*Tetrahedron* Vol 37, No. 21, pp 3693 to 3698, 1981
Printed in Great Britain

0040-4020/81/213693-06$02.00/0
Pergamon Press Ltd

# ENAMINE CHEMISTRY—XXIII†

## THE [4+2] CYCLOADDITION REACTIONS BETWEEN ENAMINOTHIONES AND ELECTROPHILIC OLEFINS AND ACETYLENES

J. B. RASMUSSEN, R. SHABANA‡ and S.-O. LAWESSON
Department of Organic Chemistry, Chemical Institute, University of Aarhus, DK-8000 Aarhus C, Denmark

(*Received in UK* 10 *November* 1980)

**Abstract**—The enamino-thione, **1c**, reacts with acrylonitrile and 2-chloroacrylonitrile at room temperature to give 3,4-dihydro-4-(1-pyrrolidinyl)-2H-thiopyrans, **4** and **5**, respectively. The reaction between 1-aryl-3-(1-pyrrolidinyl) (piperidino)-apropene-1-thiones, **1a–c** (**1d–f**), and dimethyl acetylenedicarboxylate gives 4-(1-pyrrolidinyl)(piperidino)-4H-thiopyrans, **6a–c** (**6d–f**). Compounds **1a–c** (**1d–f**) and ethyl propiolate produce 2-(1-pyrrolidinyl) (piperidino)-2H-thiopyrans, **8a–c** (**8d–f**), and a new type of rearrangement is observed. The 2D-thiopyran, **9**, is formed from **1b** and ethyl 3D-propiolate, which elucidates the mechanism. $^1H$ and $^{13}C$ NMR data of **6** and **7** are discussed.

A new procedure for the preparation of enamino-thiones[1,2] in quantitative yields has made this class of compounds readily available. The chemistry of enamino-thiones has been studied by Quiniou *et al.*[3–7] and us.[1b] In an earlier paper[1b] we showed that the alkylation of enamino-thiones, **1**, took place exclusively at sulfur giving iminium salts, **2**, which could easily be hydrolyzed to 3-aryl-3-alkyl-thiopropenal, **3** (Scheme 1).

For the preparation of S-containing heterocycles, N,N-disubstituted enamino-thiones have been reacted with electrophilic olefins,[4,6,7] ketenes[3,5] and sulfenes.[3,5] However [4+2] cycloadditions using electrophilic acetylenes as dienophiles have received very little attention.[8,9]

In our general studies on enamino-thiones we report in this paper on [4+2] cycloaddition reactions using the electrophilic olefins, acrylonitrile and 2-chloroacrylonitrile, a ketene equivalent,[10] and acetylenes, dimethyl acetylenedicarboxylate and ethyl propiolate, as dienophiles.

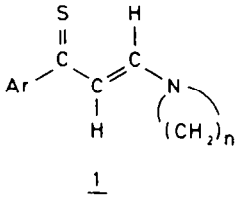
†Part XXII, see Ref.[1d].

‡On leave from the National Research Center of Egypt, Dokki, Cairo, Egypt.

### RESULTS AND DISCUSSION

The enamino-thiones, **1** (Scheme 2), used were prepared according to our earlier procedure.[1] No problems were encountered by working in larger scales, even though a wide and short column ($Al_2O_3$) had to be used for the purification to avoid lowering the yield.

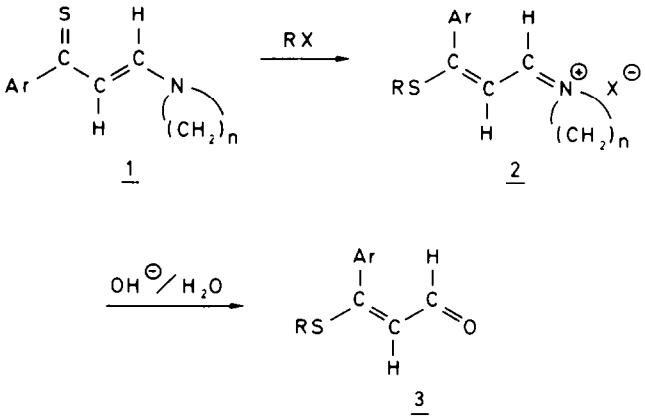
The electrophilic olefins, acrylonitrile and 2-chloroacrylonitrile, were reacted with **1c** at room temperature in benzene giving 6-aryl-3-cyano-3,4-



