Short Communication: A Novel Synthesis of 3,4-Methylenedioxyphenyl-2-propanone (MDP2P) from Helional.

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Abstract

Helional was found to form enamines with a number of secondary amines which, when oxidised, readily and cleanly produced MDP2P.

In late 2015, chemists from QHFSS attended a clandestine laboratory suspected of using helional to manufacture 3,4–methylenedioxyamphetamine (MDA) via the "twodogs" method. Analysis of the chemicals and reaction residues confirmed MDA had been produced by this route. After further investigation it also became apparent that MDMA had been produced from MDP2P at the site however the method by which this substance had been made was unclear. Following an examination of the suspects handwritten notes, it appeared likely a synthesis of MDP2P from helional was being attempted (refer to Figure 1). Based on the chemicals and equipment seized and the information derived from the notes, an hypothesis was formed that the production had been carried out in three steps; production of proline methyl ester **2**, the reaction of helional **1** with the proline methyl ester to form an enamine intermediate **3**, and the subsequent oxidation of the enamine intermediate to MDP2P **4**.

As this pathway to MDP2P has not previously been reported in the literature, a series of trial reactions were carried out to test the hypothesis. Processes and materials used were based on those

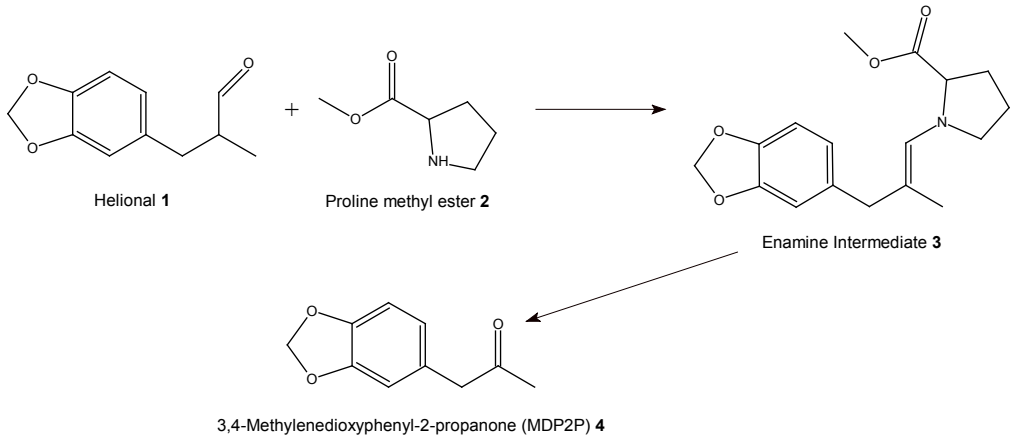

Figure 1: Synthesis of MDP2P from helional

believed to have been employed by the clandestine laboratory operator. The work carried out to date has been to establish proof of concept only; consequently the reactions are yet to be optimised.

Preliminary work has also been conducted to investigate the viability of substituting other secondary amines into the production scheme.

METHODS AND MATERIALS

All reagents and solvents were purchased from commercial sources and were used without further purification.

General method for the formation of enamine intermediates [1, 2].

Helional was dissolved in either chloroform or dichloromethane containing activated molecular sieves. The secondary amine was also dissolved in the same solvent and added to the helional solution. The mixture was stirred for several hours at room temperature. After this time, the molecular sieves were removed and in most cases the reaction solution was transferred directly to the oxidisation step with no further preparation. In the instances where a change of solvent was necessary, the dichloromethane was evaporated under reduced pressure to leave the crude enamines as clear to pale yellow viscous oils.

Alternative method for the formation of enamine intermediates [1, 3].

Azeotropic distillation conditions were also applied in enamine formation where the boiling point of the secondary amine under examination permitted. A reaction vessel fitted with a Dean and Stark head was charged with a solution of helional in toluene and brought to gentle reflux. The secondary amine was dissolved in toluene and added slowly and the mixture held at reflux until no more water collected in the trap. The solution was cooled then either stripped of toluene to effect a solvent change, or subjected directly in toluene to the oxidation process.

