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Communication

Thiocyanation

Thiocyanation of *N,N*-Dialkylhydrazonoyl Bromides: An Entry to Sulfur-Containing 1,2,4-Triazole Derivatives

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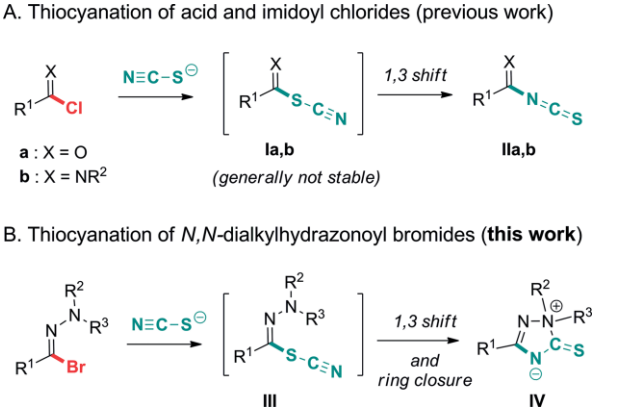
Abstract: A simple and practical one-pot protocol involving sequential C–H bromination and thiocyanation of readily available aldehyde-derived *N,N*-dialkylhydrazones has been established for the synthesis of 5-thioxo-1,2,4-triazolium inner salts. Application of the method toward the synthesis of value-added 3-sulfanyl-1,2,4-triazoles through N→S alkyl group transfer has also been demonstrated.

Introduction

Organic thiocyanates (R-SCN) have been implicated as key intermediates in the synthesis of diverse valuable organosulfur compounds. Many synthetic methods have been developed over the years to access SCN-derived building blocks, notably based on nucleophilic substitution of the corresponding organic halides by using thiocyanate salts as thiocyanating agents.[1] Frequently, however, the resulting organic thiocyanates rearrange to the thermodynamically more stable isothiocyanate derivatives (R-NCS) through 1,3-shift isomerization.[2] This has generally been the case for acyl (and aroyl) thiocyanates (**Ia**),[3] with only few exceptions,[4] as well as for their nitrogen derivatives, the imidoyl thiocyanates (**Ib**) (Scheme 1A).[5] This interesting feature has been shown to also have huge synthetic applications, especially in heterocyclic series,[3] due to the capacity of the central carbon atom of the N=C=S group to undergo addition of a large variety of nucleophilic reagents.

Given the importance of the hydrazone functional group in synthetic organic chemistry,[6] we became interested in exploring the thiocyanation of *N,N*-dialkylhydrazonoyl halides,[7] expecting the reaction to yield the corresponding hydrazonoyl isothiocyanates[8] as reactive intermediates with high synthetic potential.[9] Herein, we demonstrate that thiocyanation of *N,N*-dialkylhydrazonoyl bromides leads to the direct formation of uncommon 5-thioxo-1,2,4-triazolium inner salts (**IV**), and establish hydrazonoyl thiocyanates (**III**) as first-formed intermediates in this transformation (Scheme 1B). We also propose a simple and practical one-pot protocol allowing sequential bromination and thiocyanation of readily available aldehyde-derived hydrazones. Application of the triazolium inner salts to the synthesis of valuable sulfanyltriazoles through intramolecular N→S alkyl transfer is also discussed.



Scheme 1. Reactions of acid halides and their nitrogen derivatives with thiocyanate salts, involving thiocyanate to isothiocyanate rearrangement.

Results and Discussion

Preliminary investigations were conducted starting from morpholine-derived hydrazone **1a** as a model substrate (Scheme 2). Pleasingly, the opening bromination step occurred almost spontaneously (ca. 5 min as indicated by TLC) in MeCN at room temperature when using *N*-bromosuccinimide (1.1 equiv.) as brominating agent.[10] It was therefore decided to conduct the thiocyanation reaction subsequently within the same reaction flask without isolation of the hydrazonoyl bromide **2a**. An excess of sodium thiocyanate was thus added, and the reaction mixture was left to stir for 24 h, after which time analysis of the crude mixture revealed the presence of a single product. After standard extraction of water-soluble materials, the product was isolated in pure analytical form by simple crystallization and, to our surprise, its structure was established as 5-thioxo-1,2,4-triazolium inner salt **5a** (93 % isolated yield over two steps). Interestingly, *this class of zwitterionic ring compounds, which also include the related 5-oxo and 5-imino deriva-*

