Tetrahedron Letters,Vol.23,No.28,pp 2909-2912,1982 0040-4039/82/282909-04$03.00/0
Printed in Great Britain

SYNTHESIS OF 2,4-BIS(IMINO)AZETIDINES

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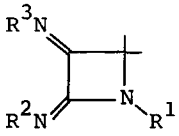
ABSTRACT. The reactions of carbodiimides with N-sulfonyl substituted ketenimines and those of bis(imino)thiazetidines with ester phosphoranes yield 2,4-bis(imino)-azetidines. The limitations of the methods are outlined.

Four-membered ring amidines[1] (imino analogues of β-lactams), as well as the corresponding imminium salts,[2] and 4-iminoazetidin-2-ones[3,4] are of current interest. For bis(imino)azetidines two possible structures (1 and 2) may be proposed of which only 1 has been reported in the literature.[5] We now describe methods for the synthesis of 2.



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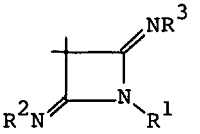
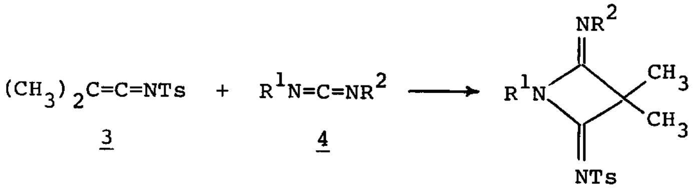


2

The first and most obvious approach to be considered would be a (2 + 2)-cycloaddition of ketenimines with carbodiimides. However, the unactivated dimethyl-N-phenylketenimine was found to be inert towards several carbodiimides, including dicyclohexylcarbodiimide and methyl-tert-butylcarbodiimide, in boiling benzene. Since the latter normally react as nucleophilic partners in [2π + 2π]-cycloaddition reactions, we also envisaged the possibility of carrying out cycloadditions with ketenimines bearing electron-withdrawing groups at the imine nitrogen atom. These ketenimines, however, are known to be unstable and can be generated only in situ.[1c,1d,6] Thus, dimethyl N-tosylketenimine 3 was prepared in situ by the reaction of N-tosyl dimethylacetamide with triphenylphosphane/bromine and triethylamine,[7] and then treated with two carbodiimides 4 at room temperature. This furnished the bis(imino)azetidines 5 and 6, albeit in low yields (see Table 1). Note also that N-acylketenimines yield Diels-Alder products when reacted with carbodiimides.[6c]



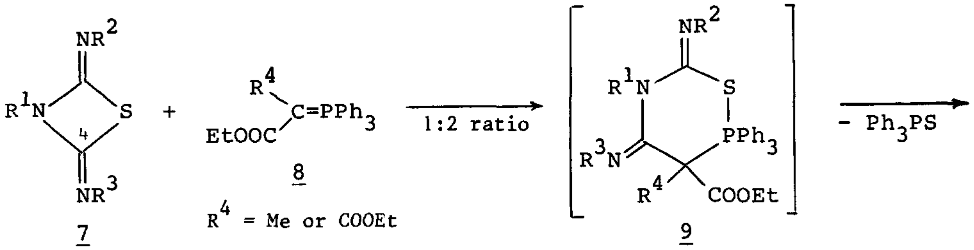
5: $R^1 = R^2 = c\text{-}C_6H_{11}$
6: $R^1 = Me$, $R^2 = t\text{-}Bu$

Table 1. 2,4-bis(imino)azetidines

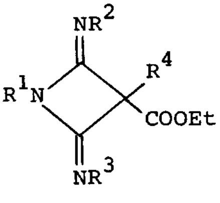
Compd	Reaction Conditions[a] solvent/temp(°C)/time	Yield(%)[b]	Mp(°C)	IR(KBr,cm^{-1}) C=N	Recovered(%)
5	CH_2Cl_2/20°/12 h	12	137	1755(m), 1605(s br)	
6	CH_2Cl_2/20°/12 h	30	87	1750(vw), 1615(s br)	
10	$CHCl_3$/45°/4 days	76	98	1775(w), 1730(m), 1670(s)	
11	$CHCl_3$/45°/14 days	13	112	1780(w), 1735(s), 1670(s)	70% 7a
12	$CHCl_3$/65°/3 days	43	104	1760 and 1740(m), 1625(s)	26% 7b
13	C_6H_6/75°/4 days	15	123	1785(s), 1630(s br)	41% 7b

[a] The products were isolated by column chromatography on silica gel with CCl_4-EtOAc (ratio 80-90:10-20) as the eluent. [b] Yields refer to purified products and were not optimized. All compounds gave satisfactory C,H analyses and spectral data (IR, ^1H NMR, ^{13}C NMR, MS) in agreement with the assigned structure.

A second approach is based on our recent findings that bis(imino)thiazetidines 7 undergo ring-transformation reactions readily, due to the presence of a thioimidate function adjacent to an extra imine function.[8] This should allow the synthesis of the title compounds by reacting 7 with phosphorus ylides. When 7a and 7b were treated with the ester phosphoranes 8 under the conditions mentioned in Table 1, the bis(imino)azetidines 10–13 were indeed formed together with triphenylphosphane sulfide. The reaction probably proceeds by attack of the ylide at the most electrophilic C_4 imine function of 7 to give an unstable six-membered phosphorus heterocycle 9, which undergoes ring contraction by elimination of triphenylphosphane sulfide.

