Tetrahedron Letters, Vol. 34, No. 40, pp. 6475-6478, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Application of the Mitsunobu Reaction in the Morphine Series.# The Reaction of 14β-chloro and 14β-bromocodeine with Phthalimide and Diphenylphosphoryl Azide

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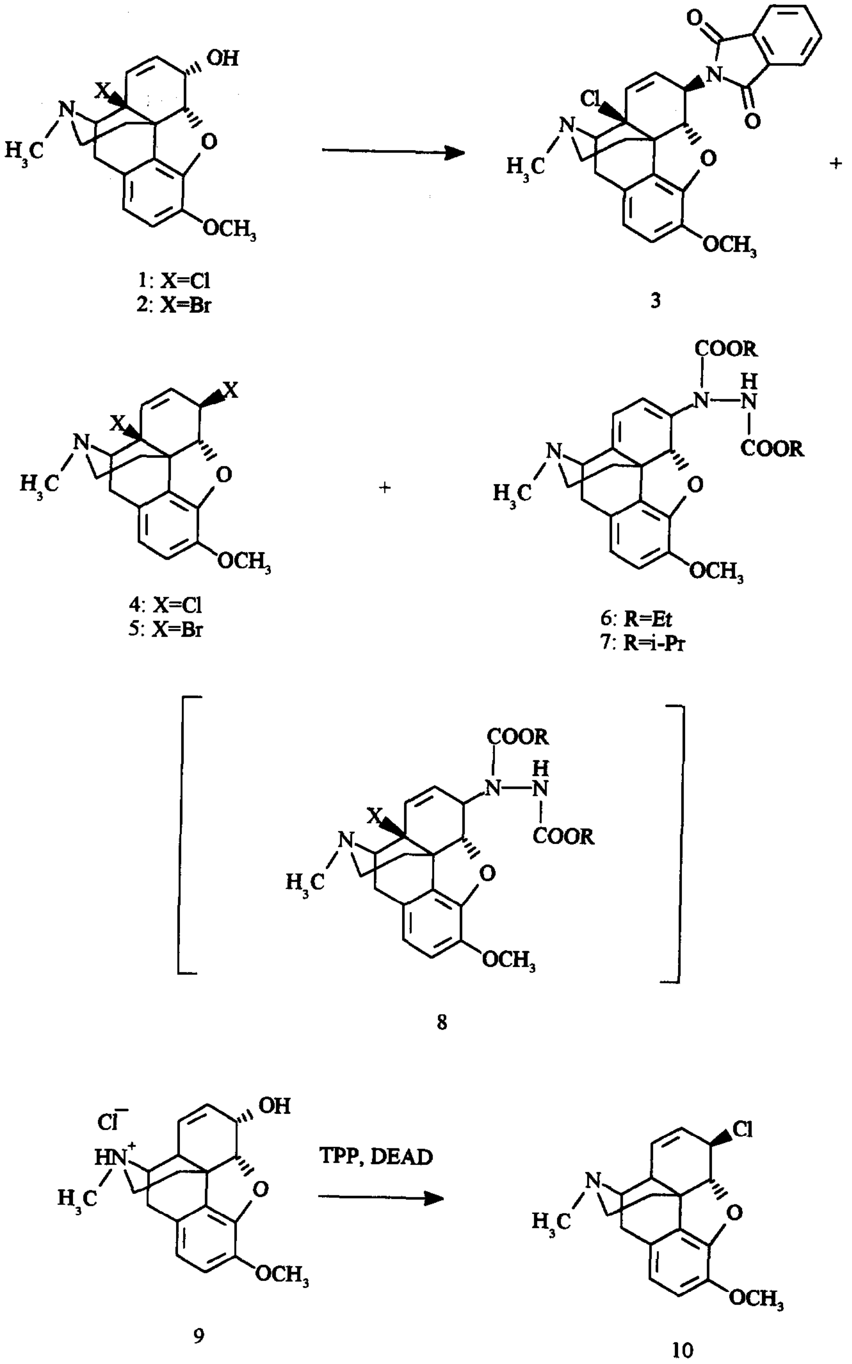
Abstract: 14β-Chlorocodeine 1 reacted with phthalimide under the conditions of the Mitsunobu reaction (with TPP and DEAD or DIAD) to give the expected phthalimide derivative 3 together with 6β,14β-dichloro-6-deoxycodeine 4 and the diene 6 or 7. 14β-Bromocodeine 2 reacted similarly but did not give any phthalimido derivative. The mechanism of these consecutive reactions has been investigated. With diphenylphosphoryl azide 6β-azido-14β-chloro 15 and 6β-azido-14β-bromo 16 derivatives were obtained.

When studying the application of the Mitsunobu reaction[1] in the field of morphine alkaloids[2-4] we have reported on the reaction of 14β-chlorocodeine (1) and 14β-bromocodeine (2) with 4-nitrobenzoic acid and chloroacetic acid under the conditions of the Mitsunobu reaction [in the presence of triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD)][5]. Characteristic features of these morphine compounds are that they are allyl halides and also allyl alcohols and that they react in different ways[6-8] - depending on the nature of the halogen atom. The products of such reactions are or can be transformed in various routes to a number of novel derivatives.

In the present communication we report on the results of the reactions of 1 and 2 with phthalimide and diphenylphosphoryl azide (DPPA)[9] in the presence of TPP and DEAD.

