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Reaction of Arylmethyl Isocyanides/Arylmethyl- amines with Xanthate Esters: A Facile and Unexpected Synthesis of Carbamothioates

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Abstract

An unexpected formation of carbamothioates by the reaction of arylmethyl isocyanides with xanthate esters in the presence of sodium hydride is reported. The products thus obtained were compared with carbamothioates obtained by the condensation of the corresponding benzylamines with xanthate esters in the presence of sodium hydride in DMF. A mechanism which is substantiated by DFT calculations to account for the unexpected reactions is proposed.

Keywords

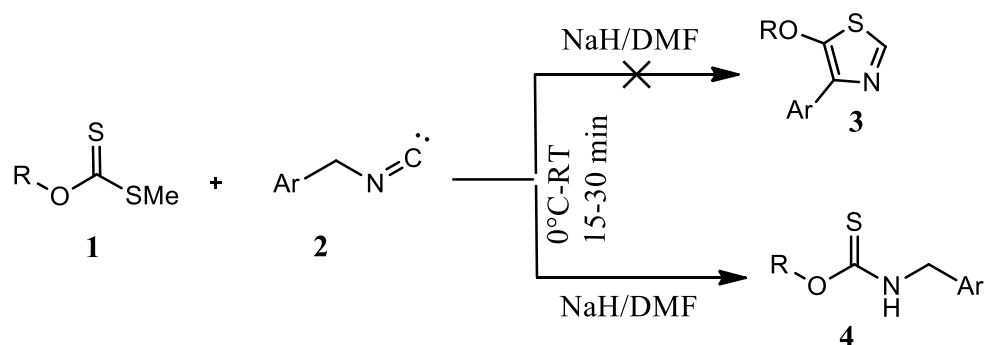
Xanthate esters; Isocyanides; Benzylamines; Carbamothioates; Sodium hydride; Density Functional Theory, Intrinsic Reaction Coordinate Analysis

Introduction

Carbamothioates are reported as antimicrobial,^[1] antifungal (tolnaflate and tolciclate drugs),^[2] antimycobacterial,^[3] human leucocyte elastase inhibitors,^[4] TRPV1 antagonists,^[5] PPAR α 1 γ dual antagonist,^[6] intermediates in the synthesis of HIV-1 integrase ligands,^[7] insecticides (cartep),^[8] and herbicides.^[9] Besides, they are also used as key intermediates in the generation of carbonyl sulfide/hydrogen sulfide,^[10] synthesis of isothiocyanates,^[11] asymmetric thioureas^[12] and thiazolidine/thioxazine.^[13] Consequently therefore, numerous synthetic methods for carbamothioates have been reported. These include reactions of chlorothioformates with amines,^[14] thiocarbonyl benzotriazoles with alcohols,^[15] copper-catalyzed reactions of α -substituted stannanes with thiocarbamates,^[16] reactions of isothiocyanates with alcohols,^[6,17] and reactions of xanthate esters with amines.^[18]

Furthermore, many methods have also been reported for the synthesis of cyclic thiocarbamates and these include reactions of isothiocyanates with aldehydes in the presence of organocatalysts,^[19] reactions of vicinal diols with potassium thiocyanate,^[20] reactions of 2-naphthol, aldehyde with thiourea catalyzed by iron nanoparticles,^[21] isothiocyanatooxindoles with ketones,^[22] ammonium isothiocyanates with chalcones^[23] and α -isothiocyanatoesters with α -keto amides.^[24] Among the synthetic methods available for the synthesis of open-chain thiocarbamates, however, any of them suffer from limitations such as the use of less stable and sensitive reactants such as chlorothioformates,^[6, 14, 16, 17] toxic stannates^[16] and isothiocyanates. In a single patent disclosure thiocarbamates were reported to have been synthesized from xanthate esters, but the methodology described is limited to only a few examples with aliphatic substituents and besides, suffers from a tedious isolation protocol.^[18]

As a part of our work on the development of new synthetic methods,^[25] we have recently reported the synthesis of thiazoles from xanthate esters.^[26] In a continuation of this on-going work, we planned to synthesize 4-aryl-5-alkoxy thiazoles **3** by the reaction of arylmethyl isocyanides **2** with xanthate esters **1** in the presence of sodium hydride in DMF (Scheme 1). Unexpectedly, however, carbamothioates **4** were instead obtained in 76-88% yields (Scheme 1). Herein we report on this intriguing finding with several examples, including a single crystal X-ray structure of one of the products so obtained. A possible plausible mechanism to explain the reaction using a Density Functional Theory (DFT) analysis is also presented in this article.



