Tetrahedron. Vol. 30, pp. 2093 to 2098. Pergamon Press 1974. Printed in Great Britain

THE FIRST SYNTHESIS OF MONOCYCLIC THIEPINS[1]

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(*Received in the UK 3 December 1973; Accepted for publication December 1973*)

Abstract—Monocyclic thiepins have been synthesized by reaction of (4-methyl-) 3-pyrrolidinothiophenes **1** with dimethyl acetylenedicarboxylate at −30°C. A [2 + 2] cycloaddition, yielding 6,7-di(methoxycarbonyl)-(4-methyl)-5-pyrrolidino-2-thiabicyclo[3.2.0]hepta-3,6-diene **2** is followed by isomerisation into 3,4-di(methoxycarbonyl)-(6-methyl-)5-pyrrolidinothiepin **3**. The predicted antiaromatic character of this class of compounds is borne out by the readiness with which they eliminate sulphur at −30°C to give the corresponding benzene. The reaction product of dicyanoacetylene and tetramethylthiophene, recently claimed to be an unusually stable thiepin, is shown to be a 2-thiabicyclo[3.2.0]hepta-3,6-diene. Its structure allows the observed thermal rearrangement at 140°C to be interpreted as a symmetry-allowed *antara,antara* Cope rearrangement.

In contrast with 1*H*-azepines and oxepins, monocyclic thiepins have never been successfully synthesized so far.[2,3] The failure of most attempts is due to the rapid extrusion of sulphur from the incipiently-formed thiepins. This phenomenon, observed even under mild conditions,[4] has been attributed to the predicted[5] antiaromatic character ($E_R = -1{\cdot}45$ kcal/mol) of the thiepin system. From recent reports on some annulated thiepin derivatives,[6-10] it was inferred that the stability of the thiepin ring can be enhanced in two ways: (i) By delocalization of the π-electrons of the thiepin ring into other π-electron systems. For instance, in benzo[*d*][6]- and benzo[*b*]thiepins[7-9] and especially in thieno[3,4-*d*]- and furano[3,4-*d*]thiepins[10] delocalization gives rise to azulene-like charge-separated structures, which contribute significantly to the ground state. (ii) By introduction of two bulky groups at C_2 and C_7 of the thiepin. Such groups cause steric hindrance in the intermediate thianorcaradiene.[11]

Therefore, our aim was to synthesize a monocyclic thiepin with strongly electron-withdrawing substituents under mild thermal conditions. Our approach was based on the synthesis of dihydrothiepins from dihydrothiophenes by ring enlargement with an ethylene moiety.[12] This route comprises the cycloaddition of an enamine of a tetrahydrothiophen-3-one to an activated acetylene, followed by isomerization of the 2- or 3-heterobicyclo[3.2.0]hept-6-ene formed.† From experience gained in applying this route to the synthesis of benzo[*b*]thiepins[9] and benzo[*b*]-oxepins[13] from the "enamine" compounds 3-pyrrolidinobenzo[*b*]thiophene and -[*b*]furan, respectively, we concluded that 3-pyrrolidinothiophenes would be suitable starting materials.

RESULTS

Reaction of 3-pyrrolidinothiophenes with electron-deficient acetylenes

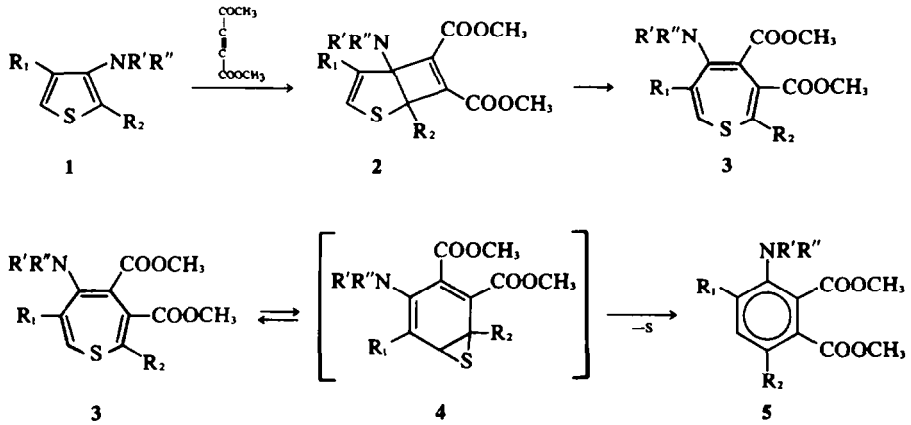
We prepared a number of 3-pyrrolidinothiophenes by oxidation of the corresponding 2,3- or 2,5-dihydrothiophenes with diisopentyl disulphide.[14] These compounds have a relatively large electron density at C_2, as can be concluded from the facility with which they enter into nucleophilic substitution reactions[14] and reactions with electron-deficient dienophiles,[15] and from the substantial upfield shift of the proton at C_2 in their NMR spectra.‡

