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5-Amino-1,2,3,4-thiatriazole: Its Acylation with Chloroformates and Chlorothioformates as a Route to 1,2,4-Thiadiazoles and 1,6,6a,Δ^4-Trithia-3,4-diazapentalenes

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Summary. Pyridine catalyzed acylation of 5-amino-1,2,3,4-thiatriazole with chloroformates and chlorothioformates afforded 3,5-bis(ethoxycarbonylamino)-1,2,4-thiadiazoles in the former and 2,5-bis(phenoxy)-1,6,6a,Δ^4-trithia-3,4-diazapentalenes in the latter case. An unstable, but isolable intermediate 2-phenoxy-1-aza-3,4-dithiolium-5-imide has been found if the chlorothioformate acylation was performed in acetonitrile in the absence of pyridine. The bis(phenoxy)trithiapentalenes are prone to nucleophilic displacement reactions at positions 2 and 5, exchanging in a stepwise manner one or both phenoxy groups. The structures of the compounds described could be inferred from their ^{1}H-NMR ^{13}C-NMR, and mass spectra and were corroborated by the comparison with the data of authentic and similar derivatives as well as by chemical means.

Keywords. Chloroformate; Chloro(di)thioformate acylation; 5-Amino-1,2,3,4-thiatriazole; Trithiadiazapentalenes.

Die Acylierung von 5-Amino-1,2,3,4-thiatriazol mit Chlorformiaten und Chlorthioformiaten als Route zu 1,2,4-Thiadiazolen und 1,6,6a,Δ^4-Trithia-3,4-diazapentalenen

Zusammenfassung. Die durch Pyridine katalysierte Acylierung von 5-Amino-1,2,3,4-thiatriazol mit Chlorameisensäureethylester führt zu 3,5-bis-(ethoxycarbonylamino)-1,2,4-thiadiazolen, während mit Chlorthioameisensäureethylester 2,5-bis(phenoxy)-1,6,6a,Δ^4-trithia-3,4-diazapentalene erhalten werden. Ohne Pyridin entsteht bei letzterer Reaktion ein wenig stabiles, aber isolierbares Zwischenprodukt: 2-Phenoxy-1-aza-3,4-dithiolium-5-imid. Die Bis(phenoxy)trithiadiazapentalene reagieren leicht mit nukleophilen Reagenzien und tauschen dabei schrittweise eine oder beide Phenoxygruppen aus.

Introduction

5-Amino-1,2,3,4-thiatriazole (**1**) can easily be further functionalised at the amino group. In spite of this obvious possibility and the fact, that **1** is known since 1896 [2], acylation reactions have hardly been attempted so far.

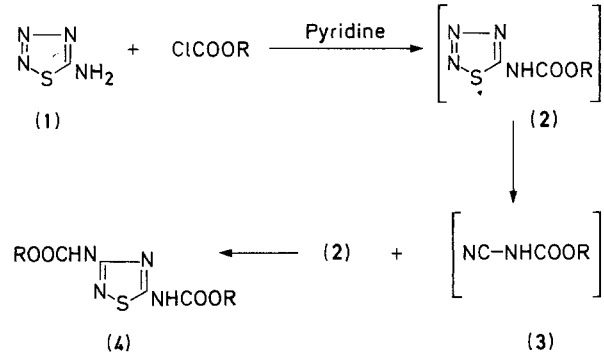
1 is known to react with isothiocyanates to 5-thioureido-1,2,4-thiadiazolin-3-thiones and 2,5-bis(aryl-amino)-1,6,6a,Δ^4-trithia-3,4-diazapentalenes [1], with iso-

cyanates to 2-substituted 5-ureido-1,2,4-thiadiazolin-3-ones [3]. Acylations with carboxylic acid chlorides resulted in the formation of 2,5-diaryl-3,4-dioxa(dithia or diarylaza)-3a,Δ^4-thia-1,6-diazapentalenes, [4, 5] whereas acetic anhydride acylation produced 3,5-bis(acetylamino)-1,2,4-thiadiazole [5]. Cyanic esters gave rise to 5-amino-3-aroxy-1,2,4-thiadiazoles [6].

We now report acylation reactions with chloroformate and chlorothioformate.

