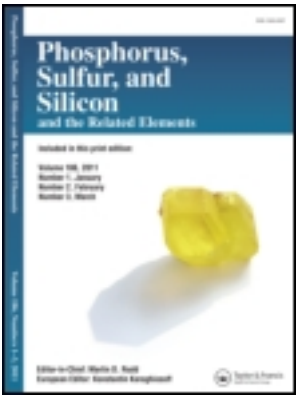

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

[4π + 2π] Cycloadditions of N-Acyl-Thioformamides

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Published online: 30 Jul 2008.

Phosphorus, Sulfur, and Silicon, 1997, Vol. 120 & 121, pp. 245–258
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[4π + 2π] Cycloadditions of *N*-Acyl-Thioformamides

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NADIA PELLOUX-LEON,[a] ROGER ARNAUD[a] and VINCENZO BARONE[b]
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Abstract Thiocarbonyl compounds, such as thioaldehydes and thioketones, are good dienophiles in the Diels-Alder reaction. Here we show that suitably substituted thioformamides can also be used in this reaction. A theoretical study of the [4π + 2π] cycloaddition of thiocarbonyls with butadiene has been performed and was used to determine the needed substituents.

Key Words : Diels-Alder reaction, Thioaldehydes, Thioamides, Thioformamides, *ab initio* calculations

INTRODUCTION

One of the most useful way to the thiopyran ring is the [4π + 2π] cycloaddition between a diene and a thiocarbonyl compound.[1,2] Some representative examples are listed in Table (1). Thioketones make good dienophiles. However, during the last fifteen years, the most studied thiocarbonyl dienophiles have been thioaldehydes.[3,4] Even though some sterically stabilized thioaldehydes have been isolated,[4] most of them are very reactive and have to be trapped *in situ*. They can be generated by various ways, for instance from sulfenyl derivatives,[3] phenacyl sulfides,[5] aldehydes,[6] or by retro-Diels-Alder reaction from dihydrothiopyrans.[7] E. Vedejs and G. W. Kirby teams gave the most prominent contributions to this field. These reactions are often stereoselective. Two examples from our laboratory are presented in Scheme (1). Thus, heating the thia-ethanoanthracenic adduct **1** in refluxing toluene in the presence of an oxygenated diene gave the expected thiopyrans. A high *endo* selectivity was observed using diacetoxybutadiene. With bis(*t*-butyldimethylsilyloxy)butadiene, the major isomer was found to result from an *exo* attack.[8]

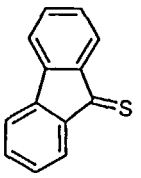
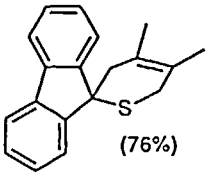
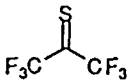
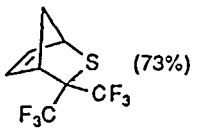
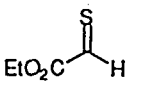
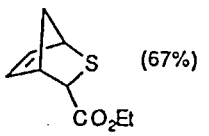
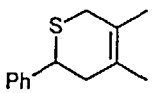
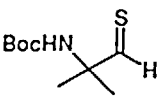
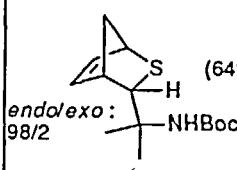
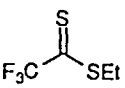
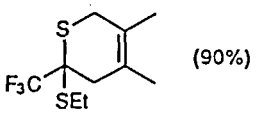
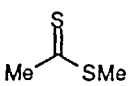
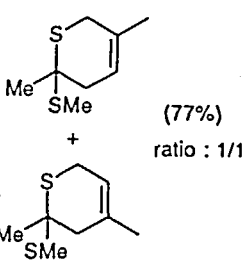
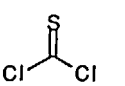
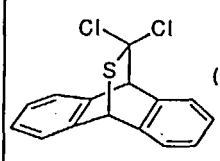
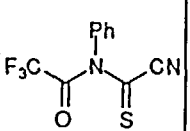
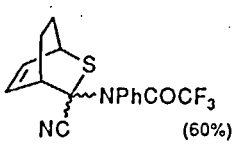
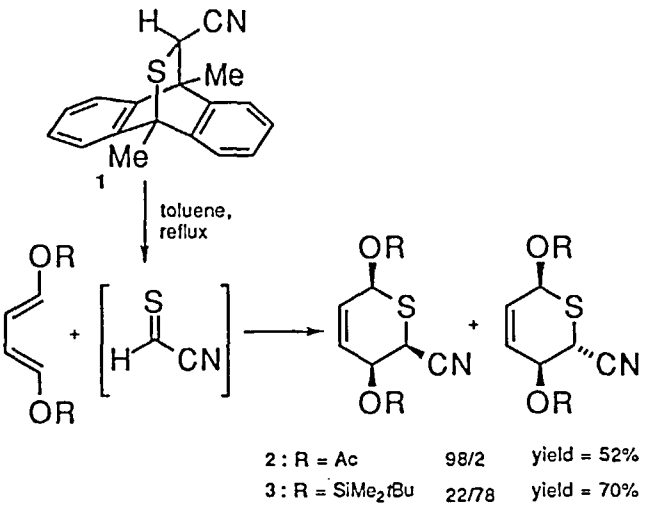
thiocarbonyl compound	diene (conditions)	adduct (yield)	ref.
	 (200°C)	 (76%)	13
	 (-78°C)	 (73%)	14
	 (r.t.)	 (67%)	3
	 (110°C)	 (92%)	7
	 (r.t.)	 (64%) *endo/exo* : 98/2	15
	 (0°C)	 (90%)	14
	 (160°C)	 (77%) ratio : 1/1	11
	anthracene (90°C)	 (60%)	16
	 (r.t)	 (60%)	17