Oxidation of enamine intermediates [3-5].

The enamine intermediates were variously dissolved in dichloromethane, chloroform, toluene or in one instance, methanol. A small amount of copper (I) chloride was added to the organic solvent and the solution transferred to a sealed vessel fitted with a stirring device. A balloon containing oxygen was attached so as to maintain a slight positive pressure within the reaction vessel. The mixture was then stirred and monitored by GCMS until it was judged to have been fully oxidised (~2 hours). The organic solvent was then washed with aqueous acid to remove the amide moiety produced by enamine cleavage, leaving MDP2P in the solvent virtually free of any undesirable contaminants. The TIC of MDP2P (Figure 2) produced via the helional-*l*-proline methyl ester enamine demonstrates a typical component profile, with unreacted helional being the only other substance present in any quantity.

RESULTS AND DISCUSSION

The reactions were conducted typically at a scale commencing with several grams of helional and commensurate weights of the secondary amines. Results show that on this scale only minimal by-products are produced. To further explore the versatility of this scheme of reactions, a number of secondary amines were condensed with helional to form the corresponding enamine, and then oxidised as described to determine their potential for MDP2P production. A summary of the results of these preliminary studies is provided in Table 1.

Secondary amine used	Enamine intermediate produced after condensation	MDP2P produced after oxidation
Diethylamine	Yes	Yes
Proline methyl ester	Yes	Yes
Morpholine	Yes	Yes
Piperidine	Yes	No
Diphenylamine	No	N/A

Table 1: Summary of results

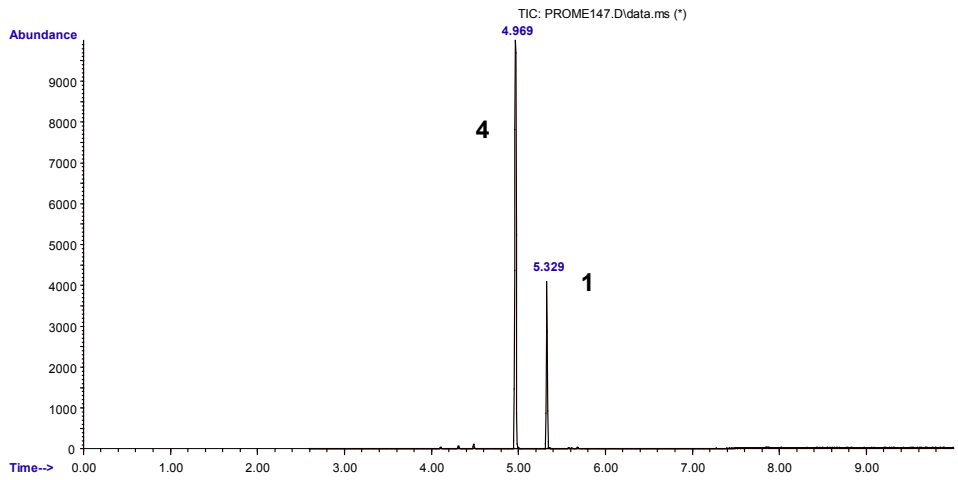

Figure 2: Typical TIC of MDP2P produced from helional

CONCLUSION

The preliminary study served to confirm the hypothesis proposed for the illicit production under investigation, that the enamine formed from the methyl ester of *l*-proline and helional can be oxidised to produce MDP2P. Further, it has been shown that a number of other secondary amines may be substituted into this reaction scheme and their helional enamines also produce MDP2P. Although the trial reactions were conducted on a small scale, the observed characteristics of this scheme indicate considerable potential for its application in illicit drug production. The precursors and reagents are not subject to controls, the processes are simple and require no technical expertise or complex equipment, and the MDP2P produced is in apparent high yield and free of contaminants. Limited testing also indicates a number of the helional enamines are stable and so offer a potential vehicle for drug precursor transport.

Work on the synthesis of MDP2P from helional via various enamine intermediates and alternative conditions for oxidative cleavage is ongoing. The findings from this program of work, including yield determinations and the characterisation of intermediates, will be presented in a future publication.

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