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One pot Synthesis of Propargylamines using Solid-Phase Extractive Isolation

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Abstract. A library of 42 diverse propargylamines was prepared using a parallel solution phase synthesis approach. The compounds resulting from the Mannich reaction of acetylenes, paraformaldehyde and secondary amines in the presence of copper(I)-chloride were purified by Solid Phase Extraction.

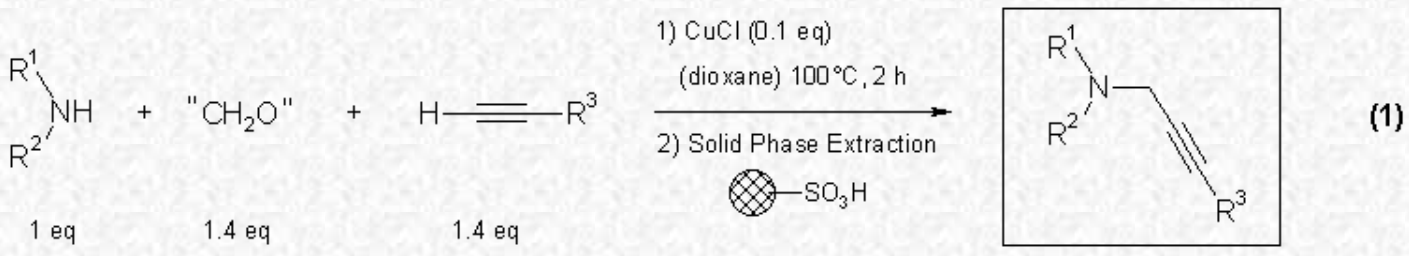
***Key words**:* propargylamines, Mannich reaction, library, Solid Phase Extraction

Propargylamines are a common feature in drugs, such as muscarinic agonists/antagonists (Oxotremorin, Oxybutynin) [1a,b][a,b] or MAO-B inhibitors [1c]. They are also useful intermediates for the preparation of potential therapeutic agents. The Mannich reaction of acetylenes, aldehydes and secondary amines represents a powerful reaction for the construction of propargylamines, and large numbers of these starting materials are commercially available or readily accessible. There are however, few reports harnessing the Mannich reaction for compound library synthesis and these reports exclusively employ solid-phase synthesis methodology [2] .

Today Solid Phase Extraction (SPE) is widely used for the purification of small compound libraries synthesized in solution [3]. Compared to preparative HPLC purification or parallel silica-gel chromatography, for example, this technique offers advantages in both equipment costs and time, for the synthesis of compound libraries. Reaction mixtures from parallel synthesis can easily be purified in a parallel fashion with commercially available disposable cartridges and a vacuum manifold.

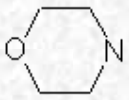
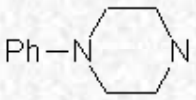
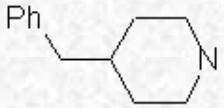
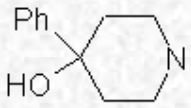
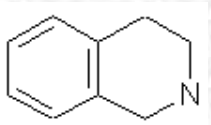
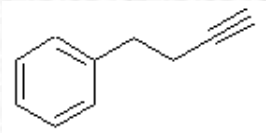
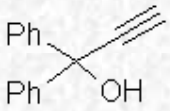
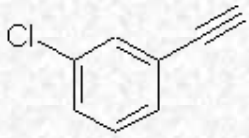
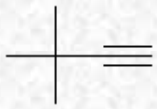
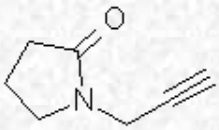
In this communication we report on the purification of propargylamines resulting from a Mannich reaction of acetylenes, paraformaldehyde, secondary amines and catalytic amounts of copper(I) chloride by SPE [4]. Acetylenes and amines were chosen to explore the scope of the reaction and to assemble a range of diverse products. All reactions produced the desired compounds, and no aqueous work-up is necessary. Using Varian SCX cartridges (containing a silica supported ethylbenzenesulfonic acid) on a Varian 20 Vac Elut manifold [5] enables 20 reaction mixtures to be purified in parallel. All compounds prepared could be isolated with moderate to good yields (average ca. 59%) and good purity (ca. 89%, Eq. 1, Table 1). Excess non-basic starting materials, which were used to drive the reaction to completion were easily separated from the basic products. We believe this clearly demonstrates the superiority of the SPE technique compared to the classical isolation of Mannich products. The propargylamine library was analyzed by ion-spray MS and HPLC [6].

Further investigations using Solid Phase Extraction as an effective tool for the purification of chemical libraries synthesized in solution are in progress.



(1)

Table 1: Mannich Adducts after SPE Purification: isolated yield (purity)

Amine / Acetylene						
	77 (100)	25 (100)	57 (100)	49 (99)	59 (90)	58 (96)
	61 (100)	33 (65)	72 (100)	43 (92)	44 (68)	58 (67)
	69 (100)	30 (100)	90 (100)	89 (100)	77 (100)	70 (100)
	47 (100)	26 (54)	21 (89)	34 (91)	54 (85)	57 (87)
	64 (100)	97 (96)	57 (93)	74 (92)	85 (92)	72 (78)
	26 (99)	46 (45)	63 (94)	99 (94)	93 (87)	70 (88)
	39 (100)	13 (86)	86 (72)	98 (56)	61 (92)	30 (90)

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References and Notes

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[4] *Synthesis:* To a solution of the amine (0.5 mmol) in dioxane (3 ml) paraformaldehyde (0.7 mmol), CuCl (0.05 mmol) and the acetylene (0.7 mmol) were added. After 10 min stirring at room temperature the mixture was heated for 2 h at 100^{O}C and cooled down to room temperature. *Purification:* 1) commercially available Varian SCX columns (1 g, 0.7 mmol ion exchange material, installed on a Varian 20 Vac Elut manifold) were pre-conditioned with 10 ml methanol. 2) the reaction mixtures were put onto these columns. 3) the non-basic material was washed off the columns with 2 times 5 ml methanol, 4) the products were eluted using 1 mol/l NH_3 solution in methanol. 5) the solvent was evaporated to yield the Mannich products.

[5] Varian™ Sample Preparation Products, see: www.varianinc.com/spp/index.html

[6] YMC-Column ODS-AQ 50 x 4,0 mm, gradient acetonitrile/water, diode array detector, 220 nm

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