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Mannich Reactions of a Resin-Bound Terminal Alkyne

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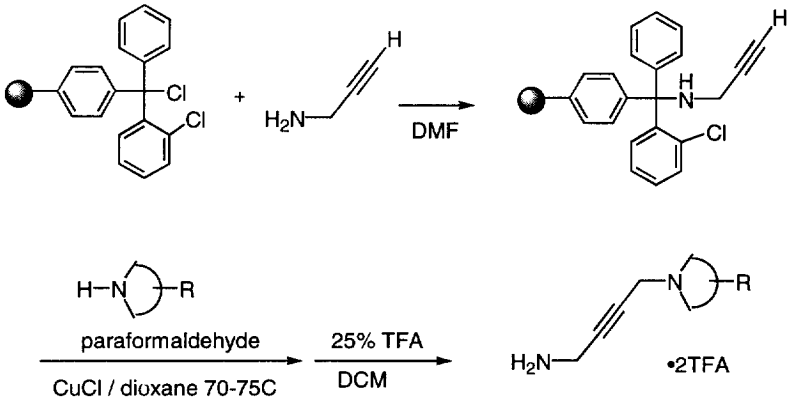
Abstract: Propargylamine was immobilized via reaction with a chlorotrityl resin. This resin-bound terminal alkyne, in the presence of a copper (I) salt, reacted with secondary amines and paraformaldehyde to afford the desired Mannich adducts. Piperazines, piperidines and pyrrolidine were used to prepare compound libraries via solid phase parallel synthesis.

Solid Phase Organic Synthesis (SPOS) is emerging as a revolutionary technology in contemporary medicinal chemistry because it facilitates the preparation of a large number of structurally related congeners in quick fashion. In recent years, many well established organic transformations have been successfully carried out on a solid support; most typically a polystyrene-based resin has been utilized.[1] Alkyne chemistry has been no exception in this regard; for example, a palladium-mediated heteroannulation methodology has been used to synthesize highly functionalized resin-bound indoles.[2] However to date, the use of resin-bound alkynes has been scarce although the Heck coupling to aryl iodides has been described.[3] The alkyne moiety itself has been modified while attached to a solid support. The carbon-carbon triple bond has been reduced[4] or alternatively, terminal alkynes, being dipolarophilic in nature, have reacted with nitrile oxides to form isoxazoles.[5]

In contrast, the application of Mannich chemistry to resin-bound substrates has been meager despite the general utility of this reaction in traditional solution-based organic synthesis.[6] One notable exception is the reaction of polymer-supported silyl enol ethers with putative imine species, formed from a benzaldehyde and an aniline, to produce the corresponding aminomethylated adducts.[7] In this work, the silyl enol ether serves as the active hydrogen component, and the aldehyde and amine are premixed in the presence of the catalyst (scandium triflate), presumably generating the requisite imine in situ.

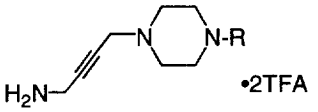
Organic soluble terminal alkynes can also serve as the active hydrogen component in solution-based Mannich reactions. Bis-alkynes have also been shown to undergo Mannich condensation without the need to preform the imine separately.[8] In such cases, a copper (I) salt is typically needed to promote aminomethylation; often such copper (I) species have poor solubility in organic solvents. We report that a resin-bound alkyne undergoes Mannich reactions to yield the corresponding aminomethylated adducts. The process is highly efficient, does not require performing the iminium species, and is not hampered by the heterogeneity of the reaction.

Commercially available 2-chlorotrityl chloride resin was swelled in DMF, propargylamine was added and the heterogeneous reaction was gently stirred for 16 hrs at ambient temperature. After washing[9] to remove excess propargylamine, the resin-bound alkyne was subjected to Mannich aminomethylation: the resin (1 mol equiv.) was swelled in dioxane, and the desired secondary amine (5 mol equiv.) was added followed sequentially by cuprous chloride (1 mol equiv.) and paraformaldehyde (10 mol equiv.). The resultant mixture was capped and heated in a block at 70-75^{0}C with shaking. After 3 hrs, the reaction was allowed to cool and the resin was washed.[10] Cleavage of the desired product from the solid support was readily accomplished by subsequent reaction with trifluoroacetic acid-dichloromethane.[11] The desired Mannich adducts were isolated as waxy TFA salts upon removal of solvents *in vacuo*. Isolated yields demonstrated that the overall conversion to product is typically >90% and HPLC and/or NMR analysis routinely indicated that the final products were >95% pure.



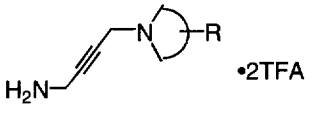
This methodology is general for secondary amines; even the sterically-encumbered 2,2,6,6-tetramethylpiperidine smoothly underwent reaction. In addition, a variety of functional groups such as ketones, esters, amides, nitriles, alcohols and ethers, as well as various heterocyclic systems, were demonstrated to be compatible under the reaction conditions (Tables 1-2). The products are useful synthetic intermediates for the preparation of potential therapeutic agents such as muscarinic receptor ligands.

