Synthesis of Dihydrothiophenes by an Amino-Directed Thioisomünchnone−Alkene Cycloaddition Reaction

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Dihydrothiophenes can easily be obtained by a general protocol involving the reaction of 2-aminothioisomünchnones with electron-deficient alkenes. The overall process can be interpreted as a sequential [3+2] cycloaddition/ring-opening cyclization reaction. The structures of the products could be unequivocally assigned by X-ray diffraction analysis. A theoretical study at a semiempirical level (PM3) with a further single-point refinement of energies at the B3LYP/6–31G* level also offers mechanistic insights into the stereochemical outcome.

Introduction

With the advent of green chemistry technologies, cycloadditions such as Diels−Alder and 1,3-dipolar reactions, often conducted in a sequential manner, have been readily incorporated into the repertory of choice by virtue of their atom-economy character, such processes ideally generating no wastes.[1,2]

In this regard, [3+2] cycloadditions of 1,3-thiazolium-4-olates, a well-known family of masked 1,3-dipoles referred to as "thioisomünchnones", have long been utilized for the construction of five- and six-membered heterocycles.[3,4] A few years ago, we reported that the presence of an dialkylamino group at the mesoionic nucleus is a key structural feature, facilitating the formation of products of varied ring size depending on the dipolarophile and the reaction conditions.[5−8] In particular, dihydrothiophenes were obtained by an unexpected reaction with nitroalkenes.[7a,7b]

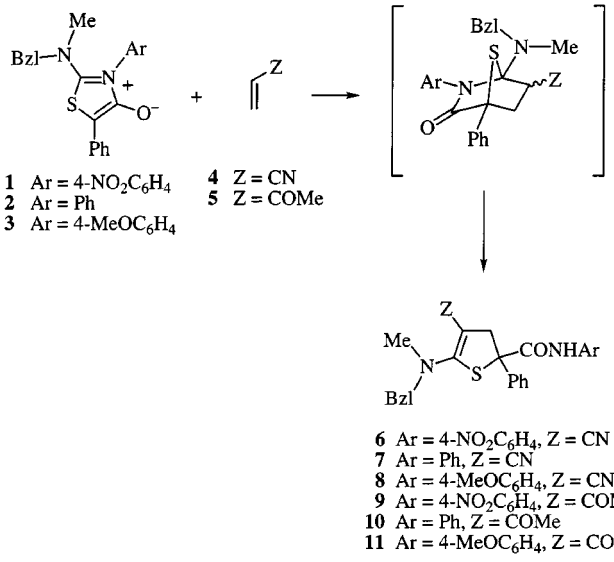
In the present paper, we extend these studies to other alkenes, and also describe diastereoselective reactions with chiral substrates. The stereochemical outcomes of such reactions have been rationalized by transition-state modeling using semiempirical and DFT-based theoretical calculations.

Results and Discussion

Synthetic Studies

Since the formation of dihydrothiophenes has hitherto only been observed in the dipolar cycloadditions of thioisomünchnones with nitroalkenes,[7a,7b] a further study has now been carried out with different, less electron-withdrawing alkenes in order to ascertain the scope and limitations of this protocol. In addition, we have also explored the reactivity of sugar-based thioisomünchnones, which offer the possibility of studying a series of key stereochemical issues, most notably the facial diastereoselection.

When thioisomünchnones **1**−**3** were treated with acrylonitrile (**4**) in CH_2Cl_2 at room temperature for 24 h, the corresponding dihydrothiophenes **6**−**8** were regiospecifically formed as the sole products (Scheme 1). The structure of **8** could be determined by single-crystal X-ray diffraction analysis[9] (Figure 1). Furthermore, the dihydrothiophenes **9**−**11** were isolated following the regiospecific reactions of **1**−**3** with methyl vinyl ketone (**5**) under the same conditions.



1 Ar = 4-$NO_2C_6H_4$
2 Ar = Ph
3 Ar = 4-$MeOC_6H_4$

4 Z = CN
5 Z = COMe

6 Ar = 4-$NO_2C_6H_4$, Z = CN
7 Ar = Ph, Z = CN
8 Ar = 4-$MeOC_6H_4$, Z = CN
9 Ar = 4-$NO_2C_6H_4$, Z = COMe
10 Ar = Ph, Z = COMe
11 Ar = 4-$MeOC_6H_4$, Z = COMe

Scheme 1

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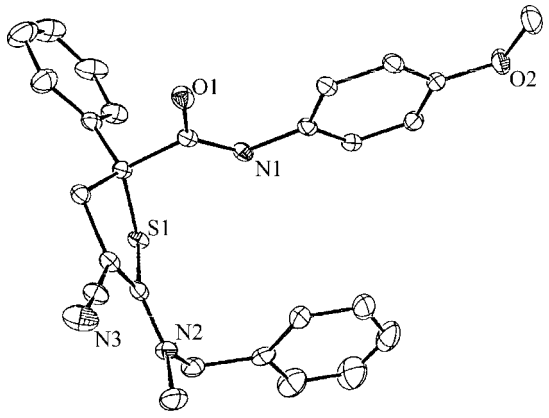
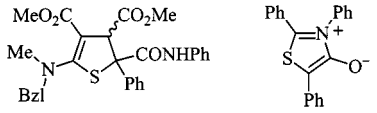


Figure 1. Structure of compound **8** determined by X-ray analysis

Mesoionic compound **2** was found to react with dimethyl maleate in both CH_2Cl_2 at room temperature and in refluxing benzene to afford the dihydrothiophene **12**, albeit in lower yields. Remarkably, neither a stable cycloadduct nor thiophene nor pyridone derivatives could be isolated or detected by NMR analyses of the crude samples, even though the latter are common products in the cycloaddition reactions of thioisomünchnones such as **13**.[10]