Results and Discussion

The reaction of 5-amino-1,2,3,4-thiatriazole (**1**) with chloroformates in pyridine at 0°C gave after 24h moderate yields of 3,5-bis(alkoxycarbonylamino)-1,2,4-thiadiazoles (**4**).



Although the mass spectra of thiadiazoles **4** showed the expected molecular ion peaks, the crucial structural information was supplied by ^{1}H- and ^{13}C-NMR spectra, which indicated two different ethyl groups (**4a**), and two signals of C_5 and C_3 at 176.8 and 158.2 ppm, respectively. These values are characteristic for bis(acylamino)-1,2,4-thiadiazoles and compare well with the structure assignment of Kurzer [7] for 3,5-bis(benzoylamino)-1,2,4-thiadiazole.

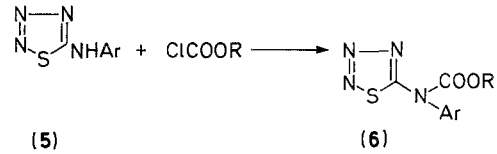
^{13}C-NMR signals indicated a nonequivalence of ester groups as well and corroborated the suggested structure of unsymmetrically substituted 1,2,4-thiatriazole.

3,5-Bis(ethoxycarbonylamino)-1,2,4-thiadiazole has previously been prepared in 8% yield by an alternative route, involving an oxidation of N-ethoxycarbonyl thiourea, and according to its analytical data [8], it was identical with the thiadiazole **4a**.

The formation of the **4** could be rationalised assuming an acylation at the amino group of the thiatriazole **1** to form an unstable carbamic acid derivative **2**, which upon loss of nitrogen and of elemental sulphur gives an alkoxycarbonyl cyanamide **3**.

Even though the alternative ring-N_3 acylation would eventually lead to the identical cyanamide **3**, we base our assumption concerning the structure of the intermediate **2**, on analogous derivatives, isolated from the reaction of 5-arylamino-1,2,3,4-thiatriazoles **5** with chloroformates.

The acylation of **5** occurred at the amino group, since an alternative ring acylation to aryliminothiatriazole **7** would have been indicated by a typical value of ^{13}C-NMR signal of C_5 at 156 ppm [9, 10], whereas the observed value of 173 ppm is characteristic for C_5 of **6**. In addition, structures **6** and **7** could be distinguished



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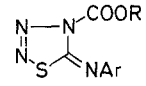


(7)

by means of ^{13}C-NMR due to the *ipso*-carbon atoms of the phenyl ring. According to the rules of L'Abbe [11] such signals of a phenylimino group would have been expected at ~150 ppm, whereas signals of carbons attached to an sp^3 hybridized nitrogen should appear at 144 ppm. A chemical shift of 136.3 ppm measured for an *ipso*-carbon of **6a** clearly falls into the latter category.

Acylation of 5-amino-1,2,3,4-thiatriazole with 2 equivalents of chlorothioformates under the above reaction conditions furnished trithiadiazapentalenes **9**, products entirely different from the chloroformate acylation.

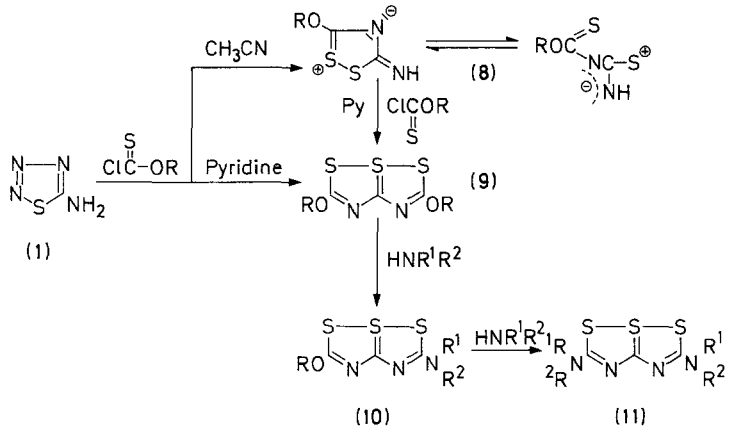
The simple pattern of their NMR spectra indicated a symmetrical skeleton; in the ^{13}C-NMR spectra there were (besides signals of aromatic carbons) only two other signals at 190 and 195 ppm. In the case of *p*-methoxyphenoxy substituted trithiadiazapentalene [(**9d**) the two *p*-methoxy] groups displayed only one signal in the ^{1}H-NMR spectrum. The mass spectra showed only a weak molecular ion peak, the principal peak ascribed to the $M^+ - OAr$ fragment.

