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Rapid $Mo(CO)_6$ catalysed one-pot deoxygenation of heterocyclic halo-benzyl alcohols with Lawesson's reagent

Xiongyu Wu, A. K. Mahalingam and Mathias Alterman*

Organic Pharmaceutical Chemistry, Department of Medicinal Chemistry, BMC, Uppsala University, PO Box 574, SE-751 23 Uppsala, Sweden

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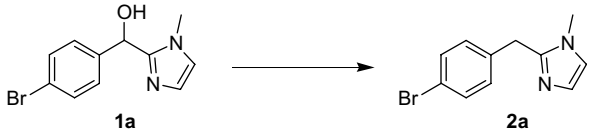
Abstract—A fast and efficient microwave promoted one-pot method for deoxygenation of heterocyclic halo-benzyl alcohols has been developed. The method does not cause dehalogenation of the substrates and provides the deoxygenated products in high yield after only 30 min.

Methods for selective replacement of hydroxyl groups by hydrogen atoms are important in organic chemistry.[1] Numerous methods have been developed for the deoxygenation of alcohols.[1–9] Ionic reactions for deoxygenation of alcohols have been reported,[8,3] but the most frequently used method is the radical Barton–McCombie deoxygenation.[9] Although many hydrogen donors and radical carriers such as silanes, dialkyl phosphites and hypophosphorous acid have been used as replacements for the toxic organotin hydride the deoxygenation method requires two steps, which results in tedious derivatisation of the hydroxyl compound. In addition, the Barton–McCombie method is also known to cause dehalogenation.[5] We here describe a fast and chemoselective $Mo(CO)_6$ catalysed one-pot deoxygenation method with Lawesson's reagent.

In an ongoing medicinal chemistry program[10,11] we were interested in obtaining *p*-halo-benzyl heterocycles. Thus, to access these structures we synthesised the secondary alcohol **1a** from the corresponding aldehyde, which after deoxygenation should provide the target compound **2a** (Scheme 1).[12] Initially we applied TFA/$NaBH_4$[8] and H_3PO_2/I_2[3] as deoxygenation reagents, but neither of these methods were able to give the deoxygenated product **2a**. Also the Wolf–Kishner[13] reduction of the corresponding ketone failed to give compound **2a**. We therefore focused on applying the two-step Barton–



Scheme 1.

McCombie method.[9] The *S*-methyldithiocarbonate derivative of **1a** was first synthesised in good yield. Tributyltin hydride with AIBN as radical initiator was applied to achieve the deoxygenation. After a reaction time of 24 h the deoxygenated compound **2a** was isolated in a modest 20% yield. This unsatisfying result encouraged us to search for a more efficient method for deoxygenation of heterocyclic halo-benzyl alcohols.

Alper and Blais[14,15] and Luh and Wong[16] have reported the use of $Mo(CO)_6$ as a convenient reagent for cleavage of carbon–sulfur bonds, using an ethereal solvent as hydrogen donor.[17,18] Since, thiols are easily prepared from their corresponding alcohols with Lawesson's reagent[19] we were interested in evaluating if these two reagents could be combined to give a one-pot deoxygenation reaction suitable for our purposes. To increase the speed of the reaction we decided to use controlled microwave heating as the energy source.[20]

The first attempt was performed by adding 0.5 equiv of Lawesson's reagent and 0.5 equiv of $Mo(CO)_6$ to compound **1a** in dioxane. The reaction mixture was thereafter heated in a microwave cavity[21] at 170 °C for

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* Corresponding author. Tel.: +46 18 471 4905; fax: +46 18 471 4474; e-mail: mathias@orgfarm.uu.se

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Table 1. Optimisation of the deoxygenation of compound **1a**[a]

Entry	$Mo(CO)_6$ (equiv)	Lawesson's Reagent (equiv)	Temperature (°C)	Isolated yield (%)
1	0.5	0.5	170	70
2	0.5	0.25	170	48
3	0.05	0.5	170	75
4	0.05	0.5	180	73
5	0.05	0.5	160	64
6	0.1	0.2 P_2S_5	180	51
7	0	0.5	170	0
8	0.05	0	170	0

[a] Reaction time 30 min.

