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Triazoles and Fused Triazoles, III:** Facile and Efficient Synthesis of 2,5-Disubstituted-*s*-triazolo[3,4-b]-1,3,4-thiadiazoles

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Summary. The development of a facile and efficient method for the synthesis of 2,5-diaryl-*s*-triazolo[3,4-b]-1,3,4-thiadiazoles **4a–e** from the corresponding 3-aryl-4-amino-5-mercapto-*s*-triazole (**2**), is described. 3-Aryl-4-arylideneamino-5-mercapto-*s*-triazoles (**3a–e**) were cyclized to compounds **4a–e** by heating in nitrobenzene for a few minutes.

Keywords. Oxidative cyclization; *s*-Triazolo[3,4-b]-1,3,4-thiadiazoles.

Triazole und kondensierte Triazole, III. Eine einfache und effiziente Synthese von 2,5-disubstituierten 1,2,4-Triazolo[3,4-b]-1,3,4-thiadiazolen

Zusammenfassung. Es wird eine einfache und effiziente Synthese von 2,5-Diaryl-1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazolen (**4a–e**) aus den entsprechenden 3-Aryl-4-amino-5-mercapto-1,2,4-triazolen (**2**) beschrieben. Die 3-Aryl-4-arylidenamino-5-mercapto-1,2,4-triazole (**3a–e**) wurden mittels Erhitzen in Nitrobenzol zu den Verbindungen **4a–e** cyclisiert.

Introduction

s-Triazoles and their fused heterocyclic products are receiving continuous attention for their diverse biological properties [1–9]. *s*-Triazolo[3,4-b]-1,3,4-thiadiazoles were reported to possess significant antifungal [8], central nervous depressant and anti-inflammatory [9] activities. Encouraged by the above mentioned findings, and in continuation of our earlier studies on triazoles and fused triazoles [10, 11], we now present a new synthesis of certain 2,5-disubstituted-*s*-triazolo[3,4-b]-1,3,4-thiadiazole derivatives as possible chemotherapeutic agents.

Results and Discussion

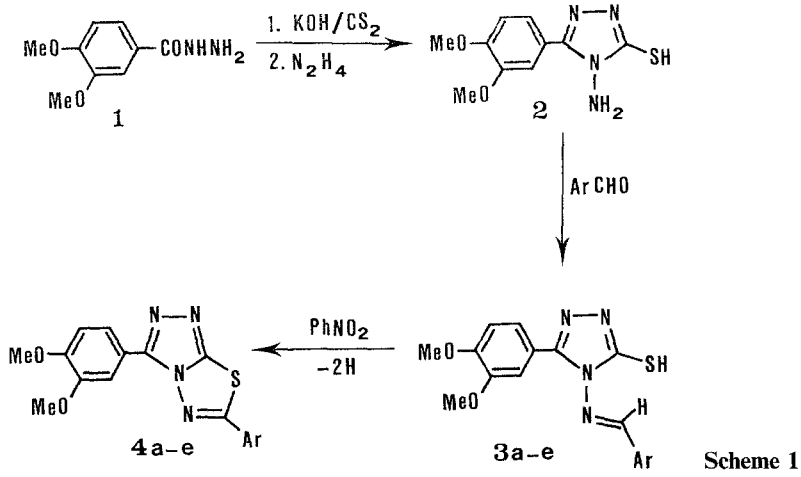
Several synthetic methods for 2,5-disubstituted-*s*-triazolo[3,4-b]-1,3,4-thiadiazoles have appeared in the literature utilizing either 1,3,4-thiadiazoles or *s*-triazoles as starting materials.

** Part II: See Ref. [11]

Kanaoka [12] described the synthesis of 2,5-dialkyl-*s*-triazolo[3,4-b]-1,3,4-thiadiazoles by reaction of 5-alkyl-2-hydrazino-1,3,4-thiadiazoles with alkyl orthoformates. The disadvantages of this method are the many steps for preparing the hydrazinothiadiazoles and their conversion to the corresponding *s*-triazolo[3,4-b]-1,3,4-thiadiazoles, in addition to the poor overall yields.