At room temperature 3-pyrrolidinothiophenes **1** reacted with dimethyl acetylenedicarboxylate in chloroform to give quantitative yields of the corresponding benzene derivatives **5**. A plausible reaction pathway is one comprising (i) cycloaddition of the 3-pyrrolidinothiophene to dimethyl acetylenedicarboxylate, (ii) isomerization of the 2-thiabicyclo-[3.2.0]hepta-3,6-diene, and (iii) desulphurization of the thiepin at room temperature (Scheme 1).

In order to prove the validity of the proposed reaction pathway we subsequently lowered the reaction temperature to −30°C and monitored the course of the reaction by PMR and IR spectroscopy, using 4-methyl-3-pyrrolidinothiophene **1b** as the substrate. In this compound, the two olefinic protons give broad singlets. The disappearance of

†Attempts to synthesize thiepins from 2,7- or 2,3-dihydrothiepins, obtained by such a reaction, via a bromination/dehydrobromination reaction or a Pummerer rearrangement of the corresponding sulphoxides were unsuccessful.[12]

‡This was also observed for other N-heteroarylpyrrolidines.[9,13]



NR'R'' = PYRROLIDINO
a: $R_1 = R_2 = H$
b: $R_1 = CH_3$, $R_2 = H$
c: $R_1 = H$, $R_2 = CH_3$

SCHEME 1.

the thiophene **1b** was accompanied by the successive formation of three novel reaction products. First, the [2 + 2]cycloadduct **2b** was formed, the concentration of which reached a maximum after 50 h (Fig 1). The second product was identified as the thiepin **3b** and the final product as the benzene derivative **5b**. When monitoring the reaction by IR spectroscopy we observed that the formation of **2b** was manifested by the appearance of an absorption band at 1643 cm^{-1}. Samples containing **2b** and/or **3b** were converted at 25°C to **5b** within five minutes. The rates of the conversions of **1**→**2**→**3**→**4** were such that the two thermally unstable products (**2b** and **3b**) could only be obtained in mixtures with the other compounds. The concentration of the thiepin **3b** reached a maximum after 90 h reaction at − 30°C (Fig 2).

Compounds **1a** and **1c** reacted in the same way although the cycloaddition of **1c** required higher temperatures (20–30°C). In this reaction no intermediates (**2c** and **3c**) could be detected.

A similar reaction of **1b** with dicyanoacetylene at − 70°C proceeded instantaneously. On the basis of PMR spectroscopic data we concluded that in this case instead of a cycloaddition a linear Michael-type of addition occurred to give **6** (δ_{H_5}7·14 ppm (s), $\delta_{H_{vinyl}}$5·85 ppm (s), δ_{CH_2N}3·30 ppm (m), δ_{CH_3}2·30 ppm (s) and δ_{CH_2}2·00 ppm (m)). At higher temperatures **6** reacted further to yield polymeric products.

Structural assignments

Structure **2b** was assigned to the cycloadduct on the basis of PMR and IR spectroscopic data. The chemical shift of H_1 (4·48 ppm, s) is characteristic