Scheme 1: Synthesis of carbamothioates from xanthate esters and benzyl isocyanides

Results and Discussion

At the beginning of our study, we conducted out the reaction between *O*-benzyl *S*-methylthiocarbonate and benzyl isocyanide in the presence of sodium hydride in DMF. The product thus obtained in 85% yield in 10 min (Table 1, Method A, entry 1) was found unexpectedly to be *O*-benzyl benzylcarbamothioate **4a**. The spectral data indicated that the product existed in *cis* and *trans* geometrical isomeric forms (rotamers) because of free rotation along the thioamide bond. When the same reaction was conducted in other solvents such as THF, acetonitrile, dioxane, DMSO or toluene in the presence of sodium hydride, none of these reactions afforded product **4a** in satisfactory yields (Table 1, Method A, entries 2-6). Replacement of NaH by DBU did not furnish any product (Table 1, Method A, entry 7). Finally, a reduction in the quantity of sodium hydride slightly decreased the yield (Table 1, Method A, entry 8).

Table 1. Optimization data for the synthesis of **4a**

Method A ^a				
Entry	Solvent	Base	Time	% Yield of 4a
1	DMF	NaH	10 min	85

2	THF	NaH	4 h	45
3	CH ₃ CN	NaH	3 h	53
4	Dioxane	NaH	4 h	48
5	DMSO	NaH	2 h	58
6	Toluene	NaH	24 h	10
7	DMF	DBU	10 h	0
8	DMF	NaH ^c	15 min	83

Method B^b

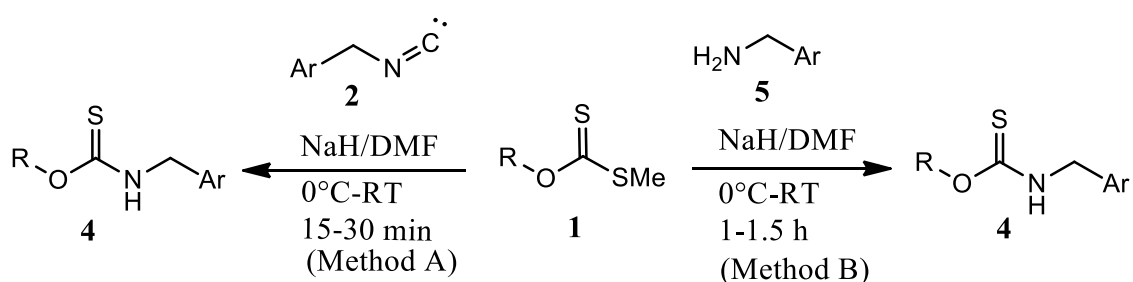
1	DMF	NaH	1 h	80
2	THF	NaH	6 h	35
3	CH ₃ CN	NaH	6 h	55
4	DMSO	NaH	3 h	58
5	Toluene	NaH	12 h	29
6	DMF	NaH ^c	1 h	74
7	DMF	DBU	24 h	0

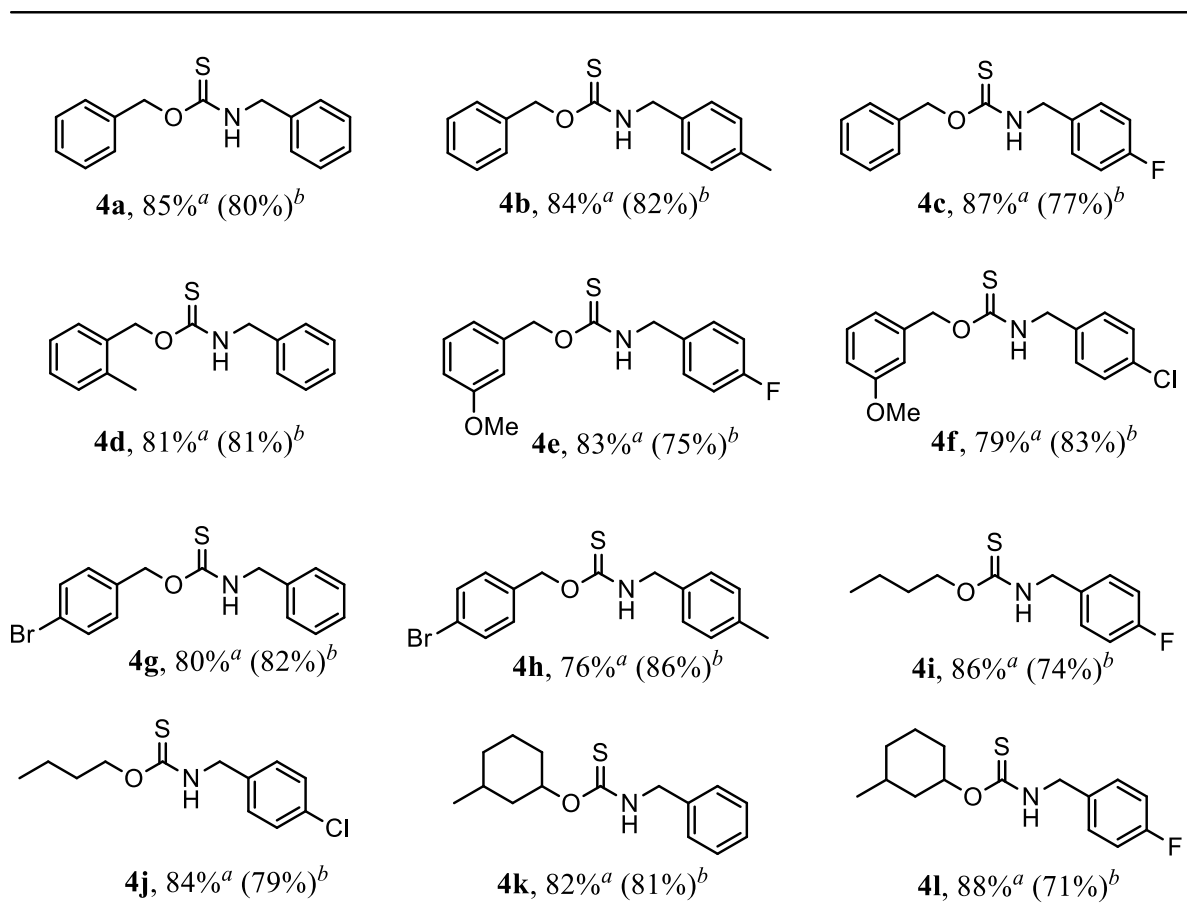
Reaction conditions: ^a O-benzyl benzylcarbamothioate (**1a**, 1.0 mmol), benzyl isocyanide (**2a**, 1.0 mmol), NaH (2.0 mmol), DMF (2.0 mL), 0°C-RT; ^b **1a** (1.0 mmol), **2a** (1 mmol), NaH (2.0 mmol), DMF (2.0 mL), 0°C-RT; ^c NaH (1.0 mmol) were used.

