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Synthesis of new acyl, furoyl, and benzoylthiocarbamates as polydentate systems. Structural study of isopropyl *N*-(2-furoyl)thiocarbamate

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Abstract—Synthesis of new acylthiocarbamates has been carried out. To establish the preferential conformation and to explain the behaviour chemically, the structure of isopropyl *N*-(2-furoyl)thiocarbamate **3m** has been determined by single-crystal X-ray analysis. The most stable conformation *E*,*Z*′ established by X-ray analysis was corroborated by semiempirical theoretical calculations.

1. Introduction

Some organic sulfur compounds such as thiocarbamates show important biological activity.[1] Most notably, acylthiocarbamates are used as biosensors,[2] elastase inhibitors,[3] and they can exhibit antineoplasic and antiinflammatory or antiarthritic[1] effects. Also molecular modelling studies of related acylthiocarbamates has been previously carried out due to they are potent non-nucleoside HIV-1 reverse transcriptase inhibitors.[4]

In addition, acylthiocarbamates have also been employed as starting compounds to obtain different heterocyclic compounds such as aminothiazoles, thietanes, aminotetrazoles, thiadiazoles, or thiadiazolines.[5] Some of these compounds are important since they are intermediates en route to variety of drugs.[6]

Thiocarbamates can react with weak bases, such as sodium or potassium carbonate, generating the corresponding anion, which can be represented through four plausible conformations as shown in Figure 1.[7] Molecular mechanics calculations onto *N*-acylthiocarbamate predict that *E*,*Z*′ is the most stable conformation.[8] Likewise, Schroeder et al. established, by using nuclear magnetic resonance, that *E*,*Z*′ was the most stable conformation in *N*-benzoyl-*O*-alkylthiocarbamates.[7] X-ray and semiempirical calculations would complete the structural determination of acylthiocarbamates in the literature and would be useful to understand the behaviour of these compounds versus electrophiles.

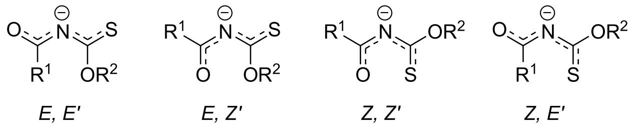
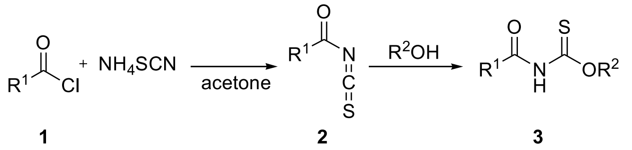


Figure 1.

Previously, we reported the synthesis of 1-benzoyl-3-alkylureas, using microwaves, through transamidation reactions,[9] and the alkylation of benzoyl and furoylthioureas as polydentate systems.[10] Here, we describe the synthesis of new acyl, furoyl and benzoylthiocarbamates and we have determined the structure of isopropyl *N*-(2-furoyl)thiocarbamate **3m** by single-crystal X-ray analysis. We have also confirmed that *E*,*Z*′ is the most stable conformation using the X-ray data and semiempirical theoretical calculations.



Scheme 1.

Keywords: Thiocarbamates; Acylthiocarbamates; Structural studies; Semiempirical methods.

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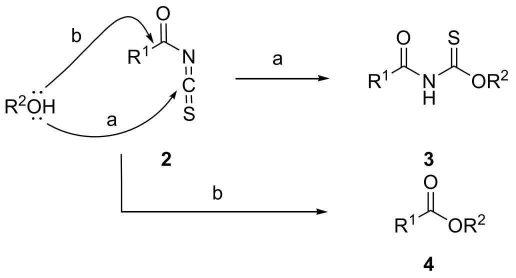
Table 1. Synthesis of compounds **3**

