.7, 114.6, 114.5, 69.9, 55.6, 48.7, 32.8, 32.7, 29.3, 25.8, 25.2, 24.9, 24.8; main rotamer; LRMS (ES+) (H_2O/CH_3CN 50/50) 811.44 $[2M + Na]^+$ (40%), 417.2156 $[M + Na]^+$ (30%), 395.2346 $[M + H]^+$ (70%), 296.1307 $[M - C_6H_{12}N]^+$ (100%); HRMS (ES+) found $[M + H]^+$ 395.2329, $C_{24}H_{31}N_2O_3$ requires M^+: 395.2346.

Acknowledgements

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