Using the optimized reaction conditions, O-benzyl S-methyldithiocarbonate reacted smoothly with 4-methylbenzylisocyanide and 4-fluorobenzylisocyanide to give the corresponding products **4b** and **4c** in 84 and 87% yields respectively (Table 2). Furthermore, S-methyl O-2-methylbenzyl carbonodithioate also underwent smooth reaction with benzyl isocyanide to give O-2-methylbenzyl benzylcarbamothioate **4d** in 81% yield. In addition, O-3-methoxybenzyl S-methyl carbonodithioate also gave carbamothioate **4e** and **4f** in 83 and 79% yields respectively, when reacted with 4-fluoro- or 4-chlorobenzyl isocyanide. The generality of the reaction was further

probed by reacting *O*-4-bromobenzyl *S*-methyl carbonodithioate with benzylisocyanide and 4-methylbenzyl isocyanide, which afforded the corresponding carbamothioates **4g** and **4h** in 80 and 76% yields respectively. Interestingly, xanthate ester synthesized from *n*-butanol, namely *O*-butyl *S*-methyl carbonodithioate also gave the corresponding *O*-butyl 4-fluoro- and 4-chlorobenzylcarbamothioates **4i** and **4j** when reacted with 4-fluoro- and 4-chlorobenzyl isocyanide in 86 and 84% yields, respectively. Finally, *S*-methyl *O*-(3-methylcyclohexyl)carbonodithioate also underwent reaction with benzylisocyanide and 4-fluorobenzylisocyanide to give the corresponding respective carbamothioates **4k** and **4l** in 82% and 88% yields, respectively.

Table 2. Substrate scope for the synthesis of carbamothioates





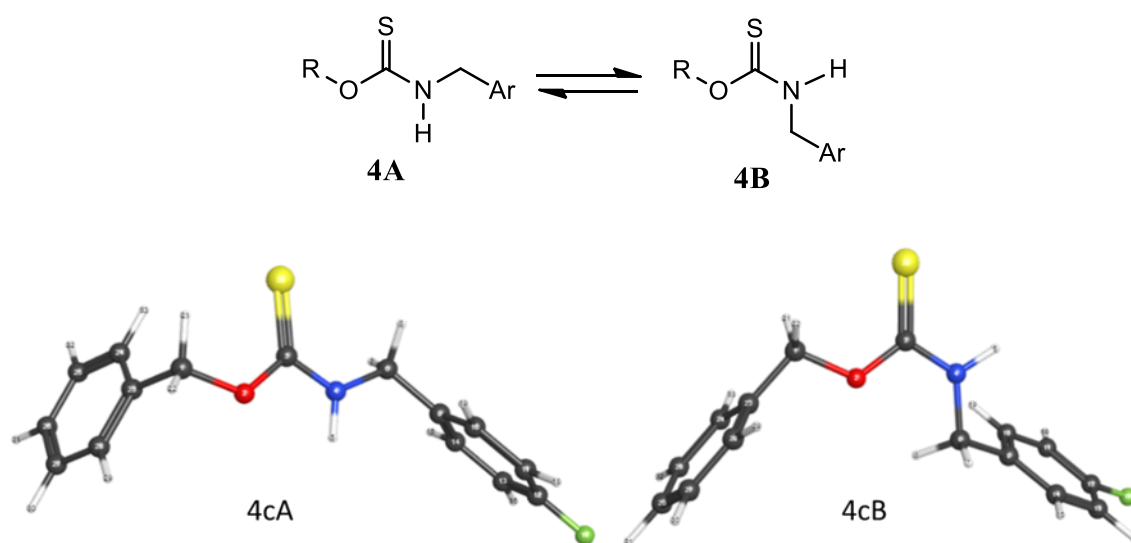
Reaction conditions: Sodium hydride (2 mmol), **1** (1 mmol), **2/5** (1 mmol), DMF (2 mL). ^a Isolated yields in method A. ^b Isolated yields in method B.