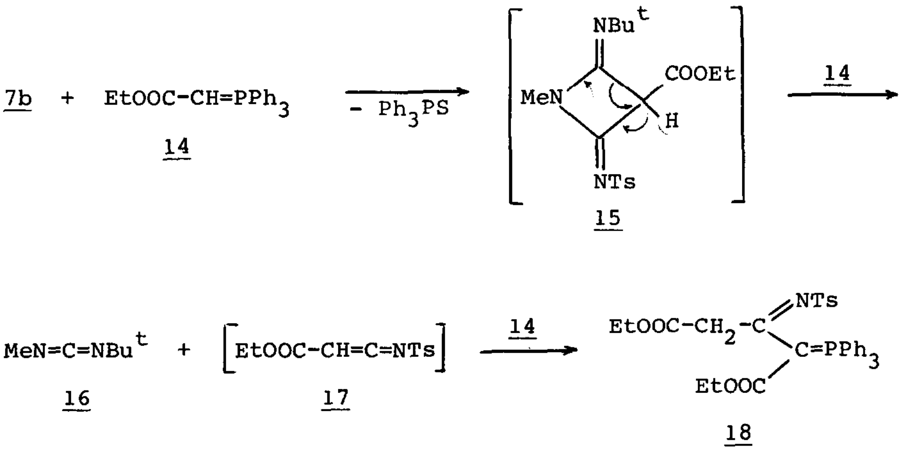


a: $R^1=R^2=c\text{-}C_6H_{11}$, R^3 = $p\text{-}NO_2C_6H_4$
b: R^1=Me, R^2=t-Bu, R^3=Ts

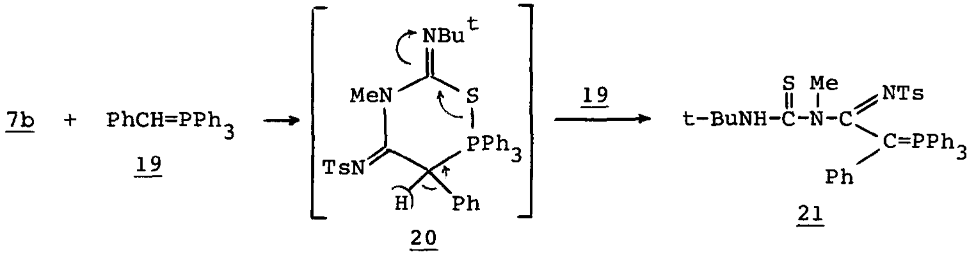


10: R^1 = R^2 = $c\text{-}C_6H_{11}$, R^3 = $p\text{-}NO_2C_6H_4$, R^4 = CH_3
11: R^1 = R^2 = $c\text{-}C_6H_{11}$, R^3 = $p\text{-}NO_2C_6H_4$, R^4 = COOEt
12: R^1 = Me, R^2 = t-Bu, R^3 = Ts, R^4 = CH_3
13: R^1 = Me, R^2 = t-Bu, R^3 = Ts, R^4 = COOEt

The method appears to be successful only when R^4 is not hydrogen. Indeed, when 7b was refluxed with carbethoxymethylenetriphenylphosphorane 14 in chloroform for 5 days, compound 18 (mp 183°C) was obtained along with methyl tert-butylcarbodiimide 16 and triphenylphosphane sulfide. We believe that 15 is formed initially, but then fragments under the influence of the basic P-ylide which abstracts the acidic hydrogen as shown on the drawing. This would yield the unstable ketenimine 17 which adds to a second molecule of 14 giving 18. The outcome of the reaction was found to be independent on whether one or two equivalents of 14 were used (yielding 18 in 16 and 33%, and recovered 7b in 46 and 23% respectively).



Finally, the reaction of 7b with two equivalents of benzylidenetriphenylphosphorane 19 (generated from the phosphonium bromide and NaH in DMSO) at room temperature furnished 21 (mp 138°C) in 11% yield, together with triphenylphosphane sulfide (13%) and N-tert-butyl-N'-tosylbenzylamidine (8%, mp 146°C, origin unknown). The formation of 21 is accounted for by ring opening of the initial adduct 20 initiated by hydrogen abstraction under the basis reaction conditions.



Acknowledgement. Financial support from the University (Research Grants) and from the "Ministerie voor Wetenschapsbeleid" is gratefully acknowledged.

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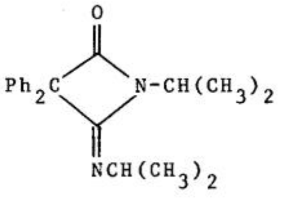
4. Attempts to convert imino-β-lactams[3] into the title compounds by reaction with iminophosphoranes were unsuccessful. For instance, (i) was heated with benzyliminotriphenylphosphorane and p-nitrophenyliminophosphorane at 80-110°C for 4 days, but no reaction was observed.



(i)

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(Received in UK 30 April 1982)