**1**

| | Ar | n |
|---|---|---|
| a | Ph | 4 |
| b | p-MeOC$_6$H$_4$ | 4 |
| c | p-BrC$_6$H$_4$ | 4 |
| d | Ph | 5 |
| e | p-MeOC$_6$H$_4$ | 5 |
| f | p-BrC$_6$H$_4$ | 5 |

Scheme 2.



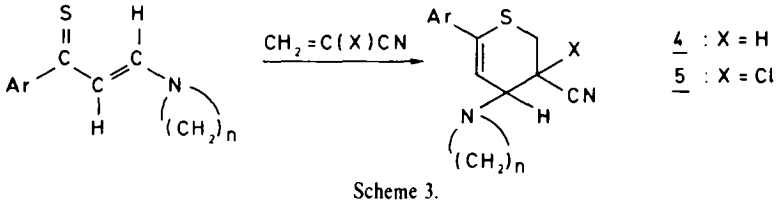
Scheme 1.

dihydro - 4 - (1 - pyrrolidinyl) - 2H - thiopyran, **4**, and 6 - aryl - 3 - chloro - 3 - cyano - 3,4 - dihydro - 4 - (1 - pyrrolidinyl) - 2H - thiopyran, **5**, respectively (Scheme 3). Compound **4**,[4-7] existing as two conformers[7] in solution ($CDCl_3$, $^{13}C$ NMR), was recrystallized directly from diethyl ether, while **5** had to be purified by column chromatography ($Al_2O_3$).

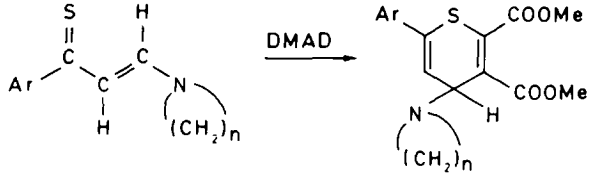
Compound **5** was characterized by $^1H$ NMR, UV, IR, MS and microanalyses (Experimental) and seems to be unstable in solution ($CDCl_3$).

When dimethyl acetylenedicarboxylate (DMAD) in excess was allowed to react with the enamino-thiones, **1**, at room temperature in benzene 6 - aryl - 2,3 - dimethoxy - carbonyl - 4 - (1 - pyrrolidinyl)(piperidino) - 4H - thiopyrans, **6a–c** (**6d–f**), were formed in high yields (Scheme 4).

As to the mechanism, it is suggested to be a [4+2] cycloaddition reaction. The structures of the 4H-thiopyrans, **6**, are proved by $^1H$-, $^{13}C$ NMR, UV, IR, MS and microanalyses. The $^1H$ NMR spectra show two doublets at $\delta = 5.95$–$6.16$ and $\delta = 4.72$–$4.92$ ($J = 5.5$–$6.0$ Hz) for the hydrogens of the thiopyran ring. The UV spectra show absorptions at $\lambda_{max} = 215$–$222$ nm and $\lambda_{max} = 245$–$267$ nm. The most abundant peak of the mass-spectra of **6** is *m/e* M-70 (M-84) corresponding to the loss of pyrrolidinyl (piperidinyl). The complete assignments of the $^{13}C$ NMR spectra are given for the compounds **6b**, **6c**, **6e** and **6f** (Table 1). The $^{13}C$ NMR data for the compounds



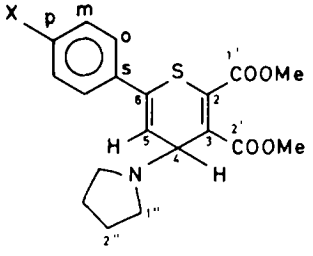

Scheme 3.