When 14β-chlorocodeine (1) was allowed to react with phthalimide in the presence of TPP and DEAD the expected 6β-phthalimido-14β-chloro-6-deoxy-codeine (3) was obtained only as a by-product (12% yield; m.p.: 194-196 °C), and two additional products were also isolated, i.e. 6β,14β-dichloro-6-deoxy-codeine (4) (yield: 13%), prepared formerly by us[8], and a diene with structure 6 (36%, m.p.: 173-175 °C).

Because of a steric hindrance due to the 14β-bromo substituent the 6β-phthalimido derivative did not form from 14β-bromocodeine (2) under the same conditions. The only products were 6 (34%) and 6β,14β-dibromo-6-deoxy-codeine (5, 25%, but this compound could not be prepared in analytically pure form because of decomposition during crystallisation).


OH
X
N
H3C
O
OCH3
1: X=Cl
2: X=Br
O
N
O
Cl
N
H3C
O
OCH3
3
+
X
X
N
H3C
O
OCH3
4: X=Cl
5: X=Br
+
COOR
H
N
N
COOR
N
H3C
O
OCH3
6: R=Et
7: R=i-Pr
COOR
H
N
N
COOR
X
N
H3C
O
OCH3
8
Cl⁻
HN⁺
H3C
OH
O
OCH3
9
TPP, DEAD
Cl
N
H3C
O
OCH3
10

Scheme 1

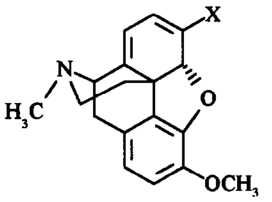
To explain the above results the reaction of 1 and 2 with TPP and DEAD were studied in the absence of acidic components, and the formation of the appropriate dihalogeno derivatives [4 (32%) and 5 (25%) from 1 and 2 respectively] and that of the diene 6 (yield: 23% from 1 and 24% from 2) was observed.

This is explained by the fact that in the absence of an HA acidic component in the Mitsunobu reaction N,N'-diethoxycarbonyl(dialkoxycarbonyl)hydrazines are produced[10,11]. We suppose that in our above experiments the primary product 8 represents such type of a substance, which upon 1,4-elimination, gives rise to the diene 6 and HA (A=Cl or Br), and thus under normal Mitsunobu conditions the dihalogeno derivatives (4 and 5) are produced. To the best of our knowledge, there is no reported precedent for the participation in a Mitsunobu reaction of a hydrogen halide which has been generated *in situ* and acts as the acid component.

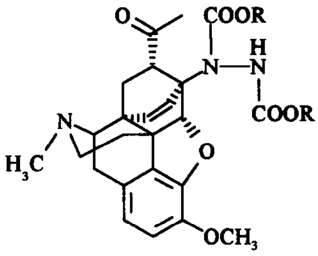
To prove the role of the *in situ* formed hydrogen halide, codeine hydrochloride (9) was allowed to react with TPP and DEAD; and the formation of 70.0 % of the α-chlorocodide 10 was observed.

When DIAD (diisopropyl azodicarboxylate) was used instead of DEAD the isopropyl ester of the corresponding N-substituted hydrazinedicarboxylic acid (7 ; m.p.: 212-214 °C) was isolated, and no significant differences in the yields, as compared to those of analogues reactions were recognised.

The structures of the prepared dihalogeno derivatives were confirmed by means of spectroscopic methods (NMR, MS). On the other hand, in DMF solution and in the absence of a nucleophile, these dihalogeno derivatives furnished the respective 6-halogeno-6-demethoxythebaine derivatives 11 and 12, prepared earlier by us[6]. The reaction of the dienes 6 and 7 with methyl vinyl ketone gave the corresponding Diels-Alder adducts 13 and 14.

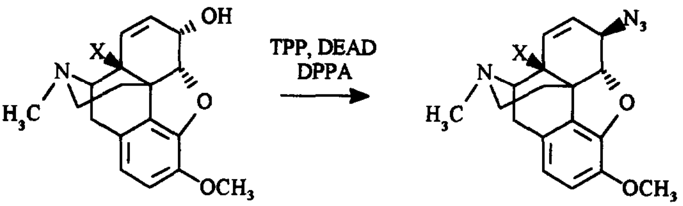


11 X=Cl
12 X=Br



13 R=Et
14 R=i-Pr

Both 1 and 2 reacted smoothly with diphenylphosphoryl azide in the presence of TPP and DEAD (or DIAD), and the 6β-azido-14β-halogeno-6-deoxy-codeine derivatives 15 (37%; m.p.: 146-148 °C) and 16 (25%; m.p.: 132-133 °C), respectively were isolated. Compound 15 is considered as an intermediate in the reaction of the tosyl ester of 14β-chlorocodeine with azide ion[8].



1 X=Cl
2 X=Br

15 X=Cl
16 X=Br

This work was supported, in part, by a grant (OTKA I/3 reg. No.:1722) obtained from Hungarian Academy of Sciences.

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Morphine Alkaloids Paper 121, for Part 120 of this series see: Berényi, S.; Czirják, M.; Makleit, S. *J. Chem. Soc., Perkin Trans., 1* (accepted for publication)

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(Received in UK 21 June 1993; accepted 5 August 1993)