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Formation of new heterocycles by intramolecular cyclization reactions of alkynethiolates with nitrogen nucleophiles

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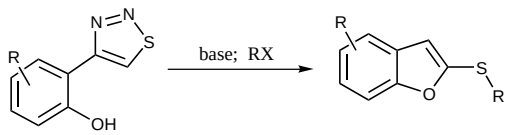
Abstract—1,2,3-Thiadiazole-4-carbohydrazides undergo base-catalyzed ring cleavage with liberation of nitrogen and recyclization to 5-thiopyrazolones, 6-thiomethylidene-1,3,4-oxadiazin-5-ones or 5-thio-7*H*-pyrazolo[5,1-*b*][1,3]thiazine-2,7-diones. © 2002 Published by Elsevier Science Ltd.

1,2,3-Thiadiazoles and 1,2,3-selenadiazoles, that are unsubstituted at the 5-position are usually easily cleaved with liberation of nitrogen and formation of alkynethiolates[1] and alkyneselenolates[2] by the action of relatively weak bases, such as alkoxides or hydroxide. The resulting acetylenic thiolates and selenolates have been widely used in organic synthesis for the synthesis of the corresponding sulfides and selenides, in cycloaddition reactions leading to new heterocycles or, after protonation, as a source of reactive thioketenes and seleno-ketenes.[3]

We recently reported a synthesis of benzofuran-2-thiolates which used the base-catalyzed decomposition of 4-(2-hydroxyaryl)-1,2,3-thiadiazoles.[4,5] The thiadiazole ring is transferred by base into a thioketene function, which cyclizes with the *ortho*-hydroxy group to form the thiolate, which can be alkylated to afford the corresponding sulfides (Scheme 1). The same reaction, applied to 1,2,3-selenadiazoles, afforded the selenides.[5,6]

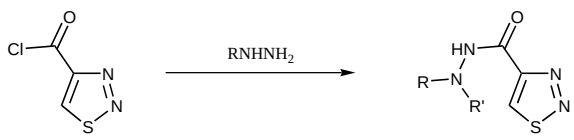
We decided to apply this methodology for the formation of nitrogen heterocycles. In order to have an entry to 1,2,3- thiadiazoles, and hence alkynethiolates, having a nucleophilic nitrogen atom, the reaction of 1,2,3-thiadiazole-4-carbonyl chloride **1**[8] with a number of hydrazines was used and 1,2,3-thiadiazole-4-carbohydrazides **2**–**4** were obtained in 60–75% overall yield. Phenyl hydrazine, on treatment with an excess of the acid chloride **1** gave the diacylated hydrazide **5** (Table 1).

When we carried out the base-catalyzed (1 equiv. of *t*-BuOK) ring cleavage of **3** and **4** followed by alkylation, either the expected 5-alkylthiopyrazolone derivatives **6a**,**b** and **7a**–**c** (with 1 equiv. of alkylating agent) or the pyrazoles **8a**,**b** and **9a** (with 2 equiv. of alkylating agent) were isolated. The same reaction conditions applied to hydrazide **2** gave no product. To obtain



Scheme 1.

Table 1. 1,2,3-Thiadiazole-4-carbohydrazides **2**–**5**, **10**



1 **2-5**

Product	R	R′	Yield (%)
2	Ph	H	75
3	PhCO	H	74
4	Ts	H	60
5	Ph	1,2,3-Thiadiazole-4-carbonyl	70[a]
10	Ts	Me	35[b]

[a] To prepare hydrazide **5** an excess of 1,2,3-thiadiazole-4-carbonyl chloride has been used.

[b] By alkylation of **4**.