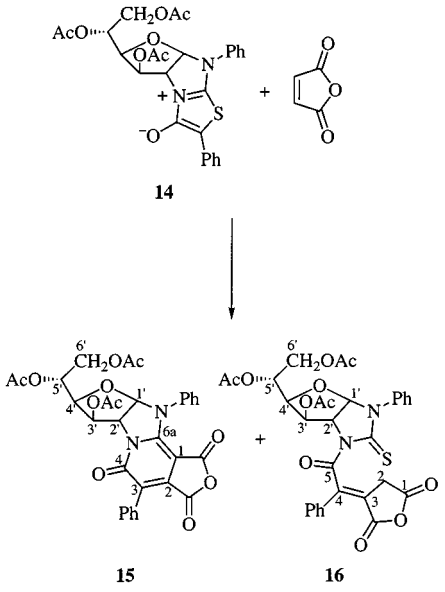


12 **13**

In addition, we chose a 1,3-thiazolium-4-olate system attached to a carbohydrate moiety **14**,[8b] which was treated with acrylonitrile and methyl vinyl ketone as examples of asymmetrically substituted dipolarophiles, and with *N*-phenylmaleimide and maleic anhydride as symmetrically substituted ones. The polycyclic mesoionic system **14** presents not only an inherent chirality due to its multiple stereogenic centers, but also possesses a rigid framework. These features have allowed us to evaluate the influence of the chiral moiety as well as the structural requirements of the reaction.

When maleic anhydride was used as the dipolarophile, two different products (**15** and **16**) were formed (Scheme 2), the ratio of which proved to be dependent on the experimental conditions.

Thus, when the reaction was carried out in CH_2Cl_2 at room temperature, **16** was isolated in 31% yield, while in refluxing toluene an increased yield of 47% could be obtained. In glacial acetic acid, **16** was isolated in 72% yield. On the other hand, **15** was detected by TLC analyses in toluene and acetic acid, although it could be isolated in 22% yield when CH_2Cl_2 was utilized. The presence of **15** was always detected due to its fluorescence, and its structure was elucidated on the basis of its spectroscopic data. In fact, its ^1H and ^{13}C NMR spectra are analogous to those of other pyridones.[8b] The ^1H and ^{13}C NMR spectra of **16**, recorded in $CDCl_3$, show two sets of signals (55:45), which

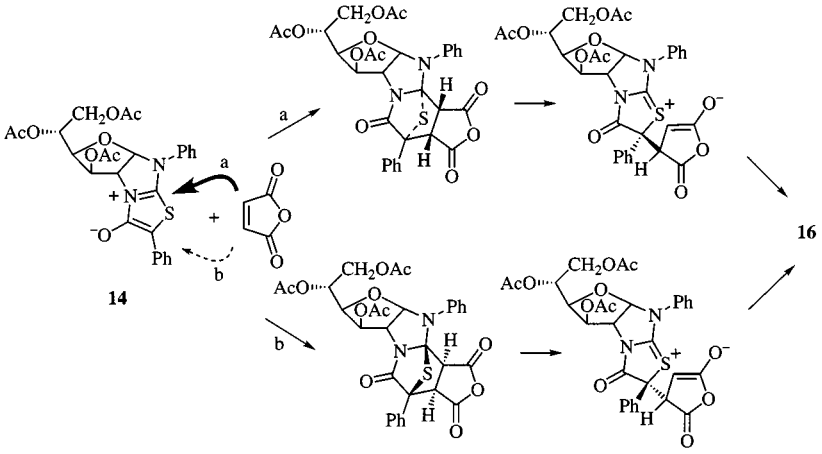


Scheme 2. Atom numbering included for NMR assignment purposes

suggest the existence of two isomers, even though only one spot was detected by TLC analysis. When NMR spectra were recorded in $[D_6]$DMSO, the ratio shifted to 80:20, which ruled out geometrical isomerism and pointed instead to conformational isomerism. This presumably stems from the restricted rotation about the N−C=O fragment. Coalescence was observed in the ^1H NMR spectrum at 330 K. Unfortunately, the calculated Gibbs energy[11] for this rotation ($\Delta G^{\neq}$ = 68.7 kJ·mol^{-1}) is lower than the value required to allow the isolation of both rotamers (at least 96 kJ·mol^{-1}, ca. 24 kcal·mol^{-1}).[12]

The formation of pyridone **15** suggests that the reaction between **14** and maleic anhydride is a 1,3-dipolar cycloaddition where the initial adduct evolves, at least partially, in a conventional manner following the elimination of hydrogen sulfide. However, an explanation is required to account for the diastereoselective formation of compound **16**, especially in such a polar solvent as acetic acid. The polycyclic system generated in the cycloaddition exhibits a strong angular tension, making it susceptible to cleavage. Such fragmentation must be initiated by bond breaking between the imidazolidine fragment at C-2 and the anhydride moiety, which would be favored by the charge delocalization at the vicinal groups or by protonation of the adjacent carbonyl group in an acidic medium. The new C−C double bond must be formed through an E2-type mechanism.