For comparison purposes, the condensation reactions of O-benzyl S-methylthiocarbamate with benzylamine in the presence of sodium hydride as the base of choice, was evaluated in various solvents such as DMF, THF, acetonitrile, DMSO and toluene (Table 1, Method B, entries 1-5). DMF was found to be the best solvent, yielding O-benzyl benzylcarbamothioate **4a** in 80% yield, over 1 h (Table 1, Method B, entry 1). A decreased amount of base reduced the yield slightly (Table 1, Method B, entry 6). Use of a weaker base such as DBU failed to form any product (Table 1, Method B, entry 7). The versatility of the synthetic methodology was further investigated by reacting O-benzyl S-methylthiocarbamate with 4-methyl- and 4-fluorobenzylamine, which respectively yielded O-benzyl 4-methylbenzylcarbamothioate **4b** and O-benzyl 4-fluorobenzylcarbamothioate **4c** in

82% and 77% yields (Table 2). *S*-Methyl *O*-2-methylbenzyl carbonodithioate reacted smoothly with benzylamine to give *O*-2-methylbenzyl benzylcarbamothioate **4d** in 81% yield. The *m*-benzyl-xanthate ester, *O*-3-methoxybenzyl *S*-methyl carbonodithioate underwent smooth condensation with 4-fluoro- and 4-chlorobenzylamine to afford the corresponding *O*-3-methoxybenzyl 4-fluoro- and 4-chlorobenzylcarbamothioates **4e** and **4f** in 75% and 83% yields, respectively. The *p*-benzyl xanthate ester: *O*-4-bromobenzyl *S*-methyl carbonodithioate also reacted successfully with benzylamine and 4-methylbenzylamine to furnish the corresponding carbamothioates **4g** and **4h** in 82% and 86% yields, respectively. Interestingly, *O*-butyl *S*-methyl carbonodithioate, the xanthate ester derived from the aliphatic alcohol, *n*-butanol, also gave the corresponding *O*-butyl 4-fluoro- and 4-chlorobenzylcarbamothioates **4i** and **4j** on reaction with 4-fluoro- and 4-chlorobenzylamine in 74% and 79% yields, respectively. Finally, the cycloalkanol xanthate ester *S*-methyl *O*-(3-methylcyclohexyl) carbonodithioate also underwent condensation with benzylamine and 4-fluorobenzylamine to give respective carbamothioate **4k** and **4l** in 81 and 71% yield respectively.

The NMR spectra of carbamothioates **4** indicated that except for **4e** and **4f**, they existed as rotamers²⁷. Alajarin et al.²⁷ noted a similar doubling of ¹H- and ¹³C-NMR signals due to rotamers in one of their *O*-benzyl-*N*-thiocarbamates. It should be noted that, the ratio of rotamers of **4** are same in both the methods (method A and B). The structure of one of the carbamothioates **4c** was confirmed by a single crystal X-ray diffraction study (CCDC reference number 1831389)²⁸ (Figure 1). The crystal data and structure refinement parameters of **4c** are given in Table 3. Bond lengths and bond angles are given Table 4. A DFT modeling study based upon the structure of **4c** for example showed that two conformers generically represented as **4A** and **4B** in Scheme 2, namely **4cA** and **4cB** respectively, had very similar computed energies

(-1208.034258 vs -1208.034403 Hartrees, respectively) thus supporting the evidence for rotamer observations in the NMR spectra. Also, DFT calculations indicated that **4cB** is 14.84 kcal/mol more stable than **4cA**. Thus, **4cB** in Figure 1 seems to be easily obtained as a single crystal than **4cA**. Further, we have analyzed the NMR of **4c** by heating at 60°C in DMSO-d₆ and recorded the spectra, where also rotamers were observed in almost same ratio as under normal condition, probably due to rapid cooling of sample solution in the NMR probe.