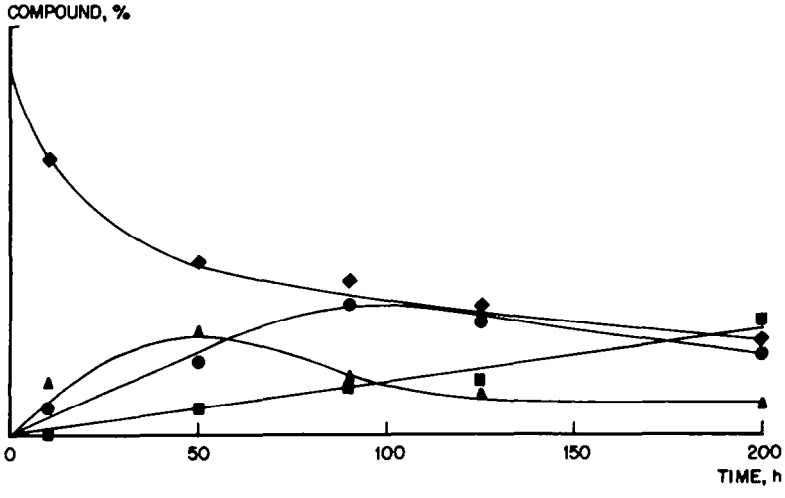
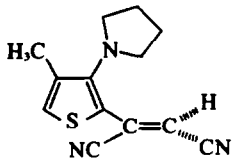
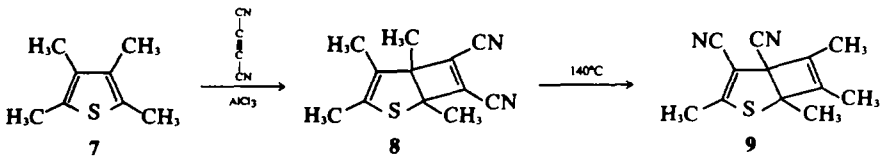


Fig 1. Relative concentrations of **1b**(◆), **2b**(▲), **3b**(●) and **5b**(■) as a function of time.



6

of a similar bridgehead proton in 2-thiabicyclo-[3.2.0]hepta-3,6-dienes.[9,16] The chemical shift of H_3 (5·76 ppm, s) is comparable with that of H_5 in dihydrothiophene (6·06 ppm). Furthermore, the upfield shift of the aminomethylene protons points to saturation of the carbon atom adjacent to the nitrogen atom.[9,12,13] The absorption at 1643 cm^{-1} is



SCHEME 2.

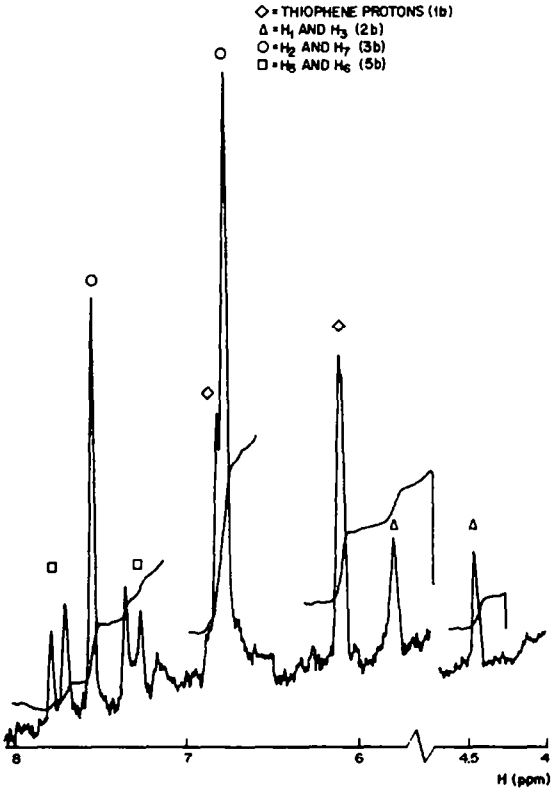


Fig 2. PMR spectrum of the mixture of 3-methyl-4-pyrrolidinothiophene (**1b**) and dimethyl acetylenedicarboxylate after 90 hr at − 30°C.

in the region characteristic of a 3,4-fused cyclobutene.[12,13,16]

Compound **3** was identified as a thiepin on the basis of its PMR spectrum and its rapid desulphurization at room temperature to give the corresponding benzene derivative **5**. The chemical shift of H_2 (δ 7·30 ppm, s) is in line with the reported values of the chemical shifts of H_7 in the corresponding 2,3-dihydrothiepins (δ 7·1–7·2 ppm[12]) and with that of H_2 in benzo[*b*]thiepins.[9] The chemical shift of H_7 (δ 6·76 ppm, s) is in the expected region (thiophene δ_{H_2} 7·31 ppm and 2,3-dihydrothiophene δ_{H_5} 6·06 ppm).