An important hint at the structure of the trithiadiazapentalene **9a** has been furnished by the intermediate, a zwitterionic derivative **8**, isolated from the reaction of **1** with chlorothioformates in acetonitrile. The mass spectrum of **8**, displayed the calculated molecular ion peak. Unfortunately solutions of **8** were too unstable for NMR measurements. When, however, **8** was allowed to react with another equivalent of chlorothioformate in pyridine, it formed a product identical with that obtained directly from the reaction of the thiatriazole **1** with two equivalents of the reagent. Based on the above facts, we ascribe to compound **9** the structure of a 2,5-bis(phenoxy)-1,6,6a,Δ^4-trithia-3,4-diazapentalene.

Due to their structure, trithiadiazapentalenes **9** are prone to nucleophilic substitution reactions: Short heating with one equivalent of an amine suffices for the exchange of one phenoxy group to give 2-amino-5-aroxy-1,6,6a,Δ^4-trithiapentalenes (**10**).

The exchange of substituents is indicated by a high-field shift of the signal of C_2 from 195 ppm in bis(phenoxy)trithiadiazapentalenes (**9**) to 181 ppm in 2-phenoxy-5-aminotrithiadiazapentalenes (**10**); other signals changed only slightly ($\Delta\delta C_{3a} = 2$ ppm) or remained unchanged (C_5).

The mass spectra were compatible with the proposed structure of phenoxy-aminotrithiadiazapentalenes (**10**) as well, the principal peak still belonging to the M^+-O*Ar* fragment with no indication of a signal at *m/z* 210 of M^+-*Ph*NCS, which would have indicated an alternative open-chain structure of the thioureido-1,2,4-dithiazole.



The reaction of **10** with another equivalent of amine furnished the same products as that of the starting phenoxydiazapentalenes **9** with two equivalents of amine, namely 2,5-diamino-1,6,6 a, Δ^4-trithia-3,4,-diazapentalenes (**11**) in appr. 80% yield. Compound **11 a** has been known since its formation in the reaction of 3-amino-5-phenylamino-1,2,4-dithiazole with phenylisothiocyanate [12]. It can, however, be prepared from much simpler precursors, namely from compound **1** and phenylisothiocyanate [13]. By a different approach the bis(dimethylamino)diazapentalene (**11 b**) was prepared from dimethylcyanamide and phosgene [14].

In addition, signals of C_2 in trithiadiazapentalenes **10 a**, **10 b** and both C_2- and C_5-signals of the bis(phenylamino) derivative **11 a** are broadened, thereby indicating a possible amino-imino tautomerism. The phenomenon is observable up to 90°C.

Reactions of the thiatriazole **1** with chlorodithioformates in pyridine or in acetonitrile, catalyzed by triethylamine or 4-dimethylaminopyridine failed to produce any identifiable products.

Experimental

M.p.s. were determined with a Kofler hot-stage apparatus. ^{1}H- and ^{13}C-NMR spectra were recorded with Tesla BS-567 and Varian CFT-20 spectrometers, respectively, in (unless otherwise specified) hexadeuteriodimethylsulfoxide and with tetramethylsilane as an internal standard. Mass spectra were obtained with a HP 5985 B GC-MS instrument.

3,5-Bis(alkoxycarbonylamino)-1,2,4-thiadiazoles **4 a–d**

20 mmol of the corresponding chloroformate were added dropwise to a stirred solution of 2.04 g (20 mmol) of 5-amino-1,2,3,4-thiatriazole (**1**) in 10 ml of pyridine and kept at 0°C. The reaction mixture was allowed to stand 24 h at room temperature and then precipitated by pouring into 30 ml of water. The white precipitates of thiadiazoles **4** were purified by crystallization.