Scheme 2: Rotamers of thionocarbamates **4** (*top*) and computer-minimized structures of **4c** (*bottom*)

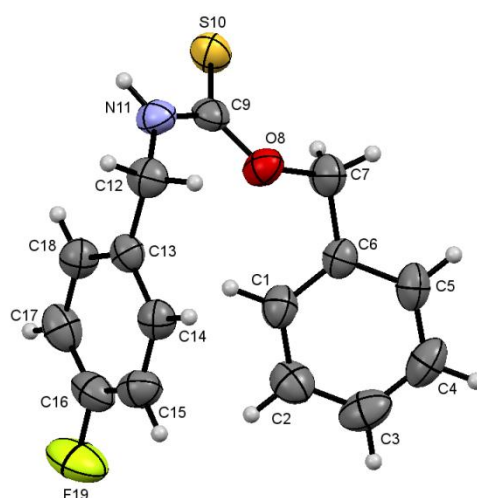


Figure 1: ORTEP diagram of O-benzyl 4-fluorobenzylcarbamothioate **4c**

Table 3: Crystal data and structure refinement for **4c**

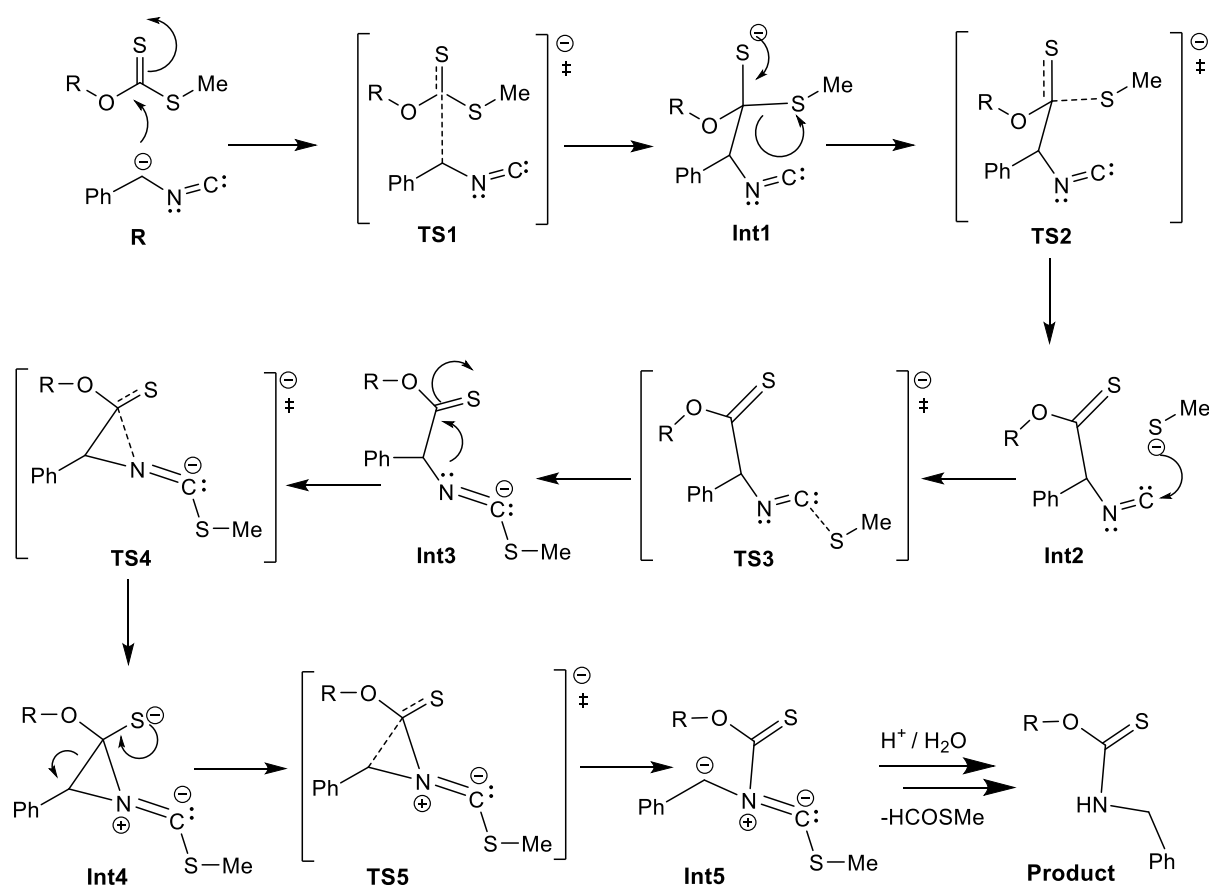
Empirical formula	C ₁₅ H ₁₄ FNOS
Formula weight	275.33
Temperature	293 K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, <i>P</i> -1
Unit cell dimensions	$a = 5.9287 (4) \text{ \AA}$, $b = 7.3176 (4) \text{ \AA}$, $c = 16.1549 (12) \text{ \AA}$. $\alpha = 101.927 (6)^\circ$, $\beta = 96.052 (6)^\circ$, $\gamma = 90.294 (5)^\circ$
Volume	681.65 (8) Å ³
Z, Calculated density	2, 681.65 (8) Mg/m ³
F ₀₀₀	288
Crystal size	0.30 x 0.25 x 0.20 mm
Theta range for data collection	2.6 to 27.5°.
Limiting indices	-7 ≤ h ≤ 6, -9 ≤ k ≤ 8, -20 ≤ l ≤ 20
Reflections collected / unique	5575 / 2265 [R(int) = 0.025]
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3125 / 0 / 172
Goodness-of-fit on F ²	1.03
Final R indices [I > 2σ(I)]	R1 = 0.0470, wR2 = 0.0991
R indices (all data)	R1 = 0.0668, wR2 = 0.1125
Largest diff. peak and hole	0.20 and -0.21 e.Å ⁻³