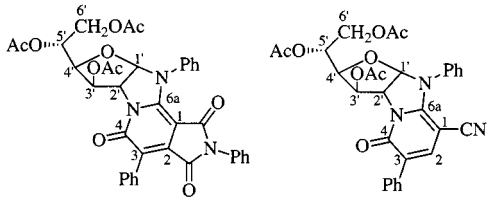
At first sight, four possible approaches of the reactants may be envisaged for the cycloaddition process (*exo*-up, *exo*-down, *endo*-up, and *endo*-down). Previous work[10b] and the steric hindrance caused by the bulky chiral fragment fused to the mesoionic heterocycle would suggest a preferential *exo*-up orientation. Scheme 3 depicts both *exo*-up and *exo*-down approaches of maleic anhydride toward the mesoionic heterocycle. Both approaches lead to an acylimidazolidine-2-thione (**16**), for which the (*Z*)/(*E*) configuration of the new carbon−carbon double bond is deter-



Scheme 3

mined by the dipolarophile *endo*/*exo* disposition and is independent of the 1,3-dipole facial selectivity. For this reason, we have tentatively assigned the (*E*) configuration to the olefinic double bond of **16**.

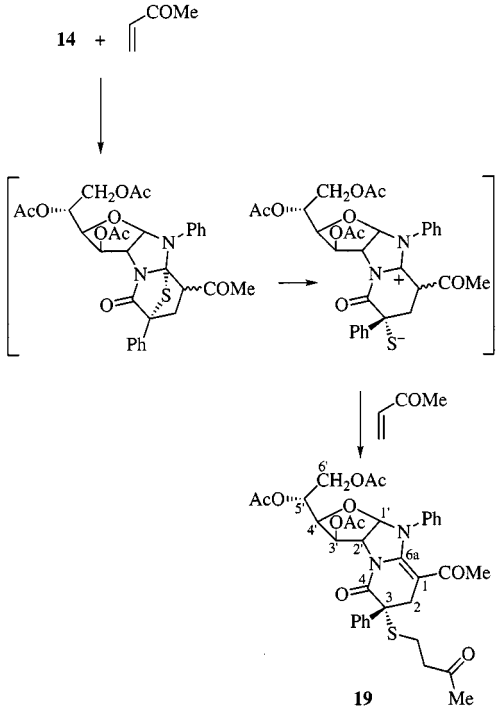
Reaction of **14** with *N*-phenylmaleimide in refluxing benzene for 15 min gave, after the extrusion of hydrogen sulfide, the α-pyridone **17** in good yield. The intermediate cycloadduct could neither be detected nor isolated.



17 **18**

When acrylonitrile was used as the dipolarophile, the reaction proceeded slowly in both refluxing toluene and benzene, although it could be completed in neat acrylonitrile under solvent-free conditions. The α-pyridone derivative **18** was obtained in excellent yield as the sole product, without any traces of dihydrothiophene (the rapid loss of hydrogen sulfide was evident at the outset). The cycloaddition process proved to be regiospecific, as demonstrated by ^{1}H and ^{13}C NMR experiments. Accordingly, attempts to isolate the intermediate cycloadduct failed.

When the heterocycle **14** was treated with neat methyl vinyl ketone under reflux, it underwent a domino cycloaddition−nucleophilic addition reaction yielding the thioether **19** (Scheme 4). This product stems from reaction of the intermediate thiolate with excess methyl vinyl ketone. The trapping of such an intermediate clearly shows, for the first time, the way in which these cycloadducts evolve to give α-pyridones. The configuration at the newly created stereogenic center of **19** should largely be determined by the *cis*-fused tricyclic system **14**. Methyl vinyl ketone will then attack the less hindered face of the mesoionic dipole (*exo*-up orientation, vide supra).



Scheme 4. Atom numbering included for NMR assignment purposes

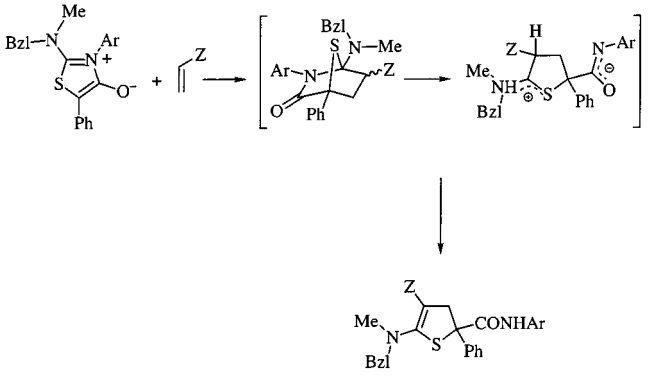
It is noteworthy that all previous work dealing with cycloadditions of thioisomünchnones with alkenes was carried out using 2-aryl- or 2-alkyl-1,3-thiazolium-4-olates.[10] In the present work, 2-(dialkylamino)thioisomünchnones have been used to obtain dihydrothiophenes.[7a,7b] Mechanistic aspects of this reaction are addressed in the following paragraphs.

It had been suggested that the mechanism for this ring-opening reaction begins with the abstraction of the proton α to the electron-withdrawing group.[7b] However, the successful experiment with methyl vinyl ketone reveals that this dissociative pathway, which relies on the acidity of this α-hydrogen atom, is unlikely to be a prime factor controlling

the reaction outcome since this proton would not be sufficiently acidic in the corresponding oxo adduct. Moreover, early studies demonstrated that 2-aryl-substituted thioisomünchnones react with dimethyl maleate and dimethyl fumarate to preferentially afford *exo* cycloadducts, which do not undergo further fragmentation despite the acidity of the aforementioned hydrogen atom.[10b]

Attempts to obtain dihydrothiophenes by treating the mesoionic heterocycle **13** with nitroalkenes led only to sluggish reactions. Either the cycloadditions proceeded slowly, even at high temperatures, giving the products in poor yields, or the intermediate cycloadducts remained unaffected.[7b]

