Stepwise Cyclization of Hydrazonoyl Cyanides with Isothiocyanates to 1,3,4-Thiadiazolines

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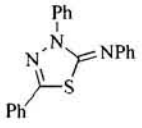
1,3,4-Thiadiazolines have been smoothly synthesized by a new stepwise cyclization of hydrazonoyl cyanides with isothiocyanates in the presence of NaH at 25 ℃.

Hydrazones are one of the important building blocks for the synthesis of heterocycles[1-4] and asymmetric synthesis.[5,6] 1,3-Dipolar cyclizations using nitrile imines have been well documented.[2,7] Earlier, Huisgen et al.[2,8] reported that 1,3-dipolar cycloaddition of arylnitrile imines with phenyl isothiocyanate gave a mixture of thiadiazoline **1** and triazolthione **2** (**1**:**2** = 2:1). This 1,3-dipolar cycloaddition was demonstrated to undergo a concerted reaction pathway. Only arylnitrile imine was used for the preparation of 2-aryl thiadiazoline probably due to the limitation of generation of alkylnitrile imine. Later, Yamamoto et al.[9] synthesized 1,3,4-thiadiazoline by the reaction of phenylhydrazones with phenyl isothiocyanate. In the case of benzaldehyde, phenylhydrazone, uncyclized chain product, thiosemicarbazone was obtained and followed by heating in benzene-hexane to give 1,3,4-thiadiazoline in reasonable yield.[9] There have been few reports concerning general syntheses of hydrazonoyl cyanide for the utilization of heterocyclic synthesis.[10,11]



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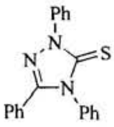

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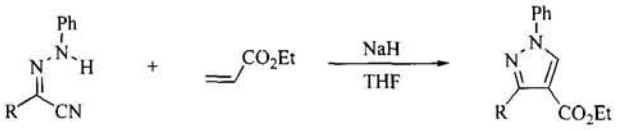
Recently, we have reported a convenient method that Pd-catalyzed dehydrogenation of α-hydrazinonitriles afforded hydrazonoyl cyanides in good yields in the presence of cyclopentene, which could applied to the synthesis of 1H-pyrazol-4-carboxylates.[12] In order to extend these findings, the reactions of hydrazonoyl cyanides with aryl- or alkyl isothiocyanates have been examined.

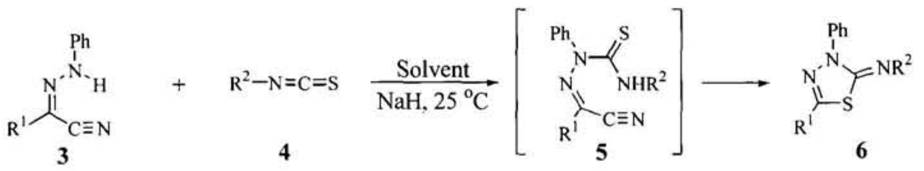


We have now found that hydrazonoyl cyanides reacted with aryl- or alkyl isothiocyanated in DMF in the presence of NaH to afford the corresponding **6** in high yields (Table 1).

On the other hand, the same reaction of **3a** or **3b** with **4a** or **4b** under same reaction conditions in THF instead of DMF as a solvent resulted in only an uncyclized thiosemicarbazone **5a** (90%, run 1) or **5b** (86%, run 5) respectively as shown in Scheme 1.