Table 4: Bond lengths [Å] and angles [°] for **4c**

Atoms	Length	Atoms	Length
S10—C9	1.6749 (17)	C7—O8—C9	120.89 (14)
F19—C16	1.363 (2)	C9—N11—C12	124.84 (16)
O8—C7	1.449 (3)	C2—C1—C6	120.41 (18)
O8—C9	1.328 (2)	C1—C2—C3	120.2 (2)
N11—C9	1.326 (2)	C2—C3—C4	120.1 (2)
N11—C12)	1.459 (2)	C3—C4—C5	119.4 (2)
C1—C2	1.376 (3)	C4—C5—C6	120.92 (19)
C1—C6	1.384 (3)	C1—C6—C5	119.08 (18)
C2—C3	1.377 (4)	C1—C6—C7	121.10 (17)
C3—C4	1.384 (4)	C5—C6—C7	119.80 (18)
C4—C5	1.382 (3)	O8—C7—C6	108.92 (15)
C5—C6	1.379 (3)	S10—C9—O8	125.28 (12)
C6—C7	1.499 (3)	S10—C9—N11	123.35 (14)
C12—C13	1.510 (2)	O8—C9—N11	111.37 (15)
C13—C18	1.388 (3)	N11—C12—C13	113.03 (14)
C13—C14	1.383 (3)	C14—C13—C18	118.53 (16)
C14—C15	1.374 (3)	C12—C13—C14	119.92 (16)
C15—C16	1.361 (3)	C12—C13—C18	121.55 (17)
C16—C17	1.368 (3)	F19—C16—C17	118.4 (2)
C17—C18	1.377 (3)	F19—C16—C15	118.77 (19)

We initially hypothesized that the isocyanides could have undergone a reductive cleavage to give the corresponding benzylamines, which could have reacted with **1** to

give **4**. A control experiment was therefore conducted with only the isocyanide under standard reaction conditions. Only unchanged isocyanide was found under these conditions thus ruling out this initial hypothesis. Several possible reaction mechanisms were considered to account for the unusual rearrangement observed. Ultimately, we employed quantum chemical calculations to shed light on the most probable reaction pathway for the rearrangement that led to the products observed, which is shown in Scheme 3. For simplicity, the reaction of benzyl isocyanide **2** with O-benzyl S-methyldithiocarbonate **1** was chosen for the calculations to form the intermediate **Int5** which, after a typical hydrolysis (not shown), formed product **4**.



Scheme 3: Proposed reaction mechanism for the formation of carbamothioates **4** and thiazoles **3** from xanthate esters and benzyl isocyanides.

All computations were carried out with the *Gaussian 09* package.²⁹ The location of all transition state geometries was carried out using the HF/6-31G(d) level. The

geometries of all reactants, transition states, and intermediates were fully optimized at the HF/6-31G(d) and B3LYP/6-31++G(d,p) levels of theory in the gas phase for simplicity. Intrinsic reaction coordinate (IRC) analysis was conducted for each transition state studied in this work to confirm that the transition states connected with the respective minima. The final IRC structures were further optimized (SI Fig.S1). Vibrational frequencies for all the optimized structures were calculated to ensure the presence of a single imaginary frequency for each transition state and the absence of imaginary frequencies for reactants, intermediates, and products, and also to obtain thermal corrections to energies at 298.15 K. The optimized geometries of reactants, transition states, intermediates and product of the proposed reaction mechanism leading to the intermediate **Int5** at the HF/6-31G(d) level of theory in are shown in Figure 2. The activation energies and free energies of activation were calculated at the B3LYP/ 6-31++g(d,p) level of theory.