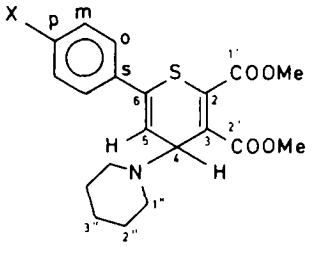



1 6

Scheme 4.

Table 1. $^{13}C$ NMR data of **6**; solvent $CDCl_3$, $\delta$-values vs TMS




6a–6c 6d–6f

| Ass.*) | 6b | 6c | 6e | 6f |
|---|---|---|---|---|
| 2 | 135.0 | 134.4 | 133.1 | 132.5 |
| 3 | 124.7 | 125.1 | 126.8 | 127.4 |
| 4 | 55.1 | 55.0 | 60.9 | 61.1 |
| 5 | 114.4 | 116.5 | 114.5 | 116.6 |
| 6 | 134.7 | 134.1 | 133.9 | 133.4 |
| 1' | 164.9 | 164.6 | 164.4 | 164.3 |
| 2' | 167.1 | 167.1 | 168.7 | 167.8 |
| 1" | 47.8 | 47.8 | 49.5 | 49.7 |
| 2" | 23.7 | 23.7 | 26.5 | 26.6 |
| 3" | | | 24.4 | 24.4 |
| s | 129.2 | 135.8 | 129.5 | 136.1 |
| o | 127.8 | 128.2 | 127.6 | 128.1 |
| m | 114.0 | 131.8 | 115.0 | 131.9 |
| p | 160.3 | 123.1 | 160.2 | 123.1 |
| x | 55.1 | | 55.1 | |

*) Assignment see text.

**6a** and **6d** need no comments (comparison with **6b**, **6c**, **6e** or **6f**). The assignments are made by off resonance decoupled spectra and coupled spectra.

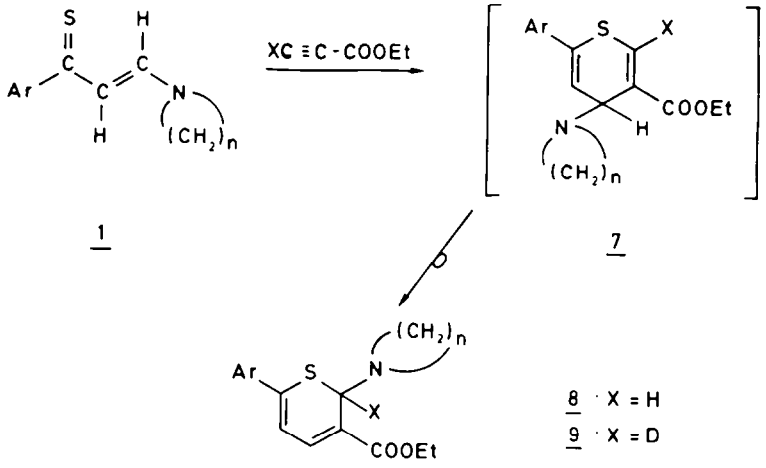
The resonances of the aromatic carbons can be calculated by usual methods.[11] The C(2) and C(6) carbons are assigned from the coupled spectra. C(2) gives a doublet ($^3J_{CCH}$ = 5.5 Hz), while C(6) gives a multiplet due to both two and three bond couplings to hydrogen. The remaining carbons of the thiopyran ring are straightforward to interpret. The assignments of the CO carbons, C(1') and C(2'), are not certain. The coupled spectra show a quartet ($^3J_{COCH_3}$ = 3.8 Hz) and a multiplet (nearly a quintet). It is suggested that the former resonance is assigned to C(1') and the latter to C(2'), because of the additional three bond coupling for the C(2') carbon to hydrogen at the C(4) carbon. The remaining assignments are obvious.