30 min. The alcohol **1a** was fully consumed and the deoxygenated compound **2a** was obtained in a 70% yield (Table 1, entry 1). By reducing the amount of Lawesson's reagent (0.25 equiv), full conversion was not achieved and consequently the isolated yield of compound **2a** was decreased (entry 2). Systematic reduction of the amount of $Mo(CO)_6$ used in the reaction revealed that a catalytic amount (5 mol %) was enough for the process to proceed to completion (entry 3). Increasing the reaction temperature to 180 °C did not improve the outcome of the reaction, and with lower temperature (160 °C) full conversion of the alcohol was not achieved (entries 4 and 5). We also applied P_2S_5 as an alternative to Lawesson's reagent (entry 6). With P_2S_5 the reaction gave full conversion, but unfortunately insoluble solids were formed in the reaction mixture. This problem could be the reason for the low isolated yield (51%). To examine if both the reagents were necessary for the deoxygenation, one reagent at a time was excluded from the reaction. Neither of the reactions in the absence of $Mo(CO)_6$ or Lawesson's reagent gave the deoxygenated product (entries 7 and 8).

To examine the scope and limitations of this microwave promoted deoxygenation method, a series of heterocyclic *p*-halo-benzyl alcohols were selected for evaluation. The results are presented in Table 2. In the initial exper-

Table 2. One-pot deoxygenation with Lawesson's reagent and $Mo(CO)_6$[a]

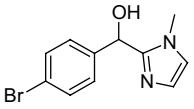
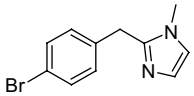
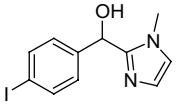
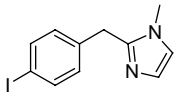
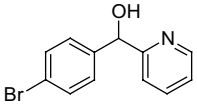
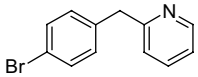
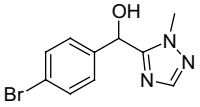
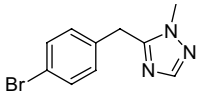
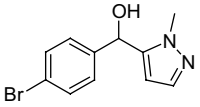
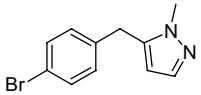
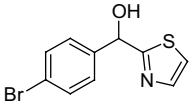
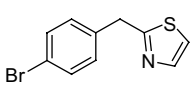
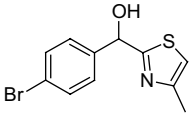
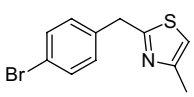
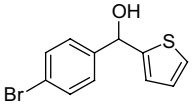
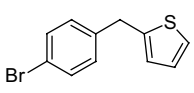
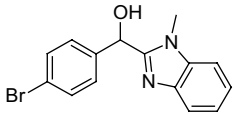
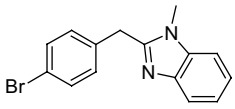
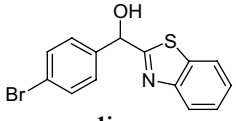
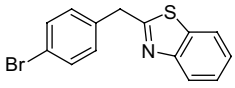
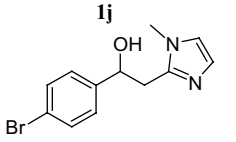
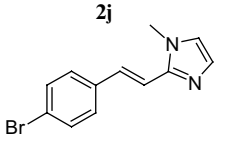
Entry	Alcohol	Product	Isolated yield (%)
1	 **1a**	 **2a**	75
2	 **1b**	 **2b**	78
3	 **1c**	 **2c**	80
4	 **1d**	 **2d**	52
5	 **1e**	 **2e**	46[b]
6	 **1f**	 **2f**	74
7	 **1g**	 **2g**	84
8	 **1h**	 **2h**	15[c]

Table 2 (*continued*)