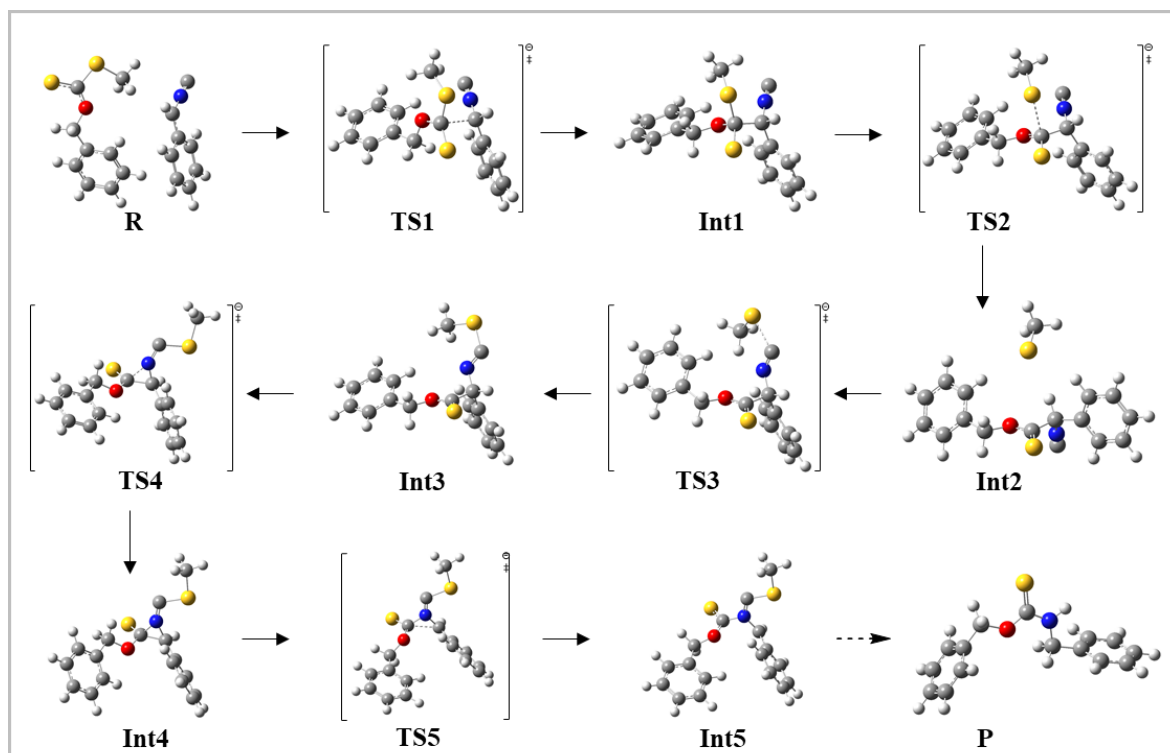


Figure 2. The optimized geometries of reactants, transition states, intermediates and product of the proposed reaction mechanism as shown schematically, above, in Scheme 3, at the HF/6-31G(d) level of theory in gas phase.

Figure 3 and Table 5 summarize the relative energies of reactants, transition states and intermediates of the proposed reaction mechanism at the B3LYP/6-31++G(d,p) level of theory in gas phase. The proposed mechanism involves five steps. The first step involves the reactant complex (shown as **R**) of the isonitrile anion and the thiocarbonyl which undergoes nucleophilic addition to generate the intermediate **Int1**, via the first transition state **TS1**. This is the fastest step in the mechanism with an activation energy of 7 kJ/mol. In the second step, anion-assisted elimination of the thiomethyl group forms the second intermediate **Int2** which consists of a tight carbene:thiosulfide pair, via transition state **TS2**. This is also a fast step with an activation energy of 44 kJ/mol. In step three, nucleophilic addition of thiomethyl anion onto the carbene carbon leads to the formation of intermediate **Int3** via transition state **TS3** with an activation energy of 95 kJ/mol. Subsequently, in the 4th step, **Int3** undergoes an intramolecular nucleophilic addition of the nitrogen lone pair onto the thiocarbonyl carbon atom to form **Int4** via **TS4**. Presumably, the negative charge on the neighbouring carbon enhances the nucleophilicity of the nitrogen's lone pair of electrons to form **TS4** and intermediate **Int4**. This is the rate-determining step with an activation energy of 113 kJ/mol. Rearrangement, via the double bond-forming and aziridine bond-breaking of **TS4** with an activation energy of 31 kJ/mol leads to the formation of **TS5**. This transition state subsequently produces intermediate **Int5**. The steps outlined above and which are supported by the extensive quantum-chemical calculations we have conducted, support the observed unusual rearrangement reaction of the methodology described herein. The final steps leading to the observed product carbamothionates occur from the final quenching hydrolysis-elimination of **Int5**. However, due to the subsequent dilute aqueous-DMF conditions we were unable to detect the presumed methylthioformate or its hydrolysis products.