4 a: $R = Et$, m.p. 229–231°C (from ethanol), yield 44%. Molecular weight for $C_8H_{12}N_4O_4S$, calc. 260.3, found 260 (M^+). NMR (δC): 176.8 (C_5), 158.2 (C_3), 154.5 and 152.2 (CO), 62.7 and 60.5 (CH_2), 14.4 and 14.1 (Me). For comparison with an authentic sample see Ref. [7].

4 b: $R = Pr^n$, m.p. 180–181°C (from acetonitrile), yield 35%. Found C 41.48, H 5.30, N 19.22; $C_{10}H_{16}N_4O_4S$ (288.3) requires C 41.65, H 5.59, N 19.43.

4 c: $R = Bu^i$, m.p. 108–110°C (from methanol), yield 39%. Found C 45.81, H 6.19, N 17.52; $C_{12}H_{20}N_4O_4S$ (316.4) requires C 45.55, H 6.37, N 17.71. NMR (δC): 178.0 (C_5) 156.6 (C_3), 154.8 and 150.6 (CO), 72.2 and 72.7 [$OCH_2CH(CH_3)_2$], 27.5 and 27.2 [$OCH_2CH(CH_3)_2$], 18.6 and 18.4 [$OCH_2CH(CH_3)_2$].

4 d: $r = Bu^n$, m.p. 160–161°C (acetonitrile), yield 47%. Found C 45.71, H 6.21, N 17.59.

5-(N-Aryl-N-ethoxycarbonylamino)-1,2,3,4-thiatriazoles **6a, b**

A dropwise addition of 10 mmol of ethylchloroformate to the cooled (0°C) solution of the corresponding 5-arylamino-1,2,3,4-thiatriazole (**5**) in 10 ml of pyridine and subsequent 24 h standing at room temperature afforded the corresponding thiatriazoles **6**, isolated from the reaction mixture by the addition of water. The crude precipitate was crystallized from a methanol/water mixture.

6a: Ar = 4-Cl−C_6H_5, m.p. 100–102°C, yield 88%. Found C 42.03, H 3.10, N 20.01; $C_{10}H_9ClN_4O_2S$ (M^+-284.7) requires C 42.03 H 3.19, N 19.68. NMR (δH): 7.5 (4 H, s, arom. H), 4.22 (2 H, q, ethyl), 1.12 (3 H, t, ethyl). NMR (δC): 172.8 (C_5), 153.5 (C=O), 136.4, 130.0, 129.5, 119.8, (C_{arom}), 65.2 (ethyl), 13.8 (ethyl).

6b: Ar = 4-CH_3O−C_6H_5, m.p. 98–100°C, yield 71%. Found C 46.88, H 4.24, N 20.33; $C_{11}H_{12}N_4O_3S$ (M^+-280) requires C 47.13, H 4.32, N 19.99. NMR (δH): 7.2 (4 H, m, arom. H) 4.22 (2 H, q, ethyl), 3.75 (3 H, s, OCH_3), 1.11 (3 H, t, ethyl). NMR (δC): 172.2 (C_5), 154.1 (C=O), 159.5, 130.0, 129.1, 114.5 ($C_{arom.}$), 65.0 (ethyl), 55.4 (OCH_3), 13.8 (ethyl).

2,5-Bis(aryloxy)-1,6,6a,Δ^4-trithia-3,4,-diazapentalenes **9a–d**

40 mmol of the corresponding chloroformate were added dropwise to the 0°C cold solution of 2.04 g (20 mmol) of the thiatriazole **1** in 15 ml of pyridine. After further 24 h at room temperature water was added, the precipitate dried and crystallized.

9a: m.p. 173–174°C (from ethanol), yield 65%. Found C 52.16, H 2.59, N 8.00; $C_{15}H_{10}N_2O_2S$ requires C 52.02, H 2.89, N 8.09.

9b: m.p. 250–251°C (from dioxane), yield 46%. Found C 43.45, H 1.95, N 6.82; $C_{15}H_8Cl_2N_2O_2S$ (415.4, M^+) requires C 43.38, H 1.94, N 6.74.

9c: m.p. 206–208°C (from ethanol), yield 81%. Found C 54.32, H 3.95, N 7.43, $C_{17}H_{14}N_2O_2S_3$ (374.5, found 374 M^+) requires C 54.52, H 3.77, N 7.48.