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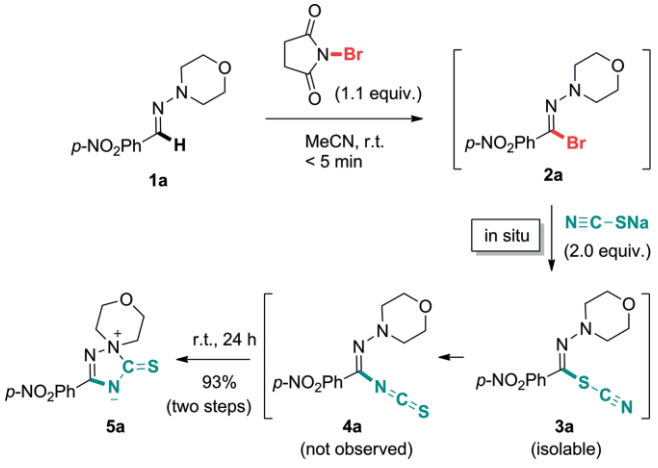
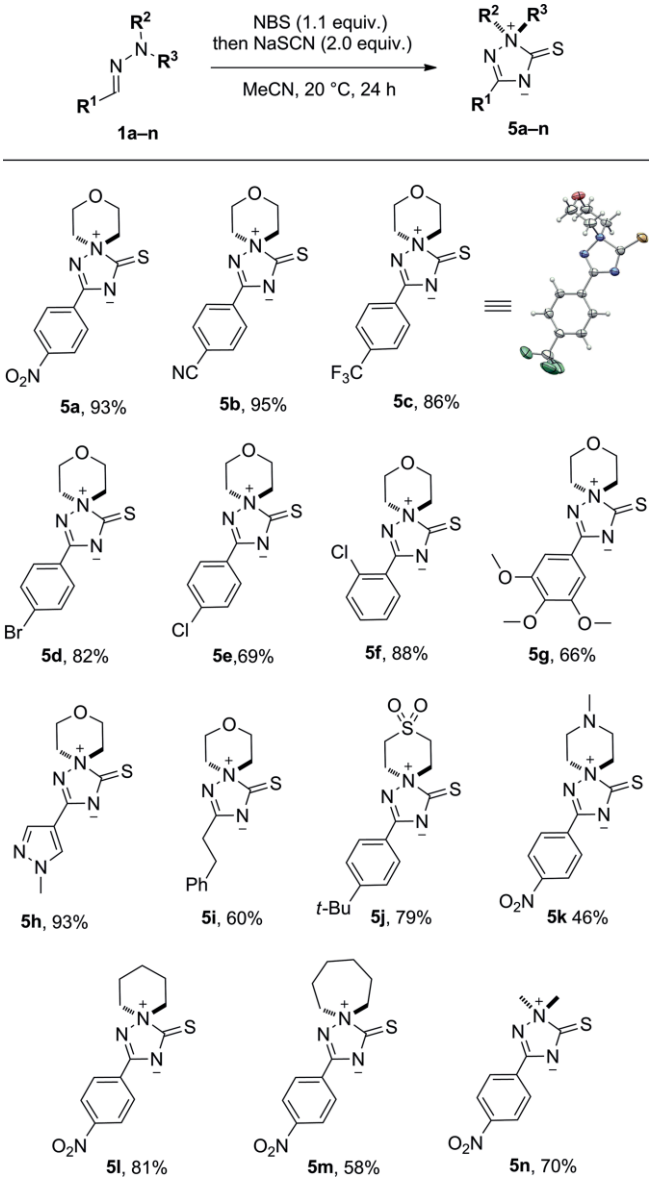
tives, had only been scarcely documented, and no synthetic utility of these compounds has been described so far.[11] This prompted us to investigate this transformation in more details.