When ethyl propiolate was allowed to react with **1** the unexpected 6 - aryl - 3 - ethoxycarbonyl - 2 - (1 - pyrrolidinyl)(piperidino) - 2H - thiopyrans, **8a–c** (**8d–f**), were formed (Scheme 5).

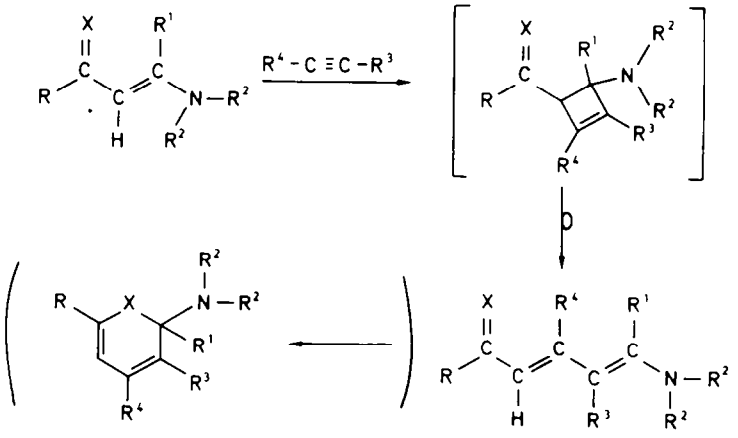
At room temperature **8** is formed in low yield, while at elevated temperature (80°) the yield is moderate. The structure of **7** was proved by means of $^1$H-, $^{13}$C NMR, UV, IR, MS and microanalyses. Besides the spectroscopic means for the structure elucidation, we prepared the 2D-thiopyran, **9**, by reacting **1b** with deuterated ethyl propiolate (Scheme 5). The 2D-thiopyran, **9**, gives information on the mechanism as well as the structure. As to the mechanism it has been reported[12,13] that certain enaminones can undergo [2 + 2] nonconcerted cycloaddition reactions followed by ring opening to give dienaminones (Scheme 6).

The formation of **9** could not have followed this mechanism (Scheme 6) since the product should be a 4D-thiopyran (dienamino-thione followed by an electrocyclic ring closure reaction). The mechanism (Scheme 5), consistent with the final product **9**, is suggested to be a [4 + 2] cycloaddition reaction followed by an allylic rearrangement reaction. Such an allylic rearrangement of 4H-, 2H-thiopyrans has been reported for hydride,[14] but as far as we know, it has not been reported for other groups. The 1,3-hydride shift was further shown to be catalyzed[14] by thiopyrylium cations.

$^1$H NMR spectra of **8** show two doublets at $\delta$ = 6.50–6.60 and $\delta$ = 7.40–7.52 (J = 7.2–7.5 Hz), respectively, and a singlet at $\delta$ = 5.46–5.76 for the thiopyran ring hydrogens. The $^1$H NMR spectrum of the mixture of **8b** and **9** shows a reduction of the integral of the singlet only, which is consistent with both **7** and **9**. The $^{13}$C




Scheme 5.




Scheme 6.

NMR spectrum of **7b** and **9** on the other hand only shows on intensity-reduction of the $sp^3$ carbon at $\delta = 61.1$, unequivocally proving **9** to be the product.† Unfortunately the intensity of the triplet (C–D coupling) is too weak to be observed. Besides $^1H$ and $^{13}C$ NMR data the UV spectra of **8** show three absorptions at $\lambda_{max}$ = 220–224, 280–299 and 364–378 nm compared to only two for compound **6**. Also a major difference between **6** and **8** is observed in the mass spectra. For the latter the most abundant peak is *m/e* M-73 showing the loss of the ethoxycarbonyl group. An additional proof for the structure of the 2H-thiopyrans, **8**, is found by comparison with 2-ethoxy-2H-thiopyrans.[6]

As for **6** the assignment of the $^{13}C$ NMR spectra for **8b**, **8c**, **8e**, **8f** is made (Table 2) by off resonance decoupled spectra, comparison with the compounds **6** and calculation of the aromatic resonances.[11] The carbons C(2) and C(5) are differentiated by off resonance decoupled spectra. The remaining assignments are straightforward to interpret.