Cycloaddition of tetramethylthiophene to dicyanoacetylene

While this work was in progress a paper was published claiming the synthesis of a monocyclic thiepin.[17] The reaction comprised the cycloaddition of tetramethylthiophene **7** to dicyanoacetylene. We found that the reaction product was not a thiepin but 6,7-dicyano-1,3,4,5-tetramethyl-2-thiabicyclo[3.2.0]hepta-3,6-diene **8**. In a joint publication we then presented the spectroscopic evidence for structure **8**.[18] Upon being heated at 140°C **8** isomerized to give **9** via an *antara,antara* Cope rearrangement.

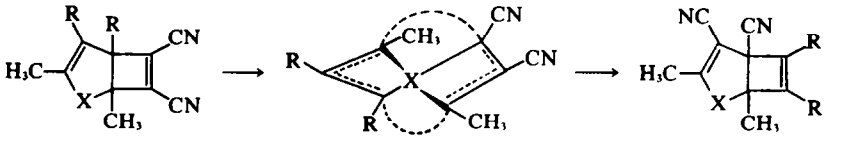
The isomerization of **8** into **9** at 140°C (and that of the corresponding 1,1-dioxide[17]) can be interpreted as a Cope rearrangement.* They are the first examples of a [3,3]*antara,antara* sigmatropic reaction of 2-*hetero*bicyclo[3,2,0]-3,6-dienes.[19]† The *supra,supra* sigmatropic reaction is in this case impossible for steric reasons.

The other two postulated pathways are (i) two subsequent *antara,supra*[1,3]sigmatropic reactions and (ii) the symmetry-allowed conrotatory opening of the cyclobutene ring followed by ring closure of the other diene moiety.

The latter route can be rejected because it would result in the formation of an energetically unfavourable seven-membered ring with a *trans* dou-

*A sigmatropic[3,3] reaction is allowed, in view of the orbital symmetry relations, both in the *supra,supra* and in the *antara,antara* way. The former route is usually observed because the transition state for the *antara,antara* reaction pathway is sterically unfavourable.

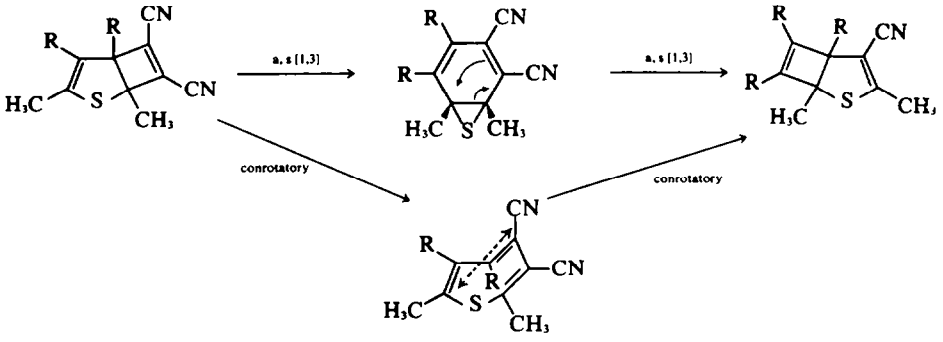
†A similar rearrangement in the carbocyclic series (**8**, S = CO or S = $C(CH_3)_2$) was recently suggested by Mukai *et al.*[20] and Baldwin *et al.*[21]



8: X = S, R = CH_3
8a: X = S, R = CH_2D
8b: X = SO_2, R = CH_3

9: X = S, R = CH_3
9a: X = S, R = CH_2D
9b: X = SO_2, R = CH_3

SCHEME 3.



SCHEME 4.

ble bond.[22] The other alternative—two subsequent *antara,supra*[1,3] sigmatropic reactions—should give rise to a thianorcaradiene as the intermediate and this would rapidly desulphurize. This leaves the [3,3]*antara,antara* sigmatropic reaction as the only possible reaction pathway for this isomerization.