Entry	3	R^1	R^2	Yield (%)
1	**3a**	*t*-Bu	Me	68
2	**3b**	*t*-Bu	Et	67
3	**3c**	*t*-Bu	*i*-Pr	70
4	**3d**	Ph	*n*-C_5H_{11}	74
5	**3e**	Ph	*s*-C_5H_{11}	78
6	**3f**	Ph	*i*-C_5H_{11}	76
7	**3g**	Ph	*n*-$C_{18}H_{37}$	72
8	**3h**	Ph	Bn	81
9	**3i**	*p*NO_2–C_6H_4	*i*-Pr	71
10	**3j**	*p*F–C_6H_4	*i*-Pr	74
11	**3k**	Furyl	Me	72
12	**3l**	Furyl	Et	74
13	**3m**	Furyl	*i*-Pr	73
14	**3n**	Furyl	Bn	78
15	**3o**	2-(2-Furyl)vinyl	Me	78
16	**3p**	2-(2-Furyl)vinyl	Et	78
17	**3q**	2-(2-Furyl)vinyl	*i*-Pr	78

2. Results and discussion

The thiocarbamates were prepared by using acid chlorides **1** and ammonium thiocyanate in acetone. The intermediate isothiocyanate **2** reacts in situ with the corresponding alcohol affording the thiocarbamate **3** (Scheme 1 and Table 1).

Although there are two electrophilic carbon centres in **2**, the major product obtained is **3**, a consequence of the alcohol addition to the isocyanate electrophilic carbon (Scheme 2).



Scheme 2.

AM1, and PM3 semiempirical calculations predict a slightly negative charge value (−0.035, and −0.00075, respectively) on the carbon in the thiocarbamoyl group in products **2** (R^1 = Ph). However, steric effects on the carbonyl group lead to products **3** in high yields instead of compounds **4**. In the case of net charges values on *C*=O, AM1 and PM3 methods predict 0.418 and 0.408, respectively.

Synthesis of acylthiocarbamates seems to be general: a variety of aliphatic and aromatic alcohols were shown to be applicable. In general, slightly higher yields were obtained from aromatic, or conjugated alcohols **3d–q** in comparison to aliphatic alcohols **3a–c**. This result could be explained taking into account that aliphatic acylisothiocyanates are more reactive than conjugated or aromatic equivalents: the decomposition of these products afforded the corresponding acid. Scheme 2 illustrates the two possible mechanisms of the reaction of alcohols with isothiocyanates **2**. When the aliphatic chain in alcohols is branched, better yields were observed in the reaction to afford **3**. When alcohols with smaller aliphatic chain were used, products **3** were obtained in lower yields due to the generation of **4**. This fact could be explained assuming steric effects, as stated before.

To study the structure of acylthiocarbamates, isopropyl *N*-(2-furoyl)thiocarbamate (**3m**) was used as compound model. Thus, X-ray diffraction and semiempirical methods were employed to reveal the most stable conformation of **3m** (Fig. 1).

X-ray analysis of **3m** shows that fragments S1=C6–N1–C5=O2 are in a nearly planar alignment with a torsion angle S1–C6–N1–C5 = −177(2)° and C6–N1–C5–O2 = −3(4)° (Fig. 2).

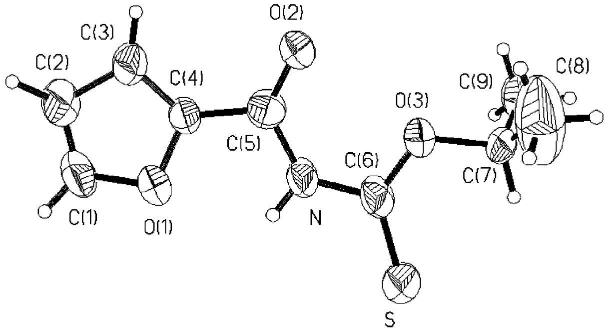


Figure 2. X-ray structure of compound **3m** showing the numbering scheme.

Asymmetry in angles C3–C4–C5 and O1–C4–C5 [131.8(5) and 118.9(4)°, respectively] could be due to the repulsion in the C3–H3···O2 system [C3·O2 = 3.006(6), H3···O2 = 2.96 Å] and the attraction in the NH···O1 system [N···O1 = 2.654(6) Å, H···O1 = 2.19 Å]. Taking into account that distances in C5–N1 and C6–N1 are 1.389(6) and 1.377(6) Å, respectively, it is possible to assume an electronic delocalization in that part of the molecule. In addition, C6–O3 bond distance [1.300(7) Å] indicates a partial double bond and a π-type conjugation in the whole system, this observation is in agreement with the previously reported results.[7]

In order to predict the minimum energy conformation, and relative stability of the possible conformers for **3m**, the