A Microwave-Enhanced, Solventless Mannich Condensation on CuI-Doped Alumina

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Abstract: Terminal alkynes react with secondary amines and *para*formaldehyde to afford Mannich adducts in the presence of cuprous iodide on alumina under microwave irradiation and solvent free conditions.

Key words: Mannich condensation, microwave irradiation, alumina, aminoalkynes

The Mannich reaction is a classic example of a three-component condensation reaction.¹ In general, formaldehyde or (*para*-formaldehyde), an amine, and an "active-hydrogen" component such as an enolizable ketone or terminal alkyne are allowed to react to afford the corresponding β -aminoketone or β -aminoalkyne. The latter Mannich adduct contains at least two potential sites for further modification, the amine and the alkyne.² In addition, β -aminoalkynes have a wide range of applications including use as pharmaceutical intermediates³ and as general synthetic building blocks.⁴

The traditional Mannich methods for synthesizing β -aminoalkynes often require drastic reaction conditions and generally utilize dioxane. The organic solvent and the metal catalyst can be difficult to handle and pose a number of waste handling problems.

We have found alumina to be a particularly useful reagent in organic synthesis because it can be modified in a variety of ways which enhance its reactivity. It also obviates a number of environmental problems.⁵ For example, using a commercially available alumina potassium fluoride mixture to which we added palladium powder, we were able to carry out Suzuki and Sonogashira coupling reactions on a wide variety of aromatic moieties without the use of solvents.⁶

Microwave irradiation of organic reactions has gained in popularity in recent years since it was found to accelerate a wide variety of transformations.⁷ In recent years a number of reports have appeared in which reactants are coated onto surfaces which themselves absorb little or no microwave energy; in these instances, the reactive species absorb the microwave energy but the bulk temperature of the reaction mixture tends to rise only modestly. This results in relatively large energy savings as well as making it possible to carry out reactions in relatively simple glassware, such as open beakers and flasks.⁸

We now wish to report a microwave-enhanced Mannich condensation of terminal alkynes with amines and *para*-

formaldehyde on CuI-doped alumina in the absence of solvents which produces the corresponding aminomethylated adducts in good yields. The process is highly efficient, does not require pre-forming the iminium species, and is not hampered by the heterogeneity of the reaction, Scheme 1.

$$R^{1}C \equiv CH + (CH_{2}O)_{n} + HNR^{2}R^{3} \qquad \frac{CuI/Al_{2}O_{3}}{MW}$$
$$R^{1}C \equiv CCH_{2}NR^{2}R^{3}$$

Scheme 1

The results are summarized in the Table. The data indicate that under microwave irradiation and solvent free conditions, aliphatic and aromatic terminals alkynes react smoothly with iminium species formed in situ in the presence of cuprous iodide and alumina. A variety of secondary amines, such as dibenzylamine, dibutylamine, piperidine, 1-phenylpiperazine and morpholine participate in a reaction with *para*-formaldehyde to afford the desired Mannich adducts.

During the investigation, we found that piperazine reacts with 1-octyne and *para*-formaldehyde (excess) to afford the diaminomethylation adduct. 1,9-Decadiyne reacts with dibutylamine and *para*-formaldehyde (excess) to generate the *bis*-aminoalkyne. Interestingly, benzylamine (a primary amine) was found to react with 1-decyne and *para*-formaldehyde (excess) to produce the *bis*-Mannich condensation product, Scheme 2.

The chemoselectivity of the reaction was investigated. When a mixture of acetophenone and 4-ethynyltoluene served as competitive acidic substrates for the Mannich reaction, only the β -aminoalkyne was formed. As anticipated, the Mannich reaction of 4-acetyl-1-ethynylbenzene generated only the β -aminoalkyne product.