DISCUSSION

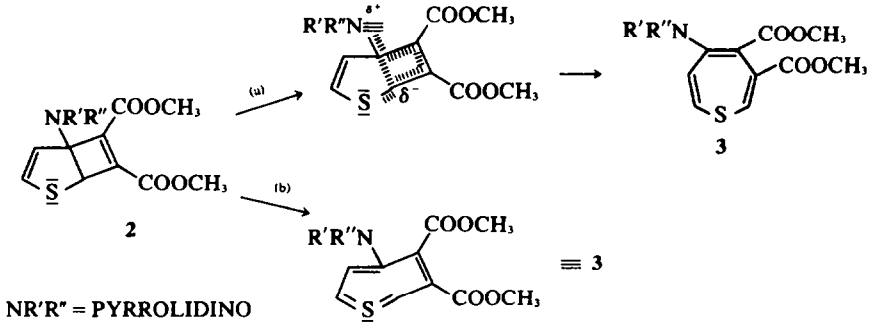
The thiepins **3** and their precursors **2** were prepared under mild reaction conditions because of the expected rapid desulphurization. We will now analyse the reasons for this successful synthesis.

(a) The high electron density at C_2 in 3-pyrrolidinothiophenes **1** is attributed to the large contribution of the polar structures to the ground state. The stabilization of the negative charge at C_2 by the sulphur atom makes these compounds almost as susceptible to electrophilic attack as normal enamines, notwithstanding the fact that the reaction entails the loss of resonance energy of the thiophene ring. Steric interference of a substituent at C_2 with the pyrrolidino group renders the cycloaddition reaction more difficult, e.g. 2-methyl-3-pyrrolidinothiophene **1c** reacts only at room temperature.[12] (b) The crucial step in our approach, the isomerization of **2** into **3**, comprises the opening of the cyclobutene ring. We have previously outlined the reasons for the enhanced rate of isomerization of cyclobutenes having an electron-donating amino substituent at one of the bridgehead carbon atoms.[9,12,13] According to the proposed "donor-acceptor" mechanism the rate of isomerization of 2-heterobicyclo[3.2.0]hepta-3,6-dienes will be further enhanced by the presence, in the 2-position, of a heteroatom that can stabilize a negative charge at the adjacent carbon atom.[9]

Whereas 2-thiabicyclo[3.2.0]hept-6-enes[12] and 2-oxabenzo[*b*]bicyclo[3.2.0]hepta-3,6-dienes,[13] isomerize only at 100–110°C ($T_{10^{-3}}$ = 100–110°C*), 2-thiabenzo[*b*]bicyclo[3.2.0]hepta-3,6-diene does so at about 33°C.[9] In the case of **2b** $T_{10^{-3}}$ could not be measured exactly but it is lower than 20°C. This difference can be attributed to the known ability of the sulphur atom to stabilize the partial negative charge at C_1 in the transition state (a, Scheme 5).

An alternative explanation for this extremely fast isomerization might be the electrocyclic symmetry-allowed disrotatory reaction of the dihydrothiophene ring (b, Scheme 5). This system is isoelectronic with bicyclo[4.2.0]octatriene, which isomerizes rapidly to cyclooctatetraene ($\Delta H^{\ddagger}$ = 18 kcal/mol).[23] This analogy is based on the substitution of sulphur for an ethylene moiety. The role of the participation of the d-orbitals in the delocalization through sulphur has been studied extensively after the first S (IV) heterocycles had been prepared.[24] According the model of Longuet–Higgins, the delocalization takes place via overlap of two spd^2 orbitals of the sulphur with sp^2 orbitals of the adjacent carbon atoms.[25] Consequently, the isomerization of **2** to **3** is not considered to be a conrotatory ring opening of the cyclobutene moiety but is regarded as a symmetry-allowed disrotatory opening of the "pseudo" 1,3-cyclohexadiene.

*$T_{10^{-3}}$ is defined as the temperature at which $k = 10^{-3}.s^{-1}$.



SCHEME 5.

The fast desulphurization of thiepins is interpreted in terms of a two-step process on the basis of the following arguments: (i) The thiepin is not stabilized by delocalization of its 8 π-electron system. Calculations by Dewar and Trinajstic revealed a negative resonance energy (− 1·45 kcal/mol).[5] (ii) Ring closure of the *cis,cis,cis*-hexatriene to give a thianorcaradiene **4** is a symmetry-allowed *disrotatory* process. The activation energy of the conversion of a thiepin **3** into the thianorcaradiene **4** is expected to be low because of the analogy with the oxepin-benzene oxide (E_A = 7·2 kcal/mol).[26] (iii) The subsequent extrusion of sulphur will be fast.[7,27] The relatively high stability of the thiepins **3** is due to the presence of the two electron-withdrawing methoxycarbonyl groups.[9] These substituents lower the electron density in the 8 π-electron system and consequently diminish the *anti*-aromatic character.