9d: m.p. 212–213°C (from dioxane/water), yield 51%. Found C 50.21, H 3.48, N 6.60, $C_{17}H_{14}N_2O_4S_3$ (406.5) requires C 50.24, H 3.44, 6.89.

Preparation of the Zwitterion **8** (*R = Phenyl*)

2.04 g (20 mmol) of the thiatriazole **1** and 3.45 g (20 mmol) of the chlorothioformate were stirred in 15 ml of pyridine at room temperature until a TLC check indicated the absence of **1** (Silufol silica gel precoated analytical TLC plates, developed in a mixture of benzene/ethyl acetate 1 : 1, R_f = 0.15). The precipitated yellow solid was then collected and dried to give 3.10 g (56%) of **8**. M.p. 160–170°C (decomp.), M^- −210 corresponded to $C_8H_6N_2OS_2 \cdot HCl$. The zwitterion **8** was further used without purification.

1.23 g of **8** (*R=Ph*) and 0.861 g (5 mmol) of phenyl chlorothioformate were mixed and cooled to 0°C. Then 10 ml of pyridine of the same temperature were added and the mixture stirred 1 h at 0° and left overnight. The resulting dark brown solution was poured on a mixture of 20 g of ice and 10 ml of methanol. The precipitate was separated, dried and crystallized from ethanol. Yield 0.9 g (52 %), m.p. 173–174°C. The compound was identical with the **9a** described above.

2-Amino-5-aryloxy-1,6,6a,Δ^4-trithia-3,4,-diazapentalenes **10a–c**

10 mmol of the corresponding trithiadiazapentalene **9** and 10 mmol of aniline were refluxed in 10 ml of dioxane for 5′. On cooling trithiadiazapentalenes **10** precipitated.

10a: R = C_6H_5, R^1 = H, R^2-C_6H_5, yield 71%, m.p. 221–222°C (from ethanol/dioxane). Found C 52.50, H 3.21, N 12.36; $C_{15}H_{11}N_3OS_3$ (345.5, found 345 M^+) requires C 52.15, H 3.21, N 12.16.

10b: R = 4-CH_3O−C_6H_4, R^1-H, R^2-C_6H_5, yield 85 %, m.p. = 228–229°C (from dioxane). Found C 50.99, H 3.12, N 11.35; $C_{16}H_{13}N_3O_2S_3$ (275.5) requires C 51.18, H 3.49, N 11.17. NMR (δC): 7.3 (5 H, m, arom. H), 6.9 (4 H, q, arom H), 3.70 (3 H, s, OCH_3), 11.7 (1 H, m, NH), D_2O exchangeable.

10 c: R = 4-$CH_3O-C_6H_4$, R^1-H, R^2-4-$CH_3-C_6H_4$, yield 88%, m.p. = 230–231°C (from dioxane). Found C 52,32, H 3.89, N 10.78; $C_{17}H_{15}N_3O_2S_3$ (389.5, found 389 M requires C 52.42, H 3.89, N 10.79. NMR (δH): 7.0 (8 H, m, arom. H), 3.70 (3 H, s, OCH_3), 3.29 (3 H, s, CH_3), 11.6 (NH).

2,5-Diamino-1,6,6 a,Δ^4-trithia-3,4-diazapentalenes **11 a–c**

Method A: Equimolar amounts of the trithiadiazapentalene **10** and of aniline were refluxed 3 h in dioxane. On cooling diaminodiazapentalenes **11** precipitated.

Method B: 10 mmol of the trithiadiazapentalene **9** and 20 mmol of dimethylamine or piperidine were refluxed 2 h in 10 ml of dioxane. Upon cooling trithiadiazapentalenes **11 b** and **11 c** precipitated.

11 a: yield 83%, m.p. 224–226°C (from acetic acid). M^+ = 344 corresponds to the formula $C_{15}H_{12}N_4S_3$ (344.5), elem. analysis see Ref. [12].

11 b: yield 76%, m.p. = 227–228°C (from dioxane), for elem. analysis see Ref. [14].

11 c: yield 85%, m.p. = 214–215°C (from dioxane). Found C 47.78, H 6.29, N 17.13; $C_{13}H_{20}N_4S_3$ (328.5, found 328 M^+) requires C 47.53, H 6.16, N 17.06.

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