Table 1: Mannich Adducts Derived from Paraformaldehyde and Piperazines



R: aryl	Purity: HPLC	M+H+	R: heterocyclic	Purity: HPLC	M+H+	R: others	Purity: HPLC	M+H+
Ph[9-11]	>95%	230	2-pyridyl	>95%	231	-CH_2Ph	>95%	244
2(CN)Ph	>95%	255	4-pyridyl	>95%	231	-CH_2(3-Me)Ph	>95%	258
2(OMe)Ph	>95%	260	2-(3-CF_3)pyridyl	>95%	299	-$CHPh_2$	>95%	320
2-MePh	>95%	244	2-(5-CF_3)pyridyl	>95%	299	-CHPh(4-ClPh)	>95%	354
2,6-Me_2Ph	>95%	258	2-(3-Cl,5-CF_3)pyr.	>95%	333	-CH(4-FPh)2	>95%	356
3-ClPh	>95%	264	2-pyrazinyl	>95%	232	piperonyl	>95%	288
3-MePh	>95%	244						
3-CF_3Ph	>95%	298					Purity:	
3,4-Cl_2Ph	>95%	298					NMR	M+H+
3,5-Cl_2Ph	>95%	298				-CO_2Et	>90%	226
4-FPh	>95%	248				-CH_2CH_2OH	>90%	198
4-MePh	>95%	244				-CH_2C(O)NH*i*Pr	>90%	253
4(NO_2)Ph	>95%	275				-CHO	ca.60%	182
4-CF_3Ph	>95%	298				-CH_2C(O)morpholinyl	>90%	281
4-AcPh	>95%	272						

Table 2: Mannich Adducts Derived from Paraformaldehyde and Piperidines or Pyrrolidine



amine type	R	Purity	M+H+
pyrrolidine	---	>90% (NMR)	139
piperidine	---	>90% (NMR)	153
piperidine	4-Ph	>95% (HPLC)	229
piperidine	4-CH_2Ph	>95% (HPLC)	243
piperidine	3,5-Me_2	ca.70% (NMR)	181
piperidine	2,2,6,6-Me_4	>90% (NMR)	209
piperidine	4-N-piperidinyl	>90% (NMR)	236
piperidine	4-CO_2Et	>90% (NMR)	225
piperidine	4-OH	>90% (NMR)	169
piperidine	4-Ph-4-OH	>95% (HPLC)	245
piperidine	4-(4ClPh)-4-OH	>95% (HPLC)	279
piperidine	4-Ac-4-Ph	>95% (HPLC)	271

In conclusion, we report the first demonstration of Mannich chemistry on a resin-bound alkyne. The reaction appears to be general as evident by the diversity of the compounds that were synthesized using this methodology.

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9. Into a dry 500 ml round-bottom flask was placed 2-chlorotrityl chloride resin (14.35 g, 1.04 mmol/g, 14.9 mmol, 1 equiv.), DMF (200 ml) and a stir bar. Propargyl amine (20.0 ml, 292 mmol, approx. 20 equiv.) was added via syringe and the mixture was gently stirred for 16 hrs. The reaction was filtered through a fritted glass funnel and the resultant resin was washed: DMF (4 x 300mL), THF (3 x 300mL) and DCM (4 x 300mL). The resin was dried *in vacuo* and used in the subsequent steps. A small portion of the resin was cleaved with 25% TFA/DCM (v/v) and the solvents were removed *in vacuo* to give a white powder; NMR of this material was indistinguishable from authentic propargyl amine TFA salt.

10. A typical experimental protocol is described: The resin-bound propargyl amine from above (0.104 g, 1.02 mmol/g {theoretical}, 0.106 mmol {theoretical},1 equiv.) was placed into a screw capped fritted glass reaction vessel and dioxane (4 mL) was added. Phenylpiperazine (0.10 ml, 0.65 mmol, 6 equiv.) was added followed by solid copper(I) chloride (0.012 g, 0.12 mmol, ca. 1 equiv.) and lastly paraformaldehyde (0.036 g, 1.2 mmol, 10 equiv.). The reaction vessel was capped and placed in a dri-block heater pre-heated to about 75°C. The reaction was shaken for approximately 3 hours. The mixture was cooled and the liquid was pulled off under a gentle vacuum. The resin was washed: 3 x 10mL DMF, 3 x 10mL 5% Aq. HOAc, 3 x 10mL DMF, 3 x 10mL 7M Aq. NH_4OH, 3 x 10mL DMF and 4 x 10mL DCM.

11. Cleavage of the product from the resin was accomplished by reaction with 25%TFA/DCM (v/v) (6 mL) for 1 minute followed by washing with DCM (3 x 2mL). The solvents were removed *in vacuo*. DCM (2 mL) was added and then removed *in vacuo* to afford a waxy tan solid. NMR (CD_3OD): δ 7.30 (t, 2H), 7.05 (d, 1H), 6.96 (t, 2H), 4.28 (s, 2H), 3.97 (s, 2H), 3.45-3.60 (m, 8H). The identity and purity of every final product was determined by NMR and MS or HPLC and MS. Nuclear Magnetic Resonance spectra were obtained on a Bruker AC-300SB FT-NMR equipped with a 5 mm $^1H/^{13}C$ dual probe using DMSO-d_6 or CD_3OD for fixed frequency lock and chemical shift; HPLC were obtained on a Hewlett Packard HP1050 using a gradient (10:90 to 90:10) of acetonitrile/water with 0.1% trifluoroacetic acid as eluent and UV detection at either 217 nM or 220 nM; Mass spectra were obtained on a Micromass Platform II using electospray ionization and probe = 4.0 kV or on a Hewlett Packard HP5989 MS Engine using particle beam chemical ionization with ammonia as reagent gas.

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