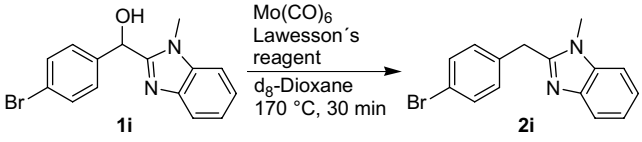
Entry	Alcohol	Product	Isolated yield (%)
9	 **1i**	 **2i**	95
10	 **1j**	 **2j**	93
11	 **1k**	 **2k**	81

[a] 0.5 mmol Alcohol, 0.05 equiv $Mo(CO)_6$, 0.5 equiv Lawesson's reagent, 2.5 mL dioxane, microwave heating: 170 °C, 30 min.
[b] 0.3 equiv $Mo(CO)_6$.
[c] Dimerised product was isolated in 30% yield.

iment it was demonstrated that bromides were not affected by the deoxygenation method, we therefore wanted to investigate an iodide substrate (entry 2). The more reactive iodide remained intact and the deoxygenated product was obtained in a good yield. The pyridine derivative (entry 3) was also a good substrate for the deoxygenation reaction, but the triazole compound gave a moderate 52% yield (entry 4). When applying the pyrazole as substrate (entry 5), full conversion was not initially achieved. The amount of $Mo(CO)_6$ was therefore increased to 0.3 equiv and full conversion was then obtained, affording the corresponding deoxygenated compound in 46% yield.

Introduction of sulfur to the heterocycle did not have a negative impact on the yield, and the two thiazoles **2f** and **2g** were obtained in good yields (entries 6 and 7). With the electron rich thiophene substrate the result was very poor (15%), due to a competing dimerisation reaction that could not be suppressed. Both benzoimidazole **1i** and benzothiazole **1j** gave excellent yields of the corresponding deoxygenated compounds (entries 9 and 10). The substrate in entry 11 possessed an extra CH_2 next to the alcohol, resulting in the formation of the olefinic product derived from abstraction of the β-hydrogen.

In the experiment without Lawesson's reagent (Table 1, entry 8) it was confirmed that the reaction proceeds via the thiol. We have also shown that $Mo(CO)_6$ was necessary for the reaction to give the dethio product (Table 1, entry 7). The suggested mechanism for desulfurisation with $Mo(CO)_6$ is via radical formation.[16] The radical mechanism hypothesis was supported by the formation of the dimeric product from the thiophene substrate (Table 2, entry 8). It is known that the α-hydrogen of ethereal solvents can be abstracted by a radical species.[17,18] To investigate the source of hydrogen in the desulfurised product we used dioxane-d_8 in the reaction with compound **1i** under the described conditions



Scheme 2.

(Scheme 2). In this reaction no incorporation of deuterium was found in the product **2i** (determined by NMR and MS). This suggests that the source of hydrogen is from the thiol or the initial hydroxyl group.

In summary, a fast microwave promoted deoxygenation reaction utilising $Mo(CO)_6$ and Lawesson's reagent has been developed. The method provides a simple one-pot reaction for the direct removal of hydroxyl groups without isolation of intermediate derivatives. The reaction does not cause dehalogenation and is suitable for nitrogen-containing substrates.

General procedure: A process vial (5 mL) was charged with **1** (0.5 mmol), $Mo(CO)_6$ (6.6 mg, 0.025 mmol), Lawesson's reagent (50.5 mg, 0.25 mmol) and dioxane (2.0 mL). The vessel was exposed to microwave heating for 30 min at 170 °C. The reaction tube was thereafter cooled to room temperature and the solvent was removed under vacuum. The crude product was purified on an aluminium oxide column with 2:8–3:7 acetone–hexane to give compounds **2a**–**g**,**i**–**k**. Compound **2h** was adsorbed on aluminium oxide and purified with 5:95 ethyl acetate–hexane.

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Supplementary data

NMR-data of all new compounds are provided in the supplementary data file. Supplementary data associated with this article can be found, in the online version at, 10.1016/j.tetlet.2005.01.012.

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21. The microwave heating was performed in a single mode cavity, Smith Synthesizer (Personal Chemistry AB, Uppsala, Sweden), producing controlled irradiation at 2450 MHz.