Table (1)



Scheme (1)

Thionoesters, dithioesters and thioamides are much more stable than thioaldehydes. Unfortunately they are usually poor dienophiles because of the electron-donating ability of their substituents (alkoxy, thioalkoxy or amino). The Diels-Alder reaction of sugar-derived thionoesters have been studied by Herczegh *et al.*.[9] Other thionoesters has been involved in inverse electronic demand cycloadditions.[10] The Diels-Alder reaction of simple dithioesters have been investigated by Beslin and Metzner.[11] Poor regioselectivities were observed with non-symmetrical dienes such as isoprene or 1,3-pentadiene.

Several thioamides have been used in [4π + 2π] cycloadditions. For instance, this is the case of cyanothioformamides ($NCC(S)NR_2$), which are typical electron-deficient thioamides.[12] The reactions of conjugated cyclic thio-imides has been reported by Tamaru *et al.*. [18] However, until our work, thioformamides have been involved only in inverse electronic demand Diels-Alder reaction because their C=S double bond is electron-rich.[10] As part of our project on the reactivity of the C=S double bond, we decided to investigate the normal electronic demand Diels-Alder reaction of thioformamide.[19] This reaction will allow rapid access to nitrogen-substituted sulfur heterocycles which could be used in the synthesis of sulfur-nitrogen analogs of sugars[20] and of many other cyclic compounds.[1]

In this paper, we present : (i) some selected results from a theoretical study of the [4π + 2π] cycloaddition of thiocarbonyls with buta-1,3-diene ; (ii) a theoretical protocol which would rationalized the choice of the substituents ; (iii) first experimental results.

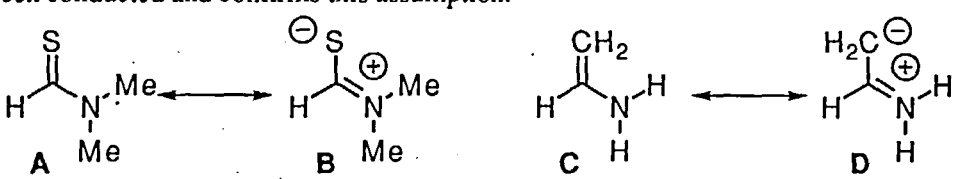
THE DIELS-ALDER REACTION OF THIOCARBONYLS WITH BUTADIENE

Figure (1) shows the transition state structure for the [4π + 2π] cycloaddition of thioformaldehyde, thioacetaldehyde, thioformylcyanide and thioformamide with *gauche* butadiene calculated at the B3LYP level (Only the *endo* TS's are presented. According to our calculations they are favored over *exo* TS's by a few kcal.mol^{-1}).[21] The length and the Pauling bond orders (n_p)[22] of the C-C and C-S forming bonds reported in Figure (1) clearly indicate early loose TS's in every cases. This is in accordance with Hammond's postulate as these four reactions were found to be exothermic (for $H_2C{=}S$, Δ_rE = -43.7, for MeC(S)H, Δ_rE = -36.1, for NCC(S)H, Δ_rE = -41.6, for $H_2NC(S)H$, Δ_rE = -16.7 kcal.mol^{-1}). Surprisingly, the reaction with thioformamide, which is considerably less exothermic than the three other ones, has an only slightly later TS. On the other hand, comparison of the values calculated for thioacetaldehyde and thioformylcyanide are in good agreement with what would be expected from the electronic effects of the substituents methyl (electron donating) and cyano (electron withdrawing). In the case of NCC(S)H, in accordance with a great electrophilic character of the sulfur, the C-S bond formation is in advance over the C-C bond. The reverse is true for thioacetaldehyde.