The compounds **6** and **8** cannot be prepared by allowing secondary amines to react with thiopyrylium salts,[15] even though these salts react with ethanol[6] or ethanethiol[6] to give the corresponding 2-substituted-2H-thiopyrans. Thus enamino-thiones are novel compounds for the synthesis of various types of substituted thiopyrans.

## EXPERIMENTAL

$^1H$ NMR spectra were recorded at 60 MHz on a Varian EM-360A spectrometer. $^{13}C$ NMR spectra were recorded at 20 MHz on a Varian CFT-20 spectrometer. TMS was used as internal standard and chemical shifts are expressed in $\delta$-values. IR spectra were recorded on a Beckman IR-18A spectrometer. UV spectra were recorded on a Perkin–Elmer 402 spectrometer. Mass spectra were recorded on a Micromass 7070 mass spectrometer operating at 70 eV using direct inlet. Elementary analyses were carried out by Novo Microanalytical Laboratory, Novo Industry A/S, Novo Allé, DK-2880 Bagsvaerd, supervised by Dr. R. E. Amsler. M.ps are uncorrected.

The enamino-thiones **1a–f** were prepared as described by us.[1] They were all recrystallized from $(Et_2)O/CH_2Cl_2$ instead of THF/petroleum.[16]

*Compound* **4**

To 2.5 mmole **1c** in 15 ml benzene were added 3.75 mmole acrylonitrile at room temp. with stirring. The reaction was complete (tlc) after 2 hr. The solvent was evaporated under reduced pressure and the crude mixture was recrystallized directly from $Et_2O$, yield 66%; m.p. = 122–126 (131–133[4]); $^{13}C$ NMR: Form A (form B); $\delta^{(a)} = 23.63$ (23.75); $\delta^{(b)} = 25.88$ (27.52); $\delta^{(b)} = 29.12$ (30.70); $\delta^{(a)} = 50.34$ (51.70); $\delta^{(b)} = 58.72$ (58.89); $\delta^{(b)} = 117.29$ (117.80); $\delta^{(c)} = 119.29$ (119.76); $\delta^{(b)} = 137.92$ (137.76). (a) Pyrrolidine carbons. (b) Carbons of the thiopyran ring. (c) CN.

*Compound* **5**

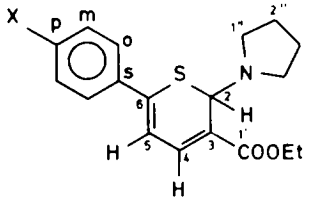
Same procedure as above. Reaction time 5 min at room temp. Attempted recrystallizations after removal of the solvent were unsuccessful. Purification was performed by column chromatography ($Al_2O_3$, eluted with 75% $CH_2Cl_2$/petroleum), yield 42%; m.p. = 96; $^1H$ NMR: $\delta = 1.80$ (4H), 3.10 (4H), 3.45 (1H, J = 1.2Hz), 3.60 (1H), 3.90 (1H, J = 1.2Hz, J = 5.8Hz), 5.90 (1H, J = 5.8 Hz), 7.40 (4 H). Microanalysis: Calc. (Found): C, 49.95 (50.38); H, 4.42 (4.31); N, 7.29 (7.36); S, 8.33 (8.59).

*Compound* **6**

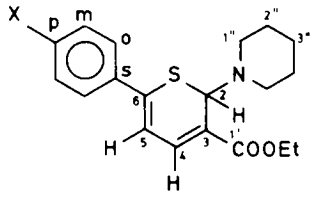
*General procedure.* To 5 mmole **1** in 30 ml benzene were added 7.5 mmole DMAD at room temp. with stirring. The reaction was complete in approx. 5 min (tlc). The solvent was removed under reduced pressure. **6b** and **6f** were recrystallized directly, while **6a**

†Nishio *et al.*[9] have reacted 3-dimethylamino-1-phenyl propene-1-thione with methyl propiolate and suggested the product to be a 4H-thiopyran.