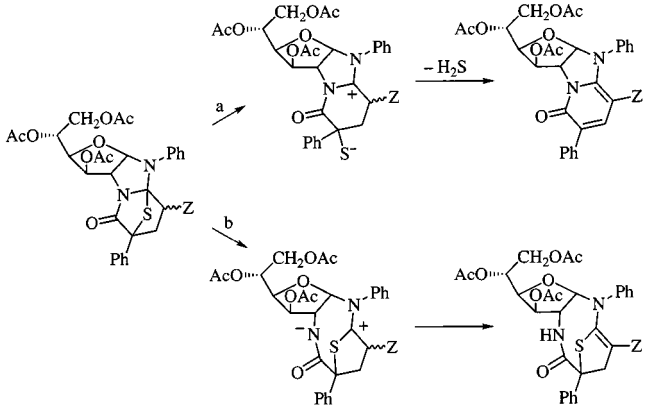
Therefore, a plausible explanation for the consistent and unexpected cleavage leading to dihydrothiophenes might be based on the electronic influence of the exocyclic nitrogenated substituent, which is likely to be capable of stabilizing the cationic-like intermediate generated by the initial endocyclic C−N cleavage (Scheme 5).



Scheme 5

The stabilization provided by the lone pair of the nitrogen atom favors C−N scission with respect to both C−S cleavage with elimination of hydrogen sulfide and the concerted retro Diels−Alder process with loss of aryl isocyanate. Finally, a rapid inter- or intramolecular abstraction of the proton would result in the observed product.

The latter consideration illustrates the accelerating effect of an amino substituent at C-2 on the reactivity of thioisomünchnones, and hence on that of the resulting cycloadducts, which fragment easily. This is in contrast to the customary stability of cycloadducts encountered in alkene−thioisomünchnone cycloadditions. However, 2-(dialkylamino)thioisomünchnone **14** reacts with alkenes to give pyridones. In this case, C−S scission (Scheme 6, route a), leading to an *ortho*-fused heterocycle, must be energetically favored with respect to C−N cleavage (route b), which leads to an enlarged bicyclic system with a double bond at a bridgehead carbon atom.



Scheme 6

Theoretical Studies

The regio- and stereoselective control of the cycloadditions of compounds **1**−**3** with acrylonitrile, methyl vinyl ketone, and dimethyl maleate has been studied theoretically by performing semiempirical calculations with full optimization of the molecules at the PM3 level[13] employing the GAUSSIAN-94 package.[14]

Table 1. Energies and coefficients of frontier orbitals for reactants

Compound	MO	E [eV][a]	C_1	C_2	C_3	C_4	C_5
Ar = 4-$O_2NC_6H_4$	HOMO	−7.85	−0.19	−0.28	0.15	0.14	0.51
	LUMO	−1.81	−0.36	0.58	−0.30	−0.01	0.29
Ar = Ph	HOMO	−7.50	−0.18	−0.26	0.15	0.14	0.51
	LUMO	−1.39	−0.40	0.63	−0.37	−0.02	0.29
Ar = 4-$MeOC_6H_4$	HOMO	−7.47	−0.21	−0.26	0.15	0.14	0.53
	LUMO	−1.35	−0.39	0.64	−0.38	−0.02	0.30
CN	HOMO	−10.89	0.58	0.56	−0.25	–	–
	LUMO	−0.19	0.74	−0.61	−0.29	–	–
COMe	HOMO	−10.75	0.00	0.00	0.00	–	–
	LUMO	−0.15	0.67	−0.50	−0.49	–	–
MeOOC COOMe	HOMO	−11.25	−0.18	−0.02	−0.01	0.02	–
	LUMO	−0.53	0.64	−0.57	−0.22	0.10	–

[a] At PM3 level.

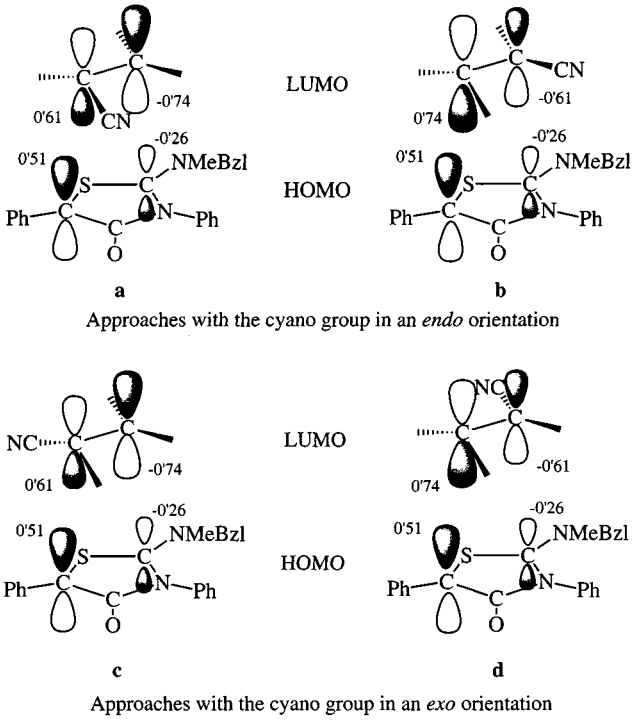


Figure 2. Primary orbital interactions for the reaction of **2** with acrylonitrile (**4**)

Table 1 shows the energies and coefficients of the frontier orbitals of the reactants. The $HOMO_{dipole}-LUMO_{dipolarophile}$ interactions show a smaller energy gap than the opposite $HOMO_{dipolarophile}-LUMO_{dipole}$ interactions, which is consistent with Sustmann's type I cycloadditions,[15] also referred to as dipole−$HOMO_{controlled}$ reactions.