The barriers heights have been calculated. They were found to be low for thioaldehydes (for $H_2C{=}S$, $\Delta E^{\neq}$ = 4.1, for MeC(S)H, $\Delta E^{\neq}$ = 9.4, for NCC(S)H, $\Delta E^{\neq}$ = 0.9 kcal.mol^{-1}). As expected, the lowest barrier was found for the electron poor thioformylcyanide. The barrier for the electron rich thioformamide is considerably higher ($\Delta E^{\neq}$ = 22.7 kcal.mol^{-1}). Thus, the reaction with thioformamide is not only the less thermodynamically favored but is also drastically obstructed by kinetic factors.

THIOFORMAMIDES AS DIENOPHILES : THEORY

Thioamides are strongly conjugated molecules. It is well known that this conjugation, which gives a partial π character to the C-N bond, results in the non-equivalence of the two methyl groups of *N,N*-dimethylthioamides in NMR spectra. A NBO (natural bond orbital) analysis of the two limit forms A and B of *N,N*-dimethylthioformamide has been conducted and confirms this assumption.



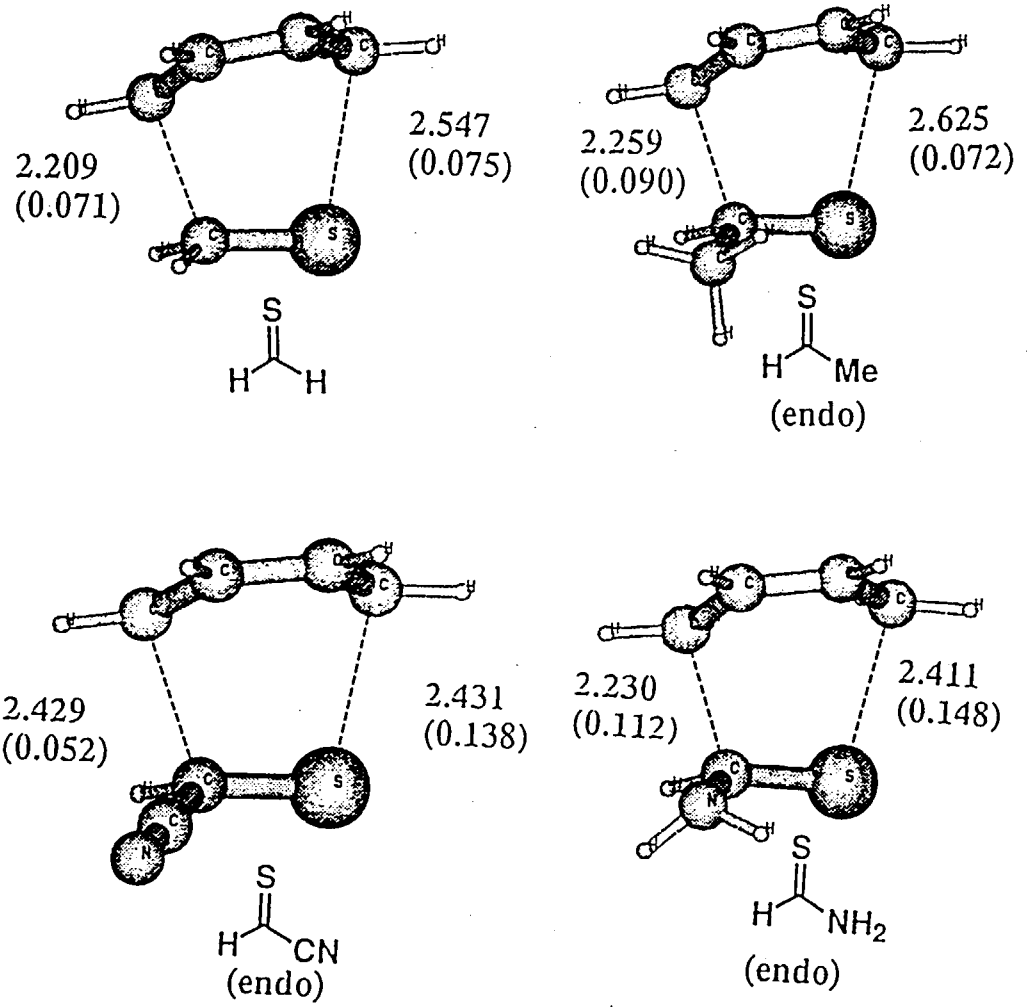


Figure (1)