Table 2. $^{13}C$ NMR data of **8**; solvent $CDCl_3$, $\delta$-values vs TMS




8a – 8c




8d – 8f

| Ass.*) | 8b | 8c | 8e | 8f |
|---|---|---|---|---|
| 2 | 61.1 | 61.2 | 65.6 | 65.6 |
| 3 | 114.5 | 115.6 | 114.8 | 115.2 |
| 4 | 134.1 | 133.7 | 135.4 | 134.8 |
| 5 | 114.6 | 116.4 | 114.8 | 116.5 |
| 6 | 145.2 | 144.1 | 145.4 | 144.3 |
| 1' | 167.1 | 167.0 | 167.2 | 167.0 |
| 1" | 46.6 | 46.8 | 47.4 | 47.4 |
| 2" | 23.8 | 23.9 | 25.6 | 25.5 |
| 3" | | | 24.1 | 24.1 |
| s | 130.3 | 137.0 | 130.4 | 137.0 |
| o | 128.4 | 128.6 | 128.5 | 128.7 |
| m | 114.0 | 131.8 | 114.1 | 131.8 |
| p | 160.7 | 123.5 | 160.8 | 123.5 |
| x | 55.2 | | 55.3 | |

*) Assignment see text

Table 3. Physical and analytical data of **6**

| Comp.[1] | Yield % | M.p./°C | UV[2] | $^1$H NMR[3] (J/Hz) |
|---|---|---|---|---|
| 6a | 73 | 102 | 220<br>248 | 6.16 (6.0)<br>4.92 (6.0) |
| 6b | 96 | 90 | 222<br>267 | 6.00 (6.0)<br>4.90 (6.0) |
| 6c | 75 | 71 | 220<br>256 | 6.10 (6.0)<br>4.90 (6.0) |
| 6d | 70 | oil | 215<br>245 | 6.05 (5.5)<br>4.72 (5.5) |
| 6e | 82 | 79 | 215<br>265 | 5.95 (5.5)<br>4.75 (5.5) |
| 6f | 95 | oil | 220<br>255 | 6.01 (5.5)<br>4.75 (5.5) |

1) Microanalyses in agreement with calculated values. 2) EtOH. 3) 4H-Thiopyran ring; $CDCl_3$.

Table 4. Physical and analytical data of **8**

| Comp.[1] | Yield[2] % | M.p./°C | UV[3] | $^1$H NMR[4] (J/Hz) |
|---|---|---|---|---|
| 8a | 53 | 82 | 224<br>281<br>366 | 5.70<br>6.60<br>7.40 } (7.2) |
| 8b | 52 | 90 | 224<br>296<br>373 | 5.70<br>6.58<br>7.46 } (7.2) |
| 8c | 55 | 102 | 222<br>285<br>364 | 5.76<br>6.64<br>7.50 } (7.2) |
| 8d | 50 | 103 | 220<br>280<br>367 | 5.50<br>6.58<br>7.52 } (7.5) |
| 8e | 51 | 92 | 225<br>299<br>378 | 5.46<br>6.50<br>7.50 } (7.5) |
| 8f | 56 | 110 | 223<br>286<br>368 | 5.50<br>6.58<br>7.50 } (7.5) |

1) Microanalyses in agreement with calculated values. 2) Yield after recrystallization from ether/petroleum. 3) Ethanol. 4) 2H-Thiopyran ring; $CDCl_3$.

and **6c–e** were purified by column chromatography ($Al_2O_3$, eluted with 75% $CH_2Cl_2$/petroleum). All compounds were characterized by $^1$H, $^{13}$C NMR, UV, IR, MS and microanalyses.

*Compound* **8**

*General procedure.* To 5 mmole **1** in 20 ml benzene were added 5 mmole ethyl propiolate in 10 ml benzene at 80° with stirring. The reaction was complete in approx. 5 min (tlc). The solvent was removed under reduced pressure and **8a–f** were purified by column chromatography ($Al_2O_3$, eluted with 75% $CH_2Cl_2$/petroleum). Attempts to recrystallize directly were unsuccessful. All compounds were characterized by $^1$H, $^{13}$C NMR, UV, IR, MS and microanalyses.