3-Alkyl or aryl-4-amino-5-mercapto-*s*-triazoles were reported as excellent precursors for *s*-triazolo[3,4-b]-1,3,4-thiadiazoles. The synthesis of 5-alkyl or aryl-*s*-triazolo[3,4-b]-1,3,4-thiadiazoles was achieved by dehydrative ring closure of 3-substituted-4-acylamino-5-mercapto-*s*-triazoles with $POCl_3$ [13]. A single-step preparation of 5-alkyl or aryl-2-substituted-*s*-triazolo[3,4-b]-1,3,4-thiadiazoles from the corresponding 3-alkyl or aryl-4-amino-5-mercapto-*s*-triazoles and the corresponding monocarboxylic acid by prolonged heating with phosphorus oxychloride was described [8, 9, 11]. The synthesis of certain 5-substituted-*s*-triazolo[3,4-b]-1,3,4-thiadiazoles (with 2-amino or 2-mercapto substituents) by interaction of cyanogen bromide or carbon disulphide, respectively, with 3-substituted-4-amino-5-mercapto-*s*-triazoles has been described [14]. 5-Alkyl-2-aryl-*s*-triazolo[3,4-b]-1,3,4-thiadiazoles can be prepared by treating 3-alkyl-4-amino-5-mercapto-*s*-triazoles with arylnitriles in presence of aluminium chloride [15].

In the present study, we describe a facile and efficient method for the synthesis of certain series of 2-aryl-5-(3,4-dimethoxyphenyl)-*s*-triazolo[3,4-b]-1,3,4-thiadiazoles (Scheme 1). The starting material 3-(3,4-dimethoxyphenyl)-4-amino-5-mercapto-*s*-triazole (**2**) [11], was prepared from the corresponding hydrazide **1** by the action of carbon disulphide, followed by hydrazinolysis. The aminotriazole **2** was then reacted with a variety of aromatic aldehydes in acetic acid to furnish the corresponding anils **3a–e** in 93–98% yields. Compounds **3a–e** were cyclized to their 2,5-disubstituted-*s*-triazolo[3,4-b]-1,3,4-thiadiazoles **4a–e** by boiling in nitrobenzene for 8–15 minutes. The structures of compounds **4a–e** were assigned on the basis of elemental analysis, ^{1}H-NMR and mass spectra. The ^{1}H-NMR spectra of compounds **4a–e** showed the absence of the CH=N (δ 8.5–9.5) and SH (δ 13–14) signals.



Scheme 1

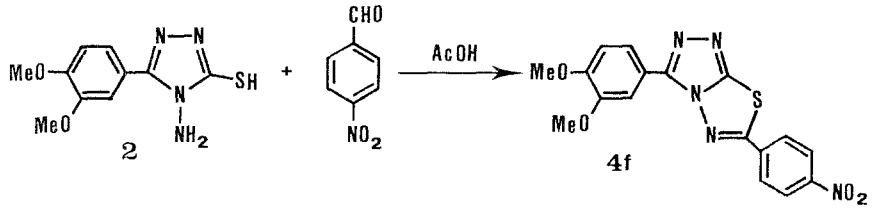
The role of nitrobenzene in this cyclization reaction was studied, in order to establish whether it is an oxidative cyclization induced by the oxidizing properties of nitrobenzene or a thermal dehydrogenation caused by the high boiling point of nitrobenzene (b.p. 210°C). Heating the compounds **3a–e** under reflux with dimethylsulphoxide (b.p. 189°C) or benzyl alcohol (b.p. 204°C) for several hours did

not yield compounds **4 a–c**, thus furnishing evidence that the cyclization process is an oxidation-reduction reaction rather than a thermal dehydrogenation.

The method described has the advantages of higher overall yields (85–90%), a shorter reaction time, utilization of safe and easily handled chemicals (aromatic aldehydes and nitrobenzene) as compared to other methods which mainly use acyl halides, $POCl_3$ and pyridine; in addition, the starting compounds (3-substituted-4-amino-5-mercapto-*s*-triazoles) are easily accessible by either the Hoggarth [16] or Reid and Heindel [17] methods.

Attempted preparation of compounds **4 a–e** in one step by reaction of compound **2** with the aromatic aldehydes using nitrobenzene as a solvent was unconvenient and gave poor yields, which may be explained by the fact that some of the aldehyde were oxidized by nitrobenzene to the corresponding carboxylic acid (TLC).

The reaction of compound **2** with *p*-nitrobenzaldehyde in boiling acetic acid (Scheme 2) yielded *s*-triazolo[3,4-b]-1,3,4-thiadiazole (**4 f**, identified by its m.p. [11] and spectral data) rather than the uncyclized anil. The difference in the behaviour of *p*-nitrobenzaldehyde towards compound **2** may be explained by the fact that the unisolated anil is oxidized *in situ* by *p*-nitrobenzaldehyde. This observation adds another evidence to the assumption that the cyclization of compounds **3 a–e** into **4 a–e** is an oxidative cyclization (*vide supra*).