length in Å; brackets: n_p

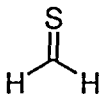
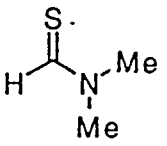
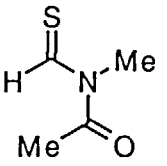
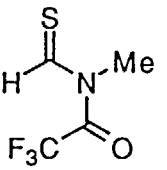
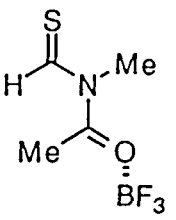
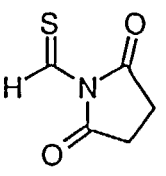
bond length[Å]	$d_{C\text{-}S}$ ($d_{C\text{-}N}$)	$n_N \longrightarrow \pi^*CS$ (occupancy of π^*CS)	ΔE_{ST} [kcal/mol]
	1.598	(0)	58.7
	1.654 (1.319)	-75.8 (0.3235)	81.3
	1.632 (1.350)	-50.5 (0.2256)	72.2
	1.623 (1.364)	-42.5 (0.1889)	69.6
	1.617 (1.370)	-38.6 (0.1714)	67.2
	1.608 (1.385)	-29.3 (0.1161)	63.8

Table (2)

A is probably the principal resonance structure with 0.5718 non-Lewis electrons. However, with only 0.6953 non-Lewis electrons, B is also a good representation of *N,N*-dimethylthioformamide. These values can be compared with those obtained for vinylamine : 0.3349 for C and 1.0819 for D. Furthermore, *ab initio* calculations predict a planar equilibrium structure for *N,N*-dimethylthioformamide, whereas for vinylamine the planar structure has been found to be the transition state for nitrogen inversion.[23]

As a consequence of this conjugation (indeed a transfer of electrons from the p lone pair n_N of nitrogen to the antibonding π^*_{CS} orbital), the C=S double bond is much longer in *N,N*-dimethylthioformamide (1.654 Å) than in thioformaldehyde (1.598 Å).

It is clear that comparing the C=S bond lengths in various thiocarbonyls could give a first indication of their reactivity in Diels-Alder reaction. Considering that thioformaldehyde is reactive and *N,N*-dimethylthioformamide unreactive, the choice of the right substituents in a series of thioamides could be monitored by calculating the C=S bond lengths.

Hint 1 : the shorter the C=S bond, the more reactive the compound.

A list of bond lengths for various thioformamides can be found in Table (2). C-N Bond lengths are also listed in Table (2). The reverse reasoning will be used for these bonds.

Hint 2 : the longer the C-N bond, the more reactive the thioamide.

As we mentioned earlier, the lengthening of the C=S bond is due to an electronic transfer from the n_N lone pair to the π^*_{CS} orbital. Not only this transfer lengthens the bond, but also it induces a stabilization of the molecule. As this transfer can not occur in the adduct after the Diels-Alder reaction, this will diminished the exothermicity of the reaction. A list of $n_N \rightarrow \pi^*_{CS}$ stabilization energies is given in table (2).

Hint 3 : the smaller this energy, the more exothermic the cycloaddition.

In normal electronic demand Diels-Alder reaction, the dienophiles is regarded as an electrophilic reactant, the diene being the nucleophile. Electrons are transferred from the dienes HOMO to the LUMO of the dienophile, here the π^*_{CS} orbital. The partial occupancy of this orbital resulting from the $n_N \rightarrow \pi^*_{CS}$ transfer will of course reduce the nucleophilic character of the thioamide and thus will disfavor the cycloaddition. Occupancies of the of the π^*_{CS} orbital have been calculated and are listed in Table (2).

Hint 4 : the smaller the π^*_{CS} occupancy, the easier the reaction (kinetic factor).