The synthesis of dibenzyl(undec-2-ynyl)amine is representative. Dibenzylamine (0.197 g, 1.00 mmol), and 1-decyne (0.138 g, 1.00 mmol) were added to a mixture of cuprous iodide (0.572 g, 3.00 mmol), *para*-formaldehyde (0.090 g, 3.00 mmol) and alumina (1.00 g) contained in a dry 10 mL round-bottomed flask. The mixture was stirred at room temperature to ensure efficient mixing. The flask was then fitted with a septum (punctured by an 18 gauge

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Table Mannich Condensation of Terminal Alkynes with Amines and para-Formaldehyde

	A 11			$V_{inld}(\sigma_i)^1$
Entry	Аікупе	Amine	Product	1 leld(%)
1	$CH_3(CH_2)_7C \equiv CH$	(C ₆ H ₅ CH ₂) ₂ NH	$(C_6H_5CH_2)_2NCH_2C \equiv C(CH_2)_7CH_3$	90
2	CH ₃ (CH ₂) ₅ C≡CH	(C ₆ H ₅ CH ₂) ₂ NH	$(C_6H_5CH_2)_2NCH_2C \equiv C(CH_2)_5CH_3$	86
3	p -CH ₃ C ₆ H ₄ C \equiv CH	(C ₆ H ₅ CH ₂) ₂ NH	$(C_6H_5CH_2)_2NCH_2C \equiv CC_6H_4CH_3-p$	80
4	C ₆ H ₅ C≡CH	HN	C ₆ H ₅ C≡CCH ₂ N	77
5	F −C≡CH	HNO	$C = CCH_2 N$	63
6	Cl C≡CH	HN_N-	$C = CCH_2 N N - C$	81
7	Br──C≡CH	[CH ₃ (CH ₂) ₃] ₂ NH	$Br - C \equiv CCH_2N[(CH_2)_3CH_3]_2$	2 72
8	CH ₃ (CH ₂) ₇ C≡CH	C ₆ H ₅ NHCH ₃	$CH_3(CH_2)_7C \equiv CCH_2N(CH_3)C_6H_5$	40

¹All yields listed refer to pure isolated products which were characterized by ¹H NMR, ¹³C NMR, MS and Microanalysis.

$$2 CH_{3}(CH_{2})_{5}C = CH + (CH_{2}O)_{n} + HN \qquad NH \qquad \underbrace{Cul/Al_{2}O_{3}}_{MW} CH_{3}(CH_{2})_{5}C = CCH_{2}N \qquad NCH_{2}C = C(CH_{2})_{5}CH_{3}$$
$$HC = C(CH_{2})_{6}C = CH + (CH_{2}O)_{n} + [CH_{3}(CH_{2})_{3}]_{2}NH \qquad \underbrace{Cul/Al_{2}O_{3}}_{MW} [CH_{3}(CH_{2})_{3}]_{2}NCH_{2}C = C(CH_{2})_{6}C = CCH_{2}N[(CH_{2})_{3}CH_{3}]_{2}$$
$$2 CH_{3}(CH_{2})_{7}C = CH + (CH_{2}O)_{n} + C_{6}H_{5}CH_{2}NH_{2} \qquad \underbrace{Cul/Al_{2}O_{3}}_{MW} [CH_{3}(CH_{2})_{7}C = CCH_{2}]_{2}NCH_{2}C_{6}H_{5}$$

Scheme 2

needle to serve as a pressure release valve), placed in the microwave oven (1000 watt, Sharp Model R-4A38) and irradiated at 30% power for 4 min. [Caution: heating volatile materials in commercial microwave ovens for extended periods can be hazardous.] After cooling, ether (4 mL) was added and the slurry stirred at room temperature to ensure product removal from the surface. The mixture was vacuum filtered using a sintered glass funnel and the product purified by flash chromatography to yield 0.312 g of dibenzyl(undec-2-ynyl)amine (90%).

In conclusion a reliable and environmentally benign method for synthesizing β -aminoalkynes has been developed which involves the use of a solvent-free mixture of cuprous iodide and alumina under microwave irradiation conditions. Carbon-carbon and carbon-nitrogen bond formation is highly efficient and does not require pre-forming the iminium species.

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