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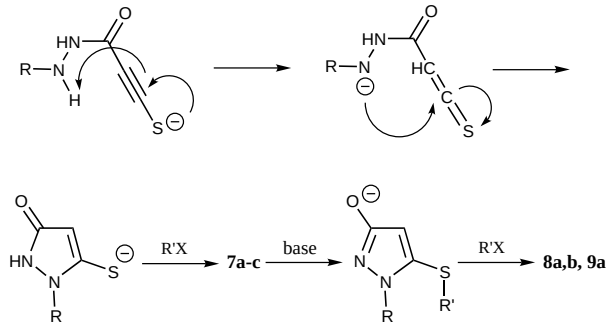
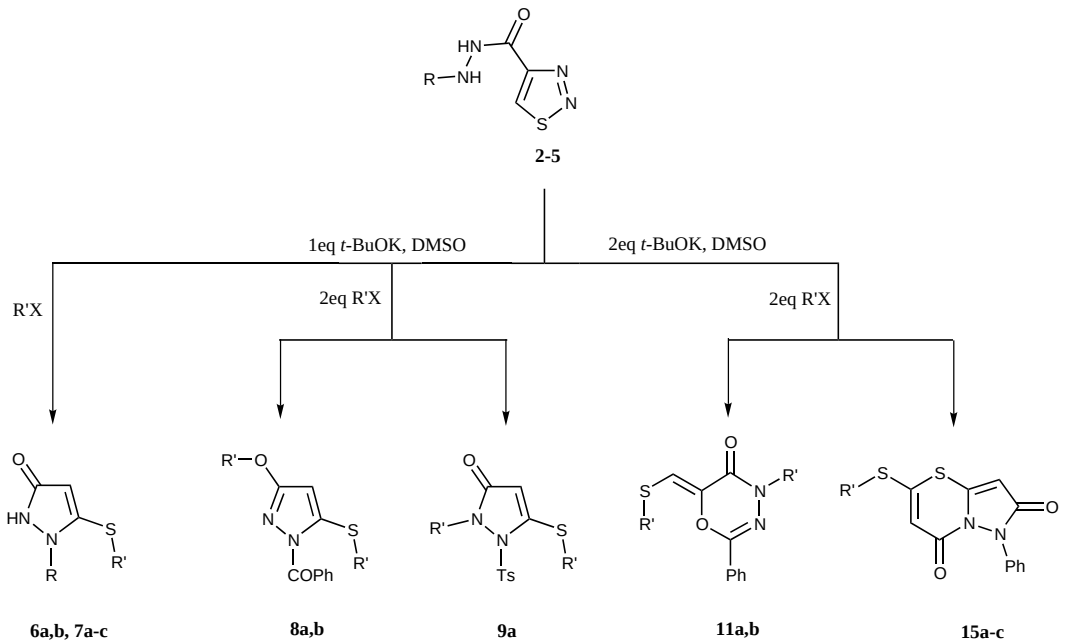
compounds **6–9** it is necessary to carry out the base-catalyzed ring cleavage of **3** and **4** about 18 h previous to the addition of alkylating agent.[9] Yields are between 20–35% after chromatography. The balance of the reaction is formed by polar, unidentified products (Table 2). In the case when the alkylating agent (methyl iodide) was present in situ in the decomposition reaction mixture of **4** a complicated mixture of reaction products was obtained, including **7a**, **9a** and the *N*-methylated hydrazide **10** (Table 1). Without alkylating agent, none of the expected pyrazolethione could be isolated after neutralization of the reaction mixture.

The pyrazoles **6–9** apparently result from a multistep process involving the cleavage of the thiadiazole ring with formation of the alkynethiolate (Scheme 2). Fast intramolecular proton shift gives the reactive thioketene, which undergoes intramolecular nucleophilic cyclization to a pyrazolone-5-thiolate anion. This thiolate is easy alkylated, forming either pyrazoles **6** and **7** or on subsequent alkylation with a second



Scheme 2.

Table 2. Ring cleavage[a] of hydrazides of **2–5** with *t*-BuOK in DMSO at 20°C followed by alkylation



Product	Substrate	R′X	R	Yield (%)
–	**2**	MeI	Ph	0
6a	**3**	MeI	PhCO	20
6b	**3**	$C_{16}H_{33}Br$	PhCO	25
7a	**4**	MeI	Ts	30
7b	**4**	$C_{16}H_{33}Br$	Ts	35
7c	**4**	$PhCH_2Cl$	Ts	34
8a	**3**	MeI	PhCO	20
8b	**3**	$C_{16}H_{33}Br$	PhCO	35
9a	**4**	MeI	Ts	23
11a	**3**	MeI	PhCO	40
11b	**3**	$PhCH_2Cl$	PhCO	51
15a	**5**	MeI	1,2,3-Thiadiazole-4-carbonyl	30
15b	**5**	$C_{16}H_{33}Br$	1,2,3-Thiadiazole-4-carbonyl	20
15c	**5**	$PhCH_2Cl$	1,2,3-Thiadiazole-4-carbonyl	25

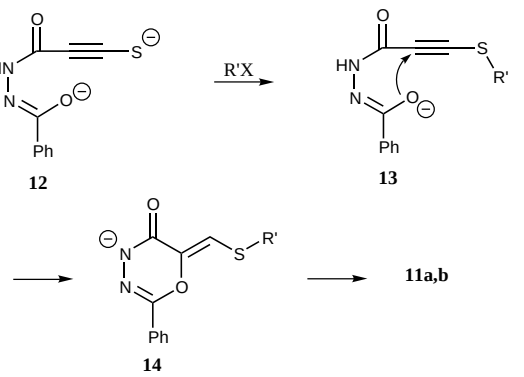
[a] The ring cleavage of hydrazides in other systems (*t*-BuOK–DMF, *t*-BuOK–MeCN, *t*-BuOK–THF, NaH–DMF, NaH–MeCN, NaH–THF at 20°C as well as BuLi or *t*-BuLi in THF at −78°C) gave no results or the yields of compounds **6–9** were very poor. The balance of these reactions is formed by unidentified products.

equivalent of methyl iodide, the dialkylated pyrazoles **8a**,**b** and **9a**. ^{13}C NMR spectroscopic analysis showed that *O*-alkylation occurred in the case of benzoyl derivative **3**. The ^{13}C NMR signals for methyl or methylene groups of **8a** and **8b** are at 56 and 65 ppm, respectively. However, we were surprised to see that the tosyl derivative **9a** was *N*-alkylated (^{13}C NMR signal for methyl at 36 ppm).