Finally, the SCD (state correlation diagram) model has yet been applied with success to cycloadditions.[24] As seen in Figure (2), in this model the barrier height is correlated to the singlet-to-triplet vertical excitation energy of the reactants. In our case, for a given diene, the S→ T transition of the thiocarbonyl group is the determining

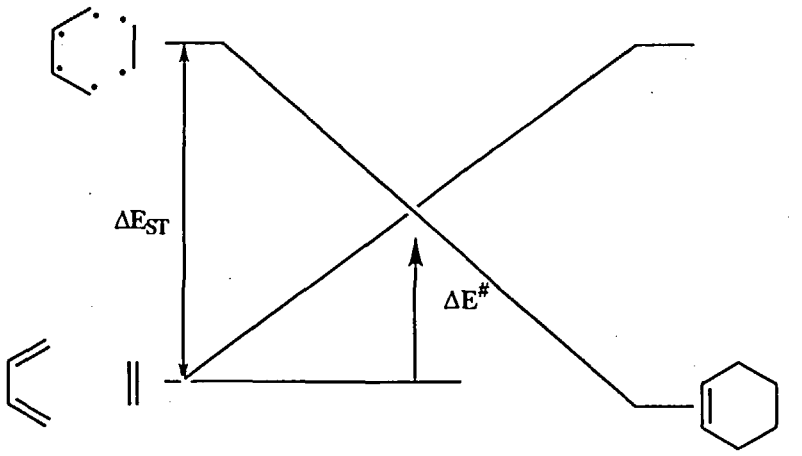


Figure (2)

factor. It is clear from Figure (2), that a great S→ T excitation energy will be correlated to a high barrier. ΔE_{ST} for thioformaldehyde and various thioformamides are listed in Table (2).

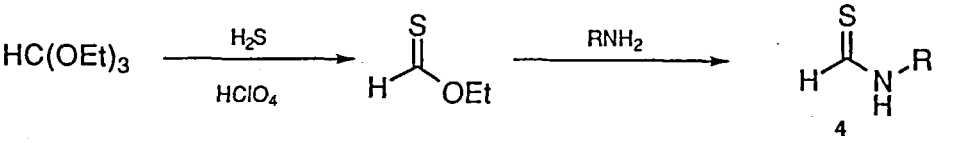
Hint 5 : the smaller ΔE_{ST}, the lower the energy barrier.

It is thus obvious from Table (2) that *N*-acylated thioformamides should be more reactive than simple thioformamides in the Diels-Alder reaction. This reactivity should be enhanced by the addition of a Lewis acid to the reaction mixture. It is also expected that *N*-trifluoroacetylated and diacylated thioformamides would be good choices.

THIOFORMAMIDES AS DIENOPHILES : PRACTICE

Preparation of *N*-acyl thioformamides

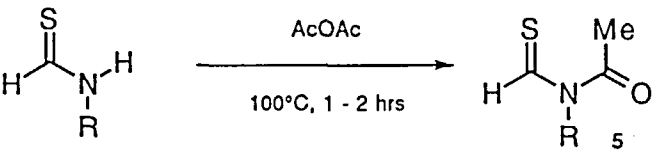
Simple thioformamides are readily accessible according to a known procedure :[25]



4

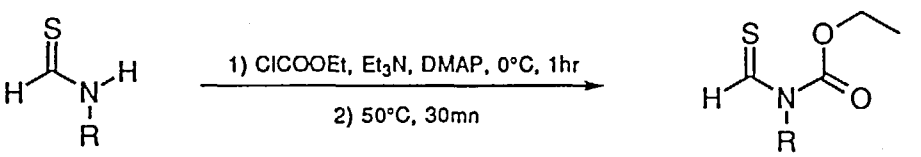
4a	R =	Ph	60%
4b		$PhCH_2$	95%
4c		PhMeCH	90%

The thioformamides **4** are stable solid compounds, that can be readily acetylated in excess acetic acid at 100°C :



5a	R =	Ph	69%
5b		$PhCH_2$	83%
5c		PhMeCH	51%

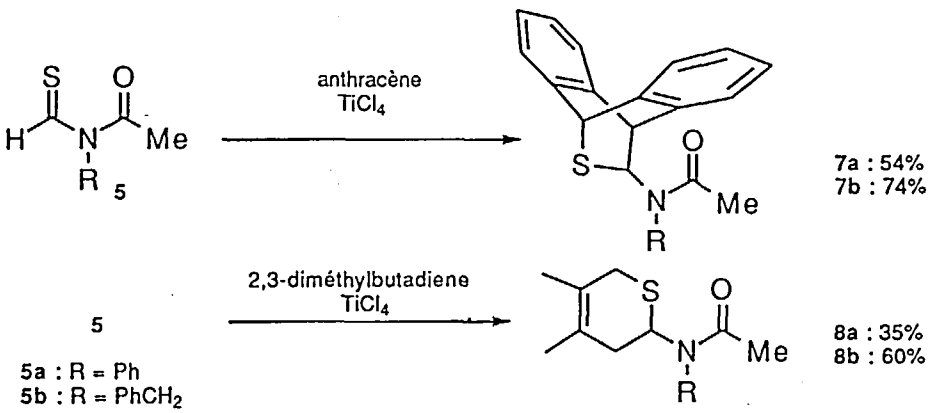
More generally, the acylation of thioformamides can be obtained with classical reagents. At low temperatures, the formation of both *N*- and *S* - acylated forms can be observed, but such mixtures isomerize readily at 50°C. The following examples are representative :