Scheme 2

Experimental Part

Melting points (uncorrected) were determined using a Fisher-Johns melting point apparatus. ^{1}H-NMR spectra were recorded on a Bruker AM (300 MHz) using *DMSO-d*$_6$ as solvent and *TMS* as an internal standard (chemical shift in δ, ppm). Mass spectra were obtained on a LKB GC-MS 9000 S instrument at 70 eV. Analytical data (C, H, S) were within ± 0.4% of the theoretical values. Melting points, crystallization solvents, yield percentages and molecular formulae of compounds **3** and **4** are listed in Table 1.

3-(3,4-Dimethoxyphenyl)-4-arylideneamino-5-mercapto-s-triazoles (**3 a–e**)

A mixture of compound **2** (2.5 g, 0.01 mol) and the appropriate aldehyde (0.01 mol), in acetic acid (15 ml), was heated under reflux for 15 min. On cooling, the precipitated solid was filtered, washed with cold acetic acid, dried and crystallized.

^{1}H-NMR (**3 b**): 3.80 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 7.06–7.12 (q, 2 H, *Ar*-H), 7.48–7.89 (m, 5 H, *Ar*-H), 8.77 (s, 1 H, CH = N) and 13.84 (s, 1 H, SH). (**3 d**): 2.19 (s, 6 H, CH_3), 3.80 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 7.21–7.81 (m, 7 H, *Ar*-H), 8.76 (s, 1 H, CH = N) and 13.72 (s, 1 H, SH).

MS (**3 b**), *m/z* (rel. int.): 359 ($M^+ + 1$, 82), 358 (M^+, 72), 339 (49), 308 (61), 277 (100) and 263 (73).

Table 1. Solvents for crystallization, melting points, yield percentages and molecular formulae of compounds **3a–e** and **4a–f**

No.	*Ar*	Solvent	M.p./°C	Yield/%	Formula
3a	*p*-ClC_6H_4	*Ac*OH	248 [11]	98	$C_{17}H_{15}ClN_4O_2S$
3b	*p*-FC_6H_4	*Ac*OH	238	98	$C_{17}H_{15}FN_4O_2S$
3c	*p*-*Me*OC_6H_4	*Et*OH	226 [11]	95	$C_{18}H_{18}N_4O_3S$
3d	*p*-$Me_2NC_6H_4$	*Et*OH	234	95	$C_{19}H_{21}N_5O_2S$
3e	2-Thienyl	*Ac*OH	231 [11]	93	$C_{15}H_{14}N_4O_2S_2$
4a	*p*-ClC_6H_4	*DMF*	281 [11]	92	$C_{17}H_{13}ClN_4O_2S$
4b	*p*-FC_6H_4	*DMF*	294	94	$C_{17}H_{13}FN_4O_2S$
4c	*p*-*Me*OC_6H_4	*DMF*	>300	90	$C_{18}H_{16}N_4O_3S$
4d	*p*-$Me_2NC_6H_4$	*Ac*OH	264	90	$C_{19}H_{19}N_5O_2S$
4e	2-Thienyl	*DMF*	273	90	$C_{15}H_{12}N_4O_2S_2$
4f	*p*-$NO_2C_6H_4$	*DMF*	286 [11]	70	$C_{17}H_{13}N_5O_4S$

2-Aryl-5-(3,4-dimethoxyphenyl)-s-triazolo[3,4-b]-1,3,4-thiadiazoles (**4a–e**)

A mixture of compound **3a–e** (1.0 g) and nitrobenzene (10 ml) was heated under reflux. After 8–15 min the clear solution became turbid and a heavy precipitate was formed. The solvent was then either distilled *in vacuo* or steam-distilled and the obtained residue was washed with hot ethanol, filtered, dried, and crystallized.

^{1}H-NMR (**4b**): 3.85 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 7.19–7.22 (d, 1H, *Ar*-H) and 7.45–7.90 (m, 6H, *Ar*-H). (**4d**): 2.20 (s, 6H, CH_3), 3.79 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3) and 7.11–7.69 (m, 7H, *Ar*-H).

MS (**4b**), *m/z* (rel. int.): 357 ($M^+ + 1$, 100), 356 (M^+, 97), 337 (88) and 306 (26). (**4c**): 369 ($M^+ + 1$, 7), 368 (M^+, 39), 337 (12), 211 (98) and 209 (100).

5-(3,4-Dimethoxyphenyl)-2-(p-nitrophenyl)-s-triazolo[3,4-b]-1,3,4-thiadiazole (**4f**)

A mixture of compound **2** (2.5 g, 0.01 mol) and *p*-nitrobenzaldehyde (1.5 g, 0.01 mol), in acetic acid (15 ml), was heated under reflux for 1 h. The separated orange precipitate was filtered, washed with acetic acid, dried and crystallized.

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