3d-*Ethyl propiolate* (60%)

Ethyl propiolate dissolved in ether was added to a catalytic amount of NaOEt and $D_2O$ in excess. After 1.5 hr 50% deuterium exchange had taken place, after 3 hr 60% ($^1$H NMR). The reaction was stopped after 3 hr and the phases separated. The ether was evaporated and the residue distilled.

2D-*Thiopyran*, **9** (+ 2H-*thiopyran*, **8b**)

Reaction and separation conditions as above, though using deuterated ethyl propiolate as dienophile, m.p. = 92. $^1$H NMR: $\delta$ = 5.75 ppm (0.4H), remaining hydrogens as for **8b**. $^{13}$C NMR: $\delta$ = 61.08 ppm has considerably lower (~ 50%) intensity compared to **8b**. The remaining absorptions are the same as for **7b**.

*Acknowledgements*—Thanks are expressed to DANIDA for a fellowship to one of us (R.S.), to FLUKA AG, CH-9470 Buchs 1, Switzerland, for a generous supply of the Lawesson Reagent (2,4 - bis(4 - methoxyphenyl) - 1,3,2,4 - di - thiadiphosphetane - 2,4 - disulfide) and to Münzing Chemie GmbH, D-71 Heilbronn, for a sample of 2-chloroacrylonitrile.

## REFERENCES


[1a]R. Shabana, J. B. Rasmussen, S. O. Olesen and S.-O. Lawesson, *Tetrahedron* **36** 3047 (1980); [b]J. B. Rasmussen, R. Shabana and S.-O. Lawesson, *Ibid* **37**, 197 (1981) and refs. therein. [c]R. Shabana, J. B. Rasmussen and S.-O. Lawesson, *Bull. Soc. Chim. Belg.* **90**, 75 (1981), [d] R. Shabana, J. B. Rasmussen and S.-O. Lawesson, *Tetrahedron* **37**, 1819 (1981).

[2]W. Walter and T. Proll, *Synthesis* 941 (1979).

[3]M. Bard, J. C. Meslin and H. Quiniou, *J. Chem. Soc.* Chem. Comm. 672 (1973) and refs. therein.

[4]J.-P. Pradere and H. Quiniou, *Ann. Chim. Italia* **63**, 563 (1973).

[5]J. C. Meslin, Y. T. N'Guessan and H. Quiniou, *Tetrahedron* **31**, 2679 (1975).

[6]J. P. Pradere, Y. T. N'Guessan and H. Quiniou, *Ibid.* **31**, 3059 (1975).

[7]J.-P. Pradere and G. Hadjukovic, *C.R. Acad. Sci. Serie C* **286**, 553 (1978) and refs. therein.

[8]D. M. McKinnon, M. E. Hassan and M. S. Chauhan, *Can. J. Chem.* **57**, 207 (1979).

[9]T. Nishio, N. Nakajima and Y. Omote, *J. Heterocyclic Chem.* **17**, 405 (1980).

[10]S. Ranganathan, D. Ranganathan and A. K. Mehrotra, *Synthesis* 289 (1977).

[11]F. W. Wehrli and T. Wirthlin, *Interpretation of Carbon*-13 *NMR Spectra*. Heyden, New York (1978).

[12]C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. G. Pierson and P. Strachan, *J. Org. Chem.* **28**, 3134 (1963).

[13]A. G. Cook, Enamines: *Syntnesis, Structure and Reactions*. Marcel Dekker, New York (1969).

[14]E. T. Østensen, A. A.-A. Abdallah, S. H. Skaare and M. M. Mishrikey, *Acta Chem. Scand.* **B(31)**, 496 (1977).

[15]B. J. Graphakos, A. R. Katritzky, G. Lhommet and H. Reynolds, *J. Chem. Soc.* Perkin I. 1345 (1980).