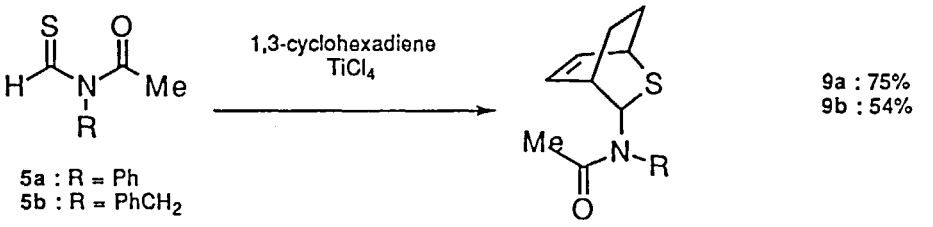


6b	R =	$PhCH_2$	80%
6c		PhMeCH	34%

Cycloadditions of *N*-acetyl-thioformamides

Our early experiments showed that *N*-acetyl-thioformamides 5 do not react with dienes at atmospheric pressure in thermal conditions. Nevertheless, they react readily at room temperature with different dienes, in fair yields, in the presence of strong Lewis acids.

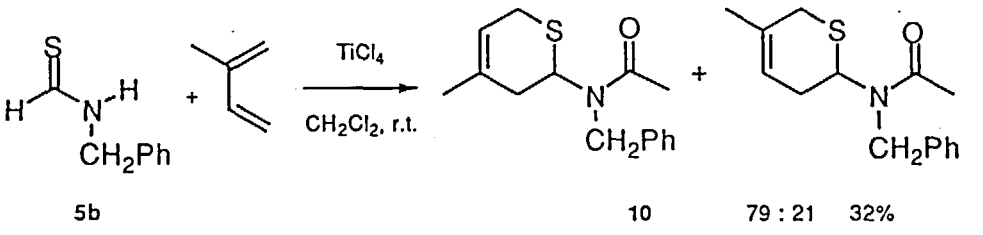




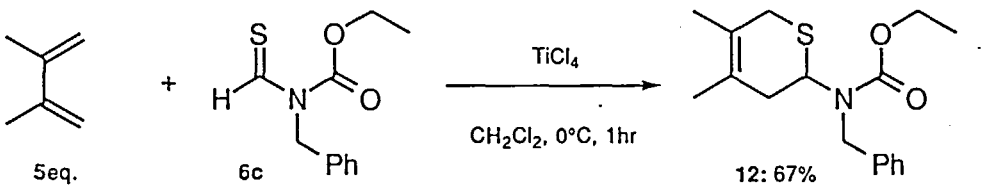
Only one diastereoisomer is observed in the adducts **9a-b** with cyclohexadiene[26] (>95%, NMR).

It is noteworthy that only strong Lewis acids : $TiCl_4$, BCl_3, $FeCl_3$, Et_2AlCl catalyze the cycloaddition. The presence of ether or dimethylsulfide inhibits the catalyst : BF_3:Et_2O, BCl_3:DMS or BCl_3 in ether produced no reaction.

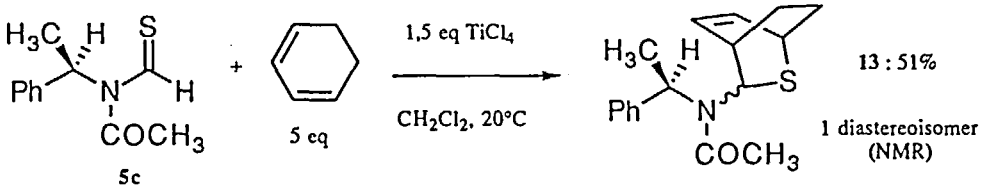
On reaction with isoprene, the regioselectivity is poor, and the orientation is classical.