In accordance with FMO postulates,[16] once the HOMO/LUMO pair closer in energy has been identified, the relative sizes of the coefficients of the atomic orbitals will predict the regioselectivity. Using the reaction of **2** with acrylonitrile (**4**) as a model, Figure 2 depicts the four approaches facing the HOMO and LUMO with the greatest coefficients.

There is a stronger polarization of the LUMO of methyl vinyl ketone and, accordingly, it should produce more regioselective processes than those of acrylonitrile. On the other hand, the coefficient of the carbonyl carbon atom in the LUMO of methyl vinyl ketone is larger than that of the cyano group in acrylonitrile. Secondary interactions may be more relevant in the former case.

The regiochemistry predicted by the FMO analysis (approaches **b** and **d**) is in agreement with the experimental results obtained for these reactions. However, it should be pointed out that the secondary interactions lead to weak antibonding effects in approach **b**, but to weak bonding effects in approach **a** (Figure 3).

In order to ascertain whether the secondary interactions could be responsible for both the regio- and stereocontrols, we located the transition states of these four hypothetical

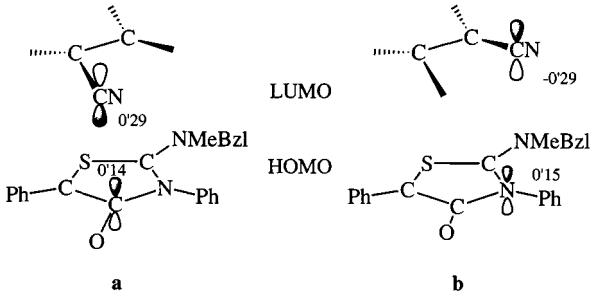


Figure 3. Secondary orbital interactions shown in the approaches **a** and **b** for the reaction of **2** and **4** where the cyano group adopts an *endo* disposition

reactions (Figure 4). In order to clarify the rest of this discussion, the transition structures arising from the different approaches **a**−**d** will be denoted as **A**−**D**, respectively. It should also be mentioned here that some authors have questioned the role, and even the existence, of secondary orbital interactions, arguing that other factors (e.g. steric or solvent effects, etc.) might really be responsible for the *endo* selectivity.[17]

The relative stabilities of these transition states, estimated by comparison of their heats of formation, demonstrate that the *exo* approach (**D**) is energetically more favorable than the *endo* approach (**B**), as predicted by FMO theory. A similar conclusion is reached from analysis of the energetic data of the four saddle points relating to the reaction of **2** with methyl vinyl ketone (Figure 5).

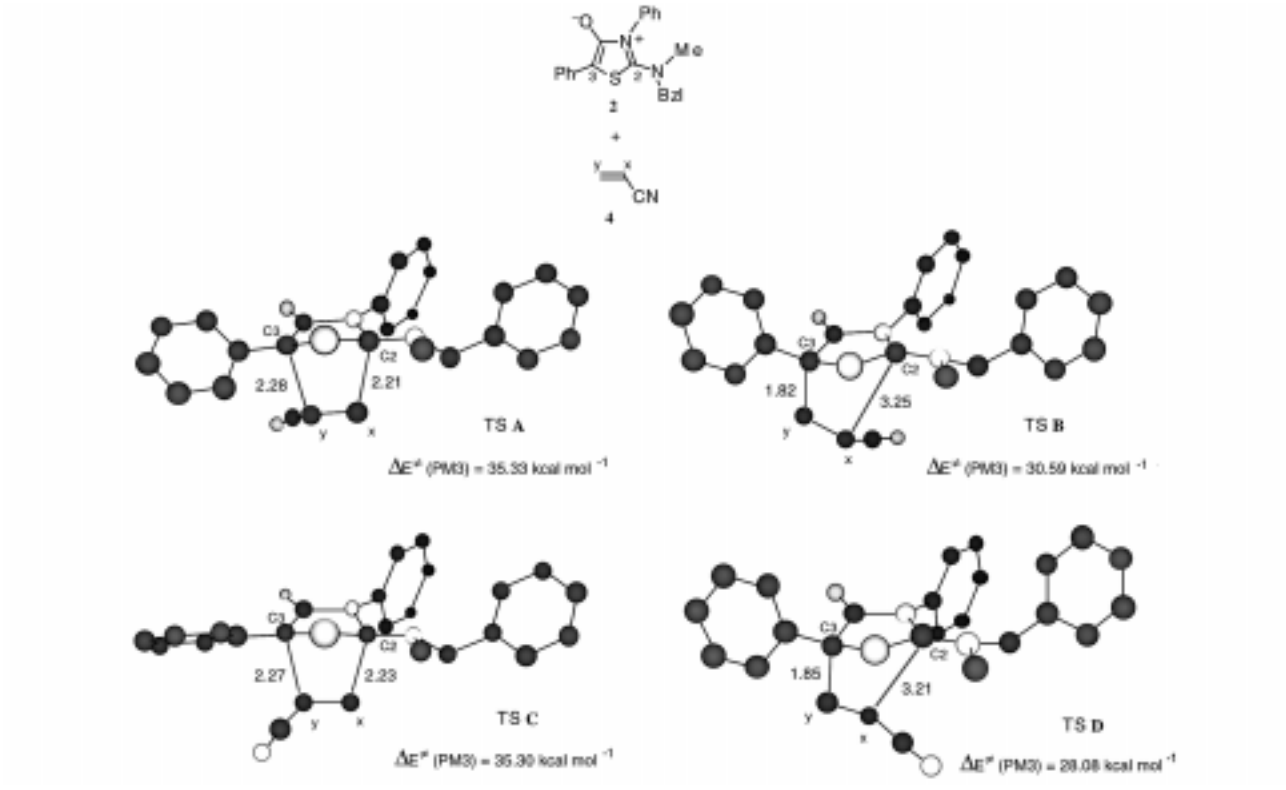


Figure 4. PM3 transition structures for the reaction between **2** and **4**; bond lengths in Å; hydrogen atoms have been omitted for the sake of clarity

