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METHYLATION OF NON-ACIDIC ALCOHOLS OF ALKALOIDS WITH TMS-DIAZOMETHANE: CONVERSION OF CODEINE TO CODEINE-6-METHYL ETHER

Christopher W. Cunningham, Linn N. Thatcher, and Andrew Coop*

Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, 20 Penn Street, Room 637, Baltimore, MD 21201, USA

Abstract – Trimethylsilyldiazomethane (TMS-CHN_2) is a convenient agent for the methylation of acidic alcohols, and is known to methylate non-acidic alcohols in CH_2Cl_2 by the addition of HBF_4. Herein, we show that silica gel acts as a suitable alternative for alkaloids, without causing precipitation of the salt from the reaction mixture.

INTRODUCTION

As part of our studies into analogues of opioids with reduced dependence potential, we required a convenient synthesis of codeine-6-methyl ether (**2**) from codeine (**1**) (Figure 1). The methylation of alcohols is an important synthetic step, both for the synthesis of target molecules and for the protection of alcohols,[1] and one commonly employed method is the Williamson ether formation, where the alcohol (or alkoxide) is treated with methyl iodide or dimethylsulfate.[1] The application of such methods to alkaloids often results in significant quaternization of the basic nitrogen, and we found that application of the published conditions of KH followed by MeI and $NaOEt$[2,3] to **1** did not give reliable yields of **2** in our hands. Our recent studies using the safe diazomethane substitute, trimethylsilyldiazomethane (TMS-CHN_2), to methylate phenolic hydroxyls of opioids,[4] led us to consider the application of this reagent to the methylation of the 6-alcohol of codeine and thus remove the need for the hazardous KH and toxic MeI. TMS-CHN_2 methylates acidic alcohols rapidly,[5] but the use of HBF_4 is required to methylate non-acidic alcohols.[6] The application of this procedure to alkaloids has been limited due to the fact that CH_2Cl_2 is the solvent of choice, and the resulting salts would be anticipated to have low solubility in the CH_2Cl_2 portion. As anticipated, the use of this procedure on **1** resulted in less than 5% conversion. As the methylation of alcohols with diazomethane can also be promoted with acids including silica gel,[7] we considered that silica

gel may promote the reaction of TMS-CHN_2 with codeine, without causing precipitation from the organic solvent.

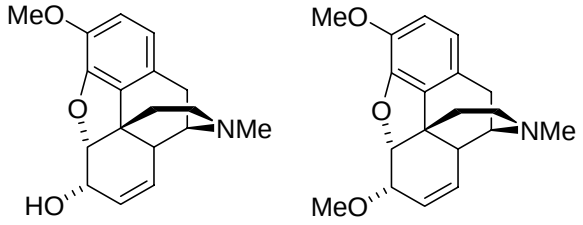

Figure 1. Structures of codeine and codeine-6-methyl ether

RESULTS AND DISCUSSION

A range of conditions were studied for the conversion of **1** to **2** with a reaction time of 4 days, and are summarized in Table 1. Initial studies using HBF_4 as the acid resulted in less than 5% yield, suggesting that the less acidic silica gel would promote the reaction without forming an insoluble salt with **1**. Initial studies (entries 1-5) showed that using CH_2Cl_2 as the solvent gave a superior yield of **1**:**2** compared to all other solvents under similar conditions.[8] This is consistent with the studies with HBF_4, where CH_2Cl_2 was the preferred solvent.[6] The solvent system used for the methylation of phenols[5] (entry 1) gave the lowest yield. All subsequent reactions were therefore studied using CH_2Cl_2 (entry 5). Reducing the number of equivalents of TMS-CHN_2 (entry 6) gave diminished results, however increasing the number of equivalents to 40 (entry 8) gave a negligible change in yield. Administration of 10 equivalents of TMS-CHN_2 per day following 1-2 drops of water on days 2-4 (entry 7) resulted in a much improved yield. Subsequent reactions followed this procedure. Entries 9 and 10 show a greatly diminished yield of product when the number of equivalents of silica is reduced. Removing all silica from the reaction led to a very low yield of product, demonstrating its importance to the reaction (entry 9). Increasing the temperature had a negative effect on yield (entry 11). Column chromatography gave an isolated yield of 63% of **2** using the conditions presented in entry 7. Thus, silica gel promotes the methylation of the non-acidic alcohol of codeine with TMS-CHN_2, and presents a safe and viable approach for the methylation of alcohols in alkaloids.

Table 1. Conditions and yields for the methylation of **1** to **2**.

Entry	Solvent	Equiv. TMS-CHN_2	Equiv. Silica[a]	Temperature (ºC)	NMR Yield of **2** (%)[b]
1	CH_3CN:MeOH, 9:1	10	10	RT	15
2	THF	10	10	RT	34
3	CH_3CN	10	10	RT	37

4	Et_2O	10	10	RT	50
5	CH_2Cl_2	10	10	RT	59
6	CH_2Cl_2	1.1	10	RT	43
7	CH_2Cl_2	10 / day[c]	10	RT	75[d]
8	CH_2Cl_2	40	10	RT	58
9	CH_2Cl_2	10 / day[c]	0	RT	19
10	CH_2Cl_2	10 / day[c]	3	RT	46
11	CH_2Cl_2	10 / day[c]	10	Reflux	47

[a]Weight equivalents; [b]Yield based on ratio of product (**2**) to starting codeine (**1**); [c]10 Equivalents of TMS-CHN_2 on day 1, 1-2 drops of water followed by 10 equivalents of TMS-CHN_2 on days 2-4. [d]Isolated yield (63%).

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8. Ratios determined by ^{1}H NMR.
9. **Optimized reaction for the conversion of 1 to 2**: A mixture of anhydrous codeine (**1**) (100 mg, 0.334 mmol), silica gel (ICN SiliTech 32-63, 60Å) (1.0 g, 10 eq), and TMS-CHN_2 (2.0 M, 1.67 mL, 10 eq) in CH_2Cl_2 (10 mL) was stirred for 4 days under an atmosphere of nitrogen. On days 2-4, 1-2 drops of water were added, follwed by an additional 1.67 mL (10 eq) TMS-CHN_2. The reaction was quenched with water, and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2, the combined organic layers dried (Na_2SO_4) and evaporated under reduced pressure. Column

chromatography (silica gel, 5% methanol/CH_2Cl_2) gave **2** (66.0 mg, 63.0 %). The identity of the product was confirmed through comparison to an authentic sample made via the published procedure.[2]