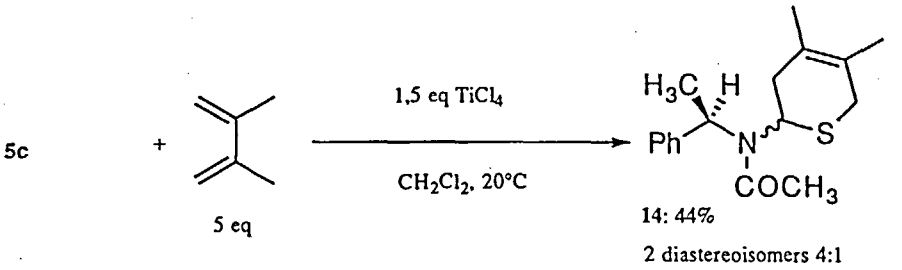


Changing from *N*- acetyl to *N*-ethoxycarbonyl thioformamides does not modify the course of the reaction.



The transposition of these results to chiral dienophiles derived from α-methylbenzylamine seemed obvious. However, it appeared that the chemical yields are poorer.





The diastereoselectivity, high with cyclohexadiene as substrate (only one diastereoisomer on the NMR scale), decreases with the open-chain 2,3-dimethylbutadiene (4:1 ratio).

Thus, in good agreement with theoretical calculations, *N*-acylthioformamides react with dienes. However, the presence of a strong Lewis acid is necessary.

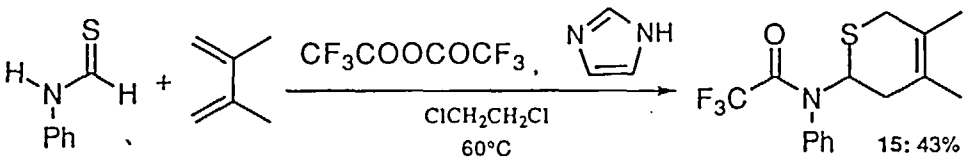
Preparation and reaction of *N*-trifluoroacetyl-thioformamides

The presence of strong Lewis acids in the reaction medium is a serious drawback of the aforementioned reaction.[3] Thus, we were particularly interested by the calculated data predicting that *N,N*-bis-acyl-thioformamides or *N*-trifluoroacetyl-thioformamides would have the same reactivity without Lewis acids than *N*-acyl-thioformamides with Lewis acids.

Practically, we were unable to prepare *N,N*-bis-acyl-thioformamides. We believe that such species are unstable in the conditions of their attempted preparation.

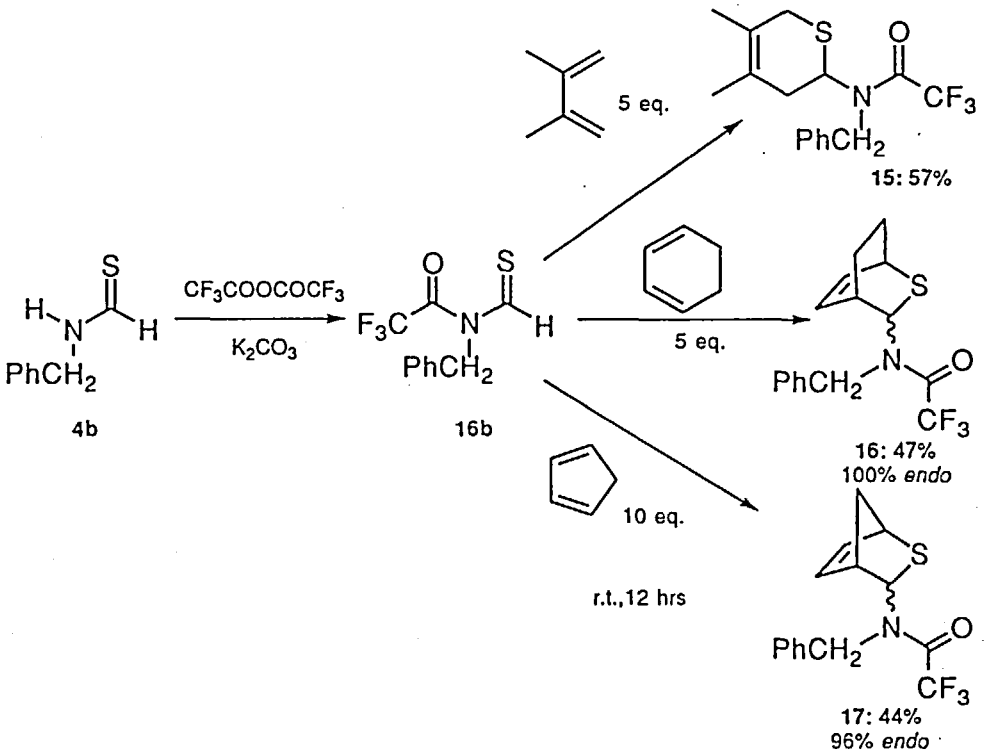
N-trifluoroacetyl-thioformamides are more accessible. They can be prepared in solution and observed by NMR. Since they are highly sensitive to hydrolysis,[17] purification on silica gel was impossible, but we could prepare and use them *in situ*.