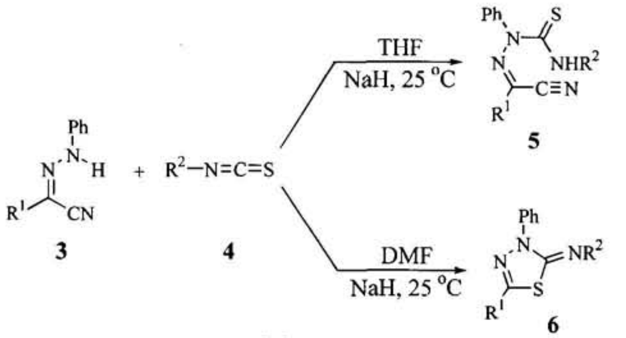
In a general experimental procedure, to a solution of N-phenylhydrazonoyl cyanide **3** (0.5 mmol) and R^2NCS (0.6 mmol) in DMF (2 ml) was added NaH (3eq.) in one portion at room temperature. After stirring for given time (Table 1), H_2O (10 ml) was added, and the reaction mixture was extracted with Et_2O (20ml X 3), dried over $MgSO_4$ and then concentrated to give

Table 1. Reaction of hydrazonoyl cyanides with R^2 NCS in the presence of NaH



Run	R^1	R^2	Solvent	Time / h	Product / 5,6	Yield / % [a]
1	i-Bu (**3a**)	Ph (**4a**)	THF	5	**5a**	90
2	i-Bu (**3a**)	Ph (**4a**)	DMF	1	**6a**	87
3	n-Bu (**3b**)	Ph (**4a**)	DMF	1	**6b**	85
4	n-Bu (**3b**)	Me (**4b**)	DMF	5	**6c**	80
5	n-Bu (**3b**)	Et (**4c**)	THF	10	**5b**	86
6	n-Bu (**3b**)	Et (**4c**)	DMF	5	**6d**	84
7	n-Bu (**3b**)	Allyl (**4d**)	DMF	5	**6e**	83

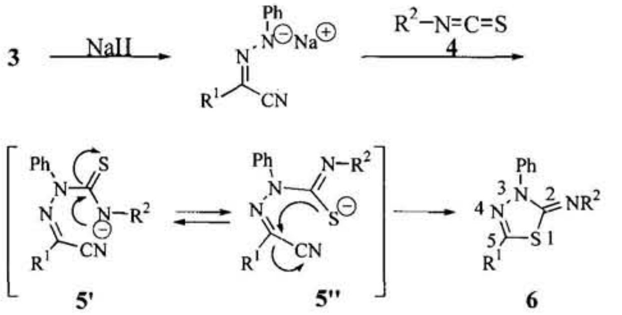
[a] Isolated yields.



Scheme 1.

crude solids, which were purified by flash column chromatography (20 cm X 2 cm, silicagel 230-400 mesh, EtOAc : n-hexane=1:9) to afford the pure **6**.

Both alkyl isothiocyanates (R^2=Me, Et and allyl) and aryl isothiocyanates (R^2=Ph) gave the high yields of cyclized product **6**. But the reaction rates of alkyl isothiocyanate are faster than those of aryl isothiocyanate (Table 1). It is noteworthy that the [2+3] cyclization occurred in DMF solvent to give **6**, but only uncyclized products **5** were obtained in THF. When **5b** (R^1=n-Bu, R^2=Et) was treated with NaH in DMF under the same reaction conditions, **6d** was actually obtained in quantitative yield. Thus, the reaction may be rationalized by a stepwise path through an intermediate **5**; i.e, an anion of hydrazonoyl cyanide formed initially by NaH would attack the carbon center of **4** to form an intermediate anion **5'** or **5''**. The stronger nucleophile of thiolate anion **5''** may attack the C-5 to result in the cyclized product **6** as shown in Scheme 2.



Scheme 2. Mechanism of Stepwise Cyclization of **3** with **4**.

The structures of **6** were determined by HRMS and by comparison of the chemical shifts of carbons at 2 and 5 position (**6a** ; 2-position 168.2 ppm and 5-position 151.7 ppm) with those from the similar compunds **1** in ^{13}C NMR spectrum (2-position 168.6 ppm and 5-position 149.9 ppm).[10] In conclusion, the present reaction provided a new general method for the preparation of 2-alkylimino-5-alkyl thiadiazolines and 2-aryl imino-5-alkyl thiadiazolines. Further studies on scope and synthetic applications are in progress.

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