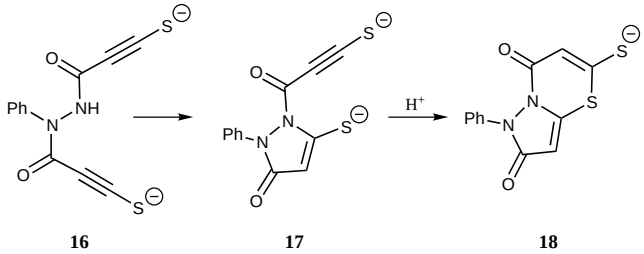
When the ring cleavage of hydrazides **3**–**5** was carried out in the presence of 2 equiv. or more of *t*-BuOK, the cyclization takes another course. Thus, the decomposition of benzoyl hydrazide **3** followed by alkylation results in 1,3,4-oxadiazin-5-one derivatives **11a**,**b**. On the other hand, the tosylhydrazide **4** under the same conditions yields benzyltolylsulfinate[7] as the only identifiable decomposition product (Table 2).

In the case of the benzoyl hydrazide **3**, we can rationalize the product obtained by the intermediacy of the alkynethiolate dianion **12**, which does not cyclize, but rather is monoalkylated to the alkynesulfide **13**, which undergoes cyclization to the six-membered ring by attack of the imidate anion on the alkynesulfide, rather than the formation of the alternative seven-membered ring (Scheme 3). The resulting anion **14** is then alkylated on nitrogen (^{13}C NMR methyl or methylene signals for **11a**,**b** at 36 and 52 ppm). We were not able to isolate monoalkylated oxadiazine derivatives from this reaction.

Finally, 1,2,3-thiadiazole-4-carbohydrazide **5**, after cleavage of two 1,2,3-thiadiazole rings, recyclization and alkylation gives the novel fused 7*H*-pyrazolo[5,1-*b*][1,3]thiazine-2,7-diones **15a**–**c** (Table 2). Here we can assume that the bis(alkynethiolate) **16** is formed first, which then cyclizes, similar to Scheme 2, to the pyrazole-5-thiolate **17**. This can undergo a second cyclization with the formation of a thiazine-6-thiolate **18**, which finally is alkylated to give the products **15a**–**c** (Scheme 4).



Scheme 3.



Scheme 4.

Acknowledgements

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9. *1-Tosyl-5-(1-hexadecylthio)pyrazol-3-one* **7b**. To a solution of hydrazide **4** (1 mmol) in DMSO (5 mL) a solution of *t*-BuOK (1 mmol) in DMSO (5 mL) was added and the reaction mixture was stirred at room temperature for 18 h. 1-Bromohexadecane (1 mmol) was added and after stirring for 6 h, the solvent was evaporated under reduced pressure at 40°C. Dichloromethane was added to the residue, the organic layer was washed twice with water, dried, evaporated, and the reaction product was purified by silica gel column chromatograpy. Yield of **7b**: 30%, mp 116–118°C. ^1H NMR ($CDCl_3$, δ, ppm): 0.88 (t, 3H, CH_3), 1.26 (s, 24H, $(CH_2)_{12}$), 1.40 (txd, 2H, $SCH_2CH_2CH_2$), 1.68 (txd, 2H, SCH_2CH_2), 2.42 (s, 3H, CH_3), 2.87 (t, 2H, SCH_2), 5.65 (s, 1H, CH_{het}), 7.26 (d, 2H *m*-CH_{arom}), 7.85 (d, 2H, *o*-CH_{arom}), and 11.31 (br s, 1H, NH_{het}). ^{13}C NMR ($CDCl_3$, δ, ppm): 14.5, 22.1 (CH_3 tosyl), 23.0, 28.5, 29.2, 29.4, 29.5, 29.8, 30.0, 32.3, 34.4 (CH_2S), 99.3 (C^4_{het}), 128.5, 130.2, 133.7, 146.0, 148.7 and 166.1 (C^5_{het} and C^3_{het}). MS 495. Found: C, 62.9; H, 8.3; N, 6.0. $C_{26}H_{42}N_2O_3S_2$. M 495. Calcd: C, 63.1; H, 8.6; N, 5.7%.