Scheme 2. Sequential C–H bromination/thiocyanation of *p*-nitrobenzaldehyde 4-morpholinylhydrazone (**1a**).

From a mechanistic point of view, formation of the triazolium inner salt is supposed to proceed first by nucleophilic substitution of the in situ generated hydrazonoyl bromide **2a** by the thiocyanate ion to give hydrazonoyl thiocyanate **3a**. The latter would isomerize to the corresponding isothiocyanate **4a**, which would then spontaneously ring close to generate the 1,2,4-triazole ring system. It is interesting that terminating the thiocyanation step only 15 min after addition of sodium thiocyanate afforded a 4:1 mixture of **3a** and **5a** (quantitative yield) by identical workup and purification steps. Furthermore, stirring this mixture in MeCN for 24 h in the absence of any other reagents led to the complete conversion into triazolium **5a**, which gives evidence for the proposed sequence of events.

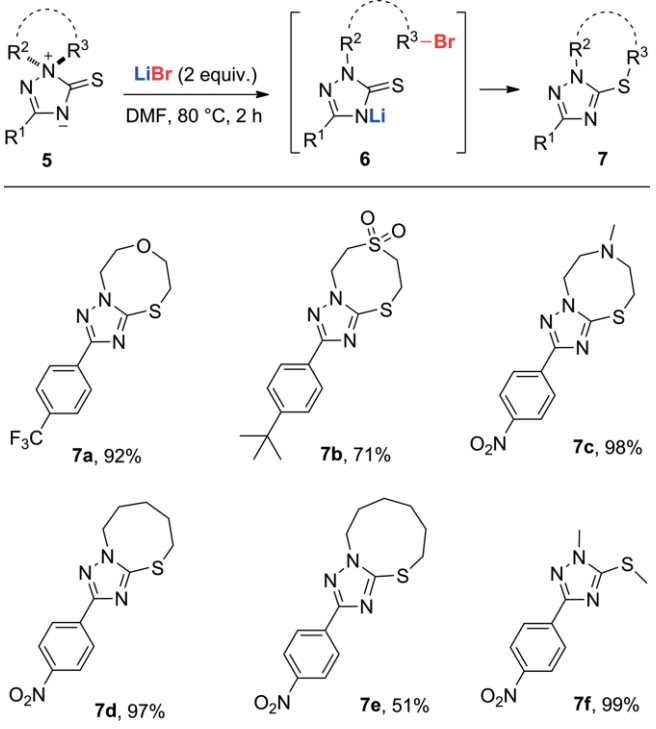
With a practical one-pot procedure established, we began to gauge the scope of the process (Scheme 3). We first examined the reactivity of various benzaldehyde-derived 4-morpholinyl hydrazones. Good to high yields were generally achieved with various substituents on the aromatic ring regardless of their electron-donating or electron-withdrawing nature (**5a**–**5g**). An X-ray structure was obtained for **5c**.[12] Overall, the reaction displayed good tolerance towards a variety of functional groups, including nitro, cyano, and halide. A pyrazolyl aldehyde hydrazone also proved to be a suitable substrate for the transformation (**5h**). Remarkably, aliphatic aldehyde-derived hydrazones may be involved in the reaction, as illustrated with **5i**. Next, the influence that the terminal amino group of the hydrazone exerts on the reaction was examined. Hydrazones bearing other cyclic amino groups, i.e., 1,1-dioxido-4-thiomorpholinyl, 4-methyl-1-piperazinyl, 1-piperidinyl, and 1-homopiperidinyl, also participated to give the desired products (**5j**, **5k**, **5l**, and **5m**, respectively) in moderate to good yields. Finally, a *N*,*N*-dimethylhydrazone proved to be a suitable substrate for this transformation as well (**5n**). It is noteworthy that all synthesized zwitterionic compounds were obtained as bench-stable solids after simple crystallisation.