First, we used classically trifluoroacetic anhydride and imidazole, the diene being present.

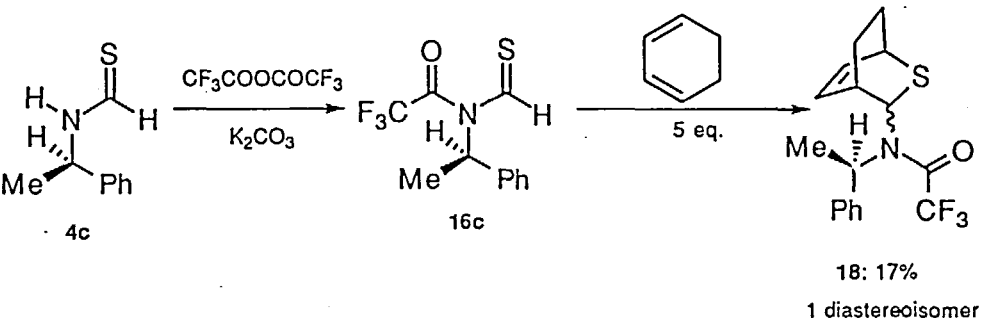


We then found more efficient and convenient to use wet solid potassium carbonate as the base. The yellow solution of dienophile obtained, after filtration, is free of acids or bases.

The *N*-benzyl derivative **16b** prepared in these conditions can react with different dienes in fair yields and good *endo* selectivity.[27]



Disappointingly, the optically active analog **16c** leads to much poorer yields of cycloadduct. We found by ^{19}F-NMR that compounds **16b** and **16c** are not stable at room temperature, and that decomposition of **16c** is much faster. Thus, in the latter case, decomposition of the dienophile competes drastically with the cycloaddition.



CONCLUSION

The theoretical approach presented above proved to be an efficient predictive tool for the selection of the required reagents for our purpose. We believe that this protocol could be readily generalizable to other reactivity problems.[28]

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8. **2*cis*** : ^{1}H NMR : 2.1 and 2.2 (2 s, 6H, 2 Me), 4.0 (d, 1H, C<u>H</u>CN, J = 6 Hz), 5.4 (dd, 1H, C<u>H</u>OR, J = 0.5 and J = 6 Hz), 5.9-6.2 (m, 3H, SC<u>H</u>OR, C<u>H</u>=C<u>H</u>). ^{13}C NMR : 20.7, 20.8, 25.5, 65.5, 67.2, 116.0 (CN), 126.0, 130.0, 169.9, 170.1 ppm.
   2*trans* : ^{1}H NMR : 2.1 and 2.2 (2 s, 6H, 2 Me), 4.1 (d, 1H, C<u>H</u>CN, J = 11 Hz), 5.7 (d, 1H, C<u>H</u>OR, J = 11 Hz), 5.9-6.0 (m, 2H, C<u>H</u>=C<u>H</u>), 6.1 (d, 1H, SC<u>H</u>OR).
   3*cis* : ^{1}H NMR : 0.1 and 0.15 (2 s, 12H, Me), 0.9 and 1.0 (2 s, 18H, *t*-Bu), 3.5 (d, 1H, C<u>H</u>CN, J = 4.7 Hz), 4.3 (m, 1H, C<u>H</u>OR), 5.2 (d, 1H, SC<u>H</u>OR), 5.7 (m, 2H, C<u>H</u>=C<u>H</u>). MS (CI) : m/z = 403 (M + NH_4^+).
   3*trans* :^{1}H NMR : 0.1 and 0.14 (2 s, 12H, Me), 0.9 and 1.0 (2 s, 18H, *t*-Bu), 3.8 (d, 1H, C<u>H</u>CN, J = 10.3 Hz), 4.4 (dd, 1H, C<u>H</u>OR, J = 0.5 and J = 10.3 Hz), 5.1 (d, 1H, SC<u>H</u>OR), 5.7 (m, 2H, C<u>H</u>=C<u>H</u>). MS (CI) : m/z = 403 (M + NH_4^+).
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27. Measured by ^{19}F-NMR.
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