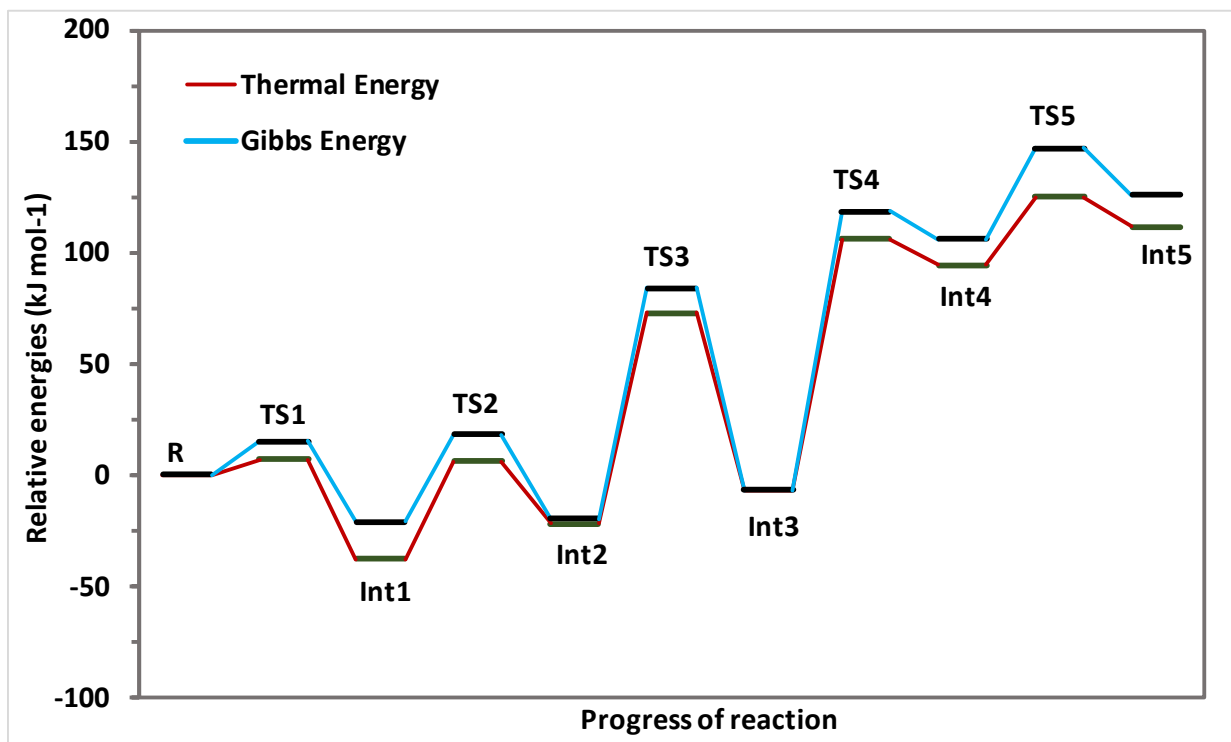


Figure 3. The relative energies of reactants, transition states and intermediates of the proposed reaction mechanism at the B3LYP/6-31++G(d,p) level of theory in gas phase.

Table 5. Activation energies (E_a ; kJ mol⁻¹) and Gibbs energies of activation (ΔG^\ddagger ; kJ mol⁻¹) at 298.15 K for the proposed reaction mechanism calculated by the B3LYP/ 6-31++g(d,p) level of theory in gas phase.

Step	E_a	ΔG^\ddagger
1 (TS1-R)	7	15
2 (TS2-Int1)	44	39
3 (TS3-Int2)	95	104
4 (TS4-Int3)	113	125
5 (TS5-Int4)	31	41
Overall (TS5-Int1)	163	168

Conclusion

In conclusion, we have developed a facile general protocol for the unexpected formation of carbamothioates by the reaction of benzyl isocyanides with xanthate

esters in the presence of sodium hydride in DMF (Method A). The rapid reaction time and simple work-up procedure are the noteworthy features of this protocol. As well, these carbamothioates were also synthesized by the condensation of xanthate esters with benzylamines in the presence of sodium hydride in DMF (Method B) for comparison. The yields obtained using method A are greater than those obtained using method B. Also, the reaction times of methods A are less than those required in method B. A probable mechanism is proposed which is supported by quantum chemical calculations. Further, work on isocyanide-cyclization reactions are currently under progress in our laboratory.

Supporting Information

Supporting Information File 1: All experimental procedures, analytical data, computational details and copies of ^1H and ^{13}C NMR spectra of all studied compounds.

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