Scheme 3. One-pot C–H bromination/thiocyanation of *N*,*N*-dialkylhydrazones: Access to 5-thioxo-1,2,4-triazolium inner salts. Reaction conditions: **1** (1.0 mmol), NBS (1.1 mmol) in 5 mL of MeCN at room temp. until complete conversion (TLC monitoring, < 15 min); then addition of NaSCN (2.0 mmol), room temp., 24 h. Yields are given for single runs and refer to analytically pure products isolated by simple crystallization.

Next, we focused our efforts on finding synthetic application of triazolium derivatives **5**. Interestingly, a diversity of sulfur-substituted 1,2,4-triazole derivatives has been reported to possess important biological properties,[13] and notably non-nucleoside HIV-1 reverse transcriptase inhibitory activity (NNRTI).[14] It was envisioned that rearrangement of the *N*-spirotriazolium inner salts through intramolecular *N*-dealkylation/*S*-alkylation steps would possibly open access to value-added sulfanyltriazoles, i.e., the triazole-fused S-heterocyclic derivatives **7**.[15] Gratifyingly, the desired transformation was achieved by simple heating of the triazolium inner salts at 80 °C in DMF in the presence of 2 equiv. LiBr (Scheme 4). Various triazole-fused heterocycles (**7a–e**) were thus obtained in mod-

erate to excellent isolated yields. Interestingly, synthesis of the known[16] methylthiotriazole **7f** demonstrated that external N→S methyl group transfer is achievable in a totally selective manner. It is remarkable that all of the N, C, and S atoms of the original thiocyanate moiety have contributed to these structures through bond formation.



Scheme 4. Rearrangement of triazolium inner salts (**5**) into 3-sulfanyl-1,2,4-triazoles (**7**). Reaction conditions: **5** (0.3 mmol), LiBr (0.6 mmol) in 1.5 mL of DMF, 80 °C. Yields are given for single runs and refer to pure products isolated by silica gel chromatography.

Conclusions

A one-pot, simple, and practical protocol has been established for the cyclization of aldehyde-derived hydrazones with thiocyanate, which involves a bromination, thiocyanation, SCN→NCS isomerization, and ring closing sequence. The protocol provides an efficient synthetic entry into rarely documented 1,2,4-triazolium inner salts, which are key intermediates for further elaboration into a diversity of value-added 3-sulfanyl-1,2,4-triazole derivatives. Further studies into the scope and synthetic applications of this method are currently underway in our laboratories, and will be reported as events merit.

Experimental Section

General Procedure A. Preparation of Triazolium Inner Salts 5: In a 25 mL round-bottomed flask equipped with a magnetic stir bar, *N*-bromosuccinimide (196 mg, 1.1 mmol) was added to a solution of the selected hydrazone (1.0 mmol) in MeCN (5 mL). The reaction mixture was sealed by a septum and stirred at room temperature until complete consumption of the starting material occurred as indicated by thin layer chromatography (< 15 min). NaSCN (162 mg, 2.0 mmol) was then added and the reaction mixture was left to stir for 24 h, after which time the reaction mixture was concentrated in vacuo and diluted with CH_2Cl_2 (20 mL). The solution was washed with water (3 × 10 mL), dried with $MgSO_4$, and concentrated in vacuo to give a solid residue. Crystallization of the residue from an appropriate mixture of dichloromethane/petroleum ether gave the triazolium inner salt in analytically pure form.

General Procedure B. Preparation of Sulfanyltriazoles 7: In a 10 mL screw-cap glass tube equipped with a magnetic stir bar, LiBr (50 mg, 0.6 mmol) was added to a solution of the selected triazolium inner salt (0.3 mmol) in DMF (1.5 mL). Then the reactor was sealed, and the reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was then cooled and diluted with CH_2Cl_2 (10 mL). The solution was washed with water (3 × 5 mL), dried with $MgSO_4$, and concentrated in vacuo to give a solid residue. Purification of the residue by flash chromatography (silica gel, appropriate mixture of cyclohexane/ethyl acetate) afforded the corresponding sulfanyltriazole.

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Keywords: Hydrazones · Cyclization · Rearrangement · Zwitterions · Nitrogen heterocycles

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