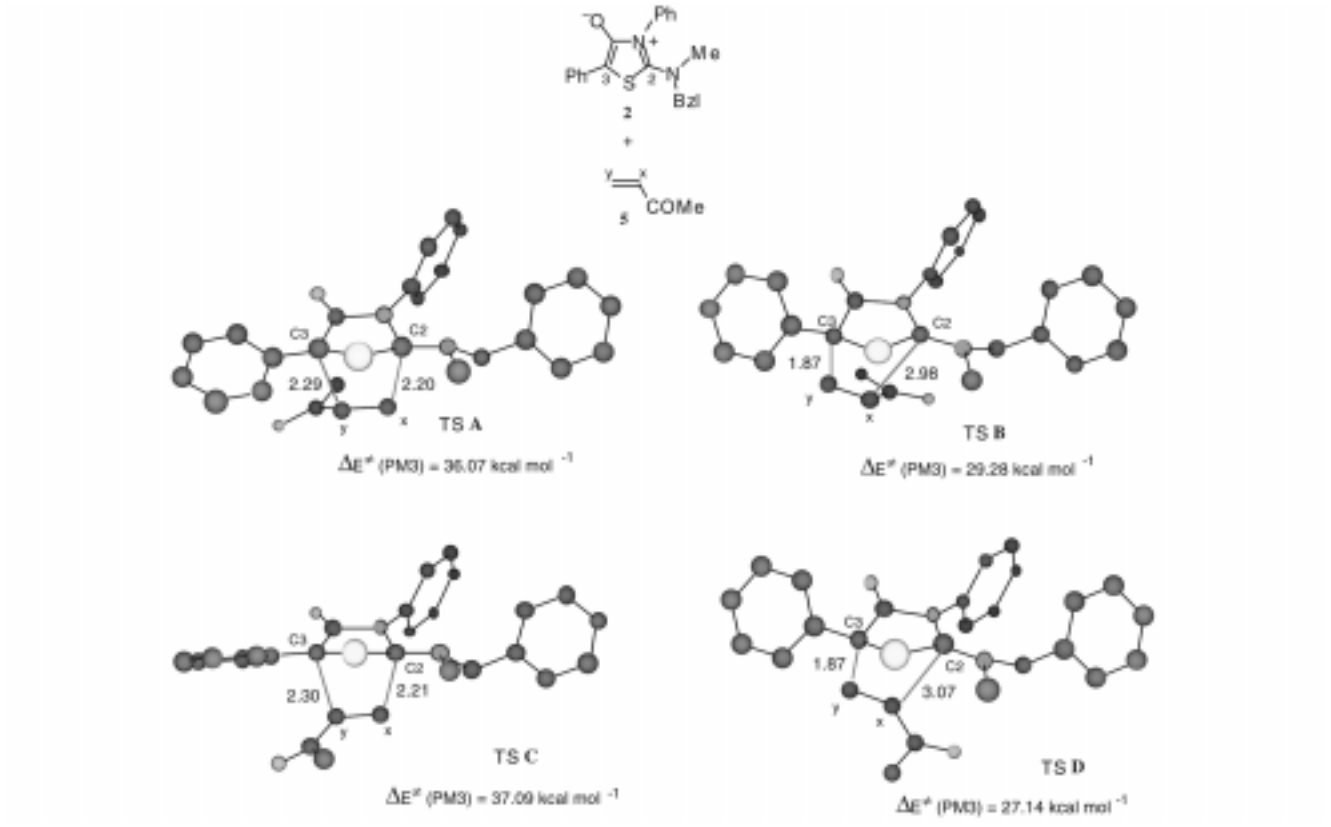


Figure 5. PM3 transition structures for the reaction between **2** and **5**; bond lengths in Å; hydrogen atoms have been omitted for the sake of clarity

Table 2. Energies and bond lengths for all computed transition structures

Reagents	TS Approach	Orientation	$\Delta E^{\neq}$ (PM3)[a]	d(C2−x)[b]	d(C3−y)[b]	$\Delta E^{\neq}$ (B3LYP/6-31G*//PM3)[a]
1 + **4**	A	*endo*	35.80	2.20	2.30	18.00
	B	*endo*	31.73	3.17	1.83	13.67
	C	*exo*	36.04	2.22	2.28	19.04
	D	*exo*	29.29	3.22	1.85	20.75
2 + **4**	A	*endo*	35.33	2.21	2.28	21.88
	B	*endo*	30.59	3.25	1.82	13.62
	C	*exo*	35.30	2.23	2.27	22.14
	D	*exo*	28.08	3.21	1.85	19.50
3 + **4**	A	*endo*	35.82	2.21	2.27	18.63
	B	*endo*	30.81	3.27	1.82	14.00
	C	*exo*	35.91	2.23	2.27	19.31
	D	*exo*	28.18	3.21	1.85	19.70
1 + **5**	A	*endo*	36.20	2.20	2.31	23.13
	B	*endo*	30.13	2.92	1.88	17.16
	C	*exo*	37.22	2.21	2.31	21.65
	D	*exo*	28.03	3.09	1.87	20.53
2 + **5**	A	*endo*	36.07	2.20	2.29	23.37
	B	*endo*	29.28	2.98	1.87	16.31
	C	*exo*	37.09	2.21	2.30	22.10
	D	*exo*	27.14	3.07	1.87	19.10
3 + **5**	A	*endo*	36.27	2.20	2.29	23.59
	B	*endo*	29.49	2.98	1.87	16.72
	C	*exo*	37.30	2.21	2.30	22.41
	D	*exo*	27.30	3.07	1.87	19.36

[a] Energy values in kcal·mol^{-1}. – [b] Bond lengths in Å.