EXPERIMENTAL

PMR spectra were recorded on a Varian H 100 spectrometer with deuteriochloroform as the solvent and tetramethylsilane as the internal reference. IR spectra were obtained on a Perkin-Elmer 457 spectrometer. The mass spectra were obtained with an AEI MS-902 instrument.

Reaction of (2- *or* 4-*methyl*-)3-*pyrrolidinothiophene* **1** *with dimethyl acetylenedicarboxylate*

A mixture of 0·01 mol of (2- or 4-methyl-)3-pyrrolidinothiophene **1** and 0·04 mol of dimethyl acetylenedicarboxylate was stirred for 4 h at room temperature. Subsequently, a mixture of diethyl ether and pentane was added. The resultant solution was purified by chromatography over silica gel with pentane/diethyl ether (1/1) to give the benzene derivatives (**5a–c**). Compound **5b** was obtained as a solid, m.p. 66–67°C (from diethyl ether/pentane) and the two other compounds were obtained as an oil. Yields: 50–80%. The PMR data are given in the Table; the mass spectra showed a parent peak (*m/e* 277 for **5b** and **5c** and 263 for **5a**), and fragmentations in agreement with the proposed structures.

Reaction of 3-*methyl*-4-*pyrrolidinothiophene* **1b** *with dimethyl acetylenedicarboxylate at* − 30°*C*

A mixture of 80·0 mg (0·48 mmol) of 3-methyl-4-pyrrolidinothiophene **1b** and 76·0 mg (0·53 mmol) of dimethyl acetylenedicarboxylate in 0·2 ml of deuteriochloroform was kept at − 30°C. The vinylic region of the PMR spectrum of the mixture was recorded at various intervals. We observed the disappearance of the thiophene (**1b**, δ_{H_2}6·04 ppm (s) and δ_{H_5}6·70 ppm (s)) and the successive formation of three novel products: **2b**: δ_{H_1}4·48 ppm (s), δ_{H_3}5·76 ppm (s) and δ_{CH_2N}2·60 ppm (broad triplet); **3b**: δ_{H_2}7·30 ppm (s), δ_{H_3}6·67 ppm (s) and δ_{CH_2N}3·10 ppm (broad triplet); **5b**: $\delta_{H_{5,4}}$7·66 ppm and 7·18 ppm (AB system, J = 8 Hz) and δ_{CH_2N}3·12 ppm (broad triplet).

The concentration of compounds **1b–5b** is shown as a function of time in Fig 2.

The IR spectrum of this reaction mixture after 100 h was recorded at − 30°C (in deuteriochloroform) and revealed an absorption at 1643 cm^{-1}, which disappeared within five minutes when the mixture was warmed up to room temperature. The corresponding reaction with 3-pyrrolidinothiophene **1a** was monitored in the same way. With 2-methyl-3-pyrrolidinothiophene **1c** no reaction was observed after 100 h at − 30°C.

Reaction of 3-*methyl*-4-*pyrrolidinothiophene* **1b** *with dicyanoacetylene at* − 60°*C*

Equimolar amounts of 3-methyl-4-pyrrolidinothiophene (**1b**) and dicyanoacetylene in deuteriochloroform were

Table

Compound	Chemical shifts (δ values), ppm				
	Arom. H	$COOCH_3$	CH_2N	CH_3	CH_2
5a	6·7–7·2 m	3·75	3·24	—	1·92
5b	7·66 and 7·18 (AB)*	3·87 and 3·81	3·12	2·26	1·88
5c	6·73 and 7·07 (AB)*	3·75	3·18	2·19	1·90

*J = 8 Hz.

mixed at −80°C, after which the dark purple mixture was warmed up to −60°C. The PMR spectrum of the resultant mixture did not contain any signals of the starting material **1b** and the following absorptions of 2 - [1',2' - di(methoxycarbonyl)vinyl] - 4 - methyl - 3 - pyrrolidinothiophene **6** were observed: δ_{H_5}7·14 ppm (s), $\delta_{H_{vinyl}}$5·85 ppm (s), δ_{CH_2N}3·30 ppm (m), δ_{CH_3}2·30 ppm (s) and δ_{CH_2}2·00 ppm (m).

When the temperature of the reaction mixture was raised to −30°C and kept at this temperature for 2 h a polymeric residue was isolated.

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