On scrutinizing all the computed transition structures (Table 2; Figure 4, Figure 5, and Figure 7), it emerges that the structures leading to the experimental products are much more asynchronous than their opposite counterparts.

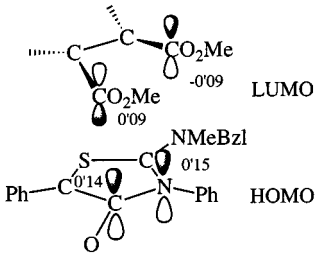


Figure 6. Secondary orbital interactions for the reaction of **2** with dimethyl maleate

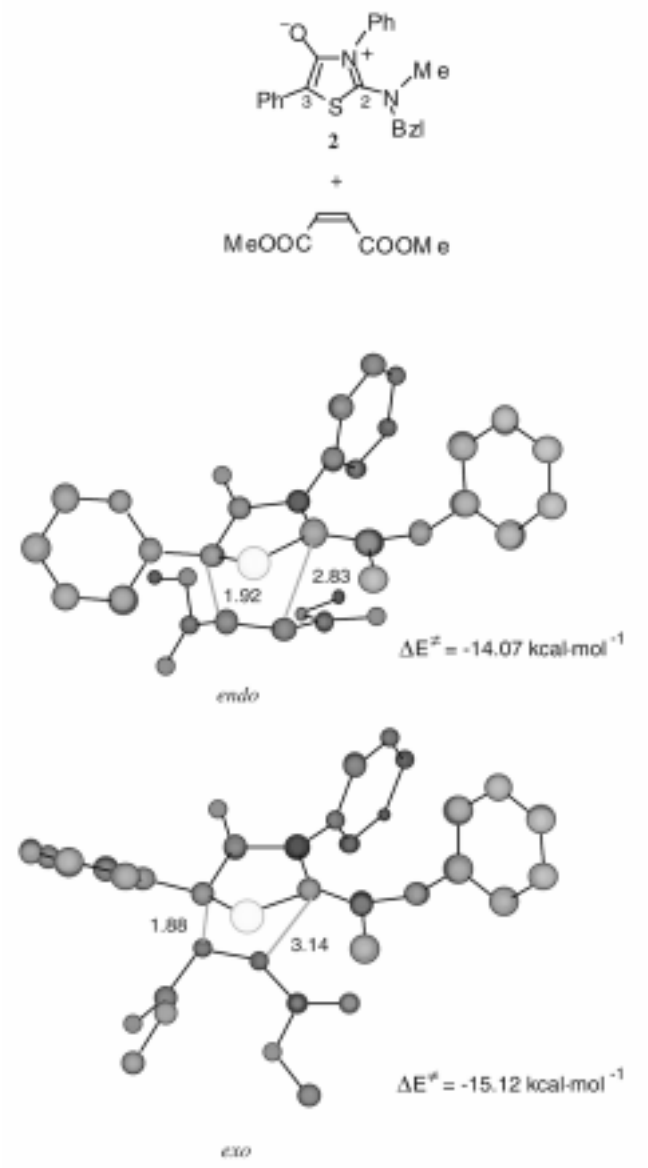


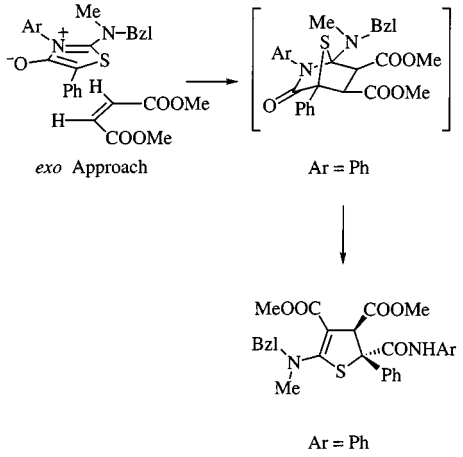
Figure 7. PM3 transition structures for the reaction between **2** and dimethyl maleate; bond lengths in Å; hydrogen atoms have been omitted for the sake of clarity

It would thus appear that such an asynchronicity constitutes a general trend in these cycloadditions.

Both transition states **B** and **D** in Figure 4 and 5 (exemplified in the cases of the reactions between **2** and **4** or **5**, respectively) would lead to the final dihydrothiophenes. Both are more stable than those with the opposite regiochemistry, **A** and **C**. Nevertheless, the energy difference between transition structures **B** and **D** (ca. 2 kcalmol^{-1}) is not large enough to completely rule out one or the other.

As the energy difference between the four saddle points for each reaction is not large enough to allow unequivocal prediction of the cycloaddition course, we performed B3LYP/6−31G*[18] single-point calculations of the transition states previously located at the PM3 level. The results are summarized in Table 2. It can be seen that in each case transition state **D** can be neglected and that only **B** need be considered. Thus, the theoretical calculations are again in agreement with the experiment.

As far as dimethyl maleate is concerned, no regioisomers are possible, although the stereoselectivity remains an uncertain issue. From the FMO viewpoint, secondary interactions, only present in the *endo* approach, are suggestive of two opposite interactions, although it is unclear as to which is larger (Figure 6). On the other hand, it is also true that the *exo* approach lacks both steric hindrance and electronic destabilization. The computed transition states at a semiempirical level reveal that the *exo* approach is energetically favored (Figure 7). This conclusion could justify the assignment of the configurations (4*R*,5*R*) and (4*S*,5*S*) to the racemic dihydrothiophene **12** obtained in the reaction of **2** with dimethyl maleate (Scheme 7).



Scheme 7

Experimental Section

General Methods: Melting points were determined with a capillary apparatus and are uncorrected. − Optical rotations were measured at 18 ± 2 °C with a Perkin−Elmer 241 polarimeter. − Analytical and preparative TLC were performed on Merck 60 GF_{254} silica gel with monitoring by UV irradiation at 254 and 360 nm or by exposure to iodine vapor. − Flash chromatography[19] was performed

on Merck 60 silica gel (230−400 mesh). − IR spectra were recorded with a Perkin−Elmer 399 or a Midac FT-IR spectrometer. − ^{1}H and ^{13}C NMR spectra were obtained with a Bruker AM 400 instrument at 400 and 100 MHz, respectively, or with a Bruker AC 200 instrument at 200 and 50 MHz, respectively, in $CDCl_3$ (Me_4Si as internal standard) unless otherwise specified. − Elemental analyses were carried out using a Leco 932 analyser at the Universidad de Extremadura, and were also provided by the Servei de Microanàlisi del CSIC, Barcelona, Spain, and the Instituto de Investigaciones Químicas del CSIC, Seville, Spain. − Mass spectra (HRMS/CI$^+$) were measured at the Universidad de Córdoba, Spain.

5-[Benzyl(methyl)amino]-4-cyano-*N*-(4-nitrophenyl)-2-phenyl-2,3-dihydrothiophene-2-carboxamide (6): To a solution of **1** (0.84 g, 2.0 mmol) in dry CH_2Cl_2 (10 mL) was added acrylonitrile (**4**, 0.11 g, 2.0 mmol) and the reaction mixture was stirred at room temperature for 24 h. The solvent was then evaporated under reduced pressure and the residue was treated with ethyl acetate to give the title compound as crystals (0.55 g, 58%). − M.p. 167−169 °C (EtOH). − IR (KBr): $\tilde{\nu}$ = 3230, 2160, 1680, 1550, 1500, 1300, 720, 680 cm^{-1}. − ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.41 (s, 1 H, NH), 8.22 (d, 2 H, Ar), 7.88 (d, 2 H, Ar), 7.55−7.16 (m, 10 H, Ar), 4.61 (d, *J* = 16.3 Hz, 1 H, C*H*$_2$Ph), 4.56 (d, 1 H, C*H*$_2$Ph), 3.86 (d, *J* = 13.8 Hz, 1 H, CH_2), 3.43 (d, 1 H, CH_2), 3.13 (s, 3 H, CH_3). − ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 169.90 (*C*ONHAr), 161.55 (C-4), 144.87, 143.07, 138.72, 136.65, 129.12, 128.90, 128.69, 127.85, 127.14, 126.40, 124.99, 120.22 (Ar), 119.58 (CN), 69.62 (C-5), 65.32 (C-2), 59.17 (*C*H$_2$Ph), 44.80 (C-3), 40.33 (CH_3). − $C_{26}H_{22}N_4O_3S$: calcd. C 66.37, H 4.71, N 11.91; found C 66.12, H 4.50, N 12.04. − HRMS: calcd. for [M + H] 471.149088; found 471.145846.

5-[Benzyl(methyl)amino]-4-cyano-*N*,2-diphenyl-2,3-dihydrothiophene-2-carboxamide (7): To a solution of **2** (0.74 g, 2.0 mmol) in dry CH_2Cl_2 (10 mL) was added acrylonitrile (**4**, 0.11 g, 2.0 mmol) and the reaction mixture was stirred at room temperature for 36 h. The solvent was then evaporated under reduced pressure and the residue was treated with ethyl acetate to give the title compound as crystals (0.56 g, 66%). − M.p. 147−149 °C (EtOAc). − IR (KBr): $\tilde{\nu}$ = 3280, 2150, 1660, 1560, 1300, 730, 720, 680 cm^{-1}. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (s, 1 H, NH), 7.48−7.11 (m, 15 H, Ar), 4.67 (d, *J* = 16.2 Hz, 1 H, C*H*$_2$Ph), 4.54 (d, 1 H, C*H*$_2$Ph), 4.13 (d, *J* = 13.8 Hz, 1 H, CH_2), 3.43 (d, 1 H, CH_2), 3.27 (s, 3 H, CH_3). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.61 (*C*ONHPh), 160.57 (C-4), 138.00, 137.16, 135.94, 129.03, 128.94, 128.55, 127.96, 126.64, 124.87, 119.81 (Ar), 119.21 (CN), 68.79 (C-5), 67.27 (C-2), 60.18 (*C*H$_2$Ph), 46.01 (C-3), 40.43 (CH_3). − $C_{26}H_{23}N_3OS$: calcd. C 73.38, H 5.45, N 9.87; found C 73.19, H 5.46, N 9.83.

5-[Benzyl(methyl)amino]-4-cyano-*N*-(4-methoxyphenyl)-2-phenyl-2,3-dihydrothiophene-2-carboxamide (8): To a solution of **3** (0.81 g, 2.0 mmol) in dry CH_2Cl_2 (10 mL) was added acrylonitrile (**4**, 0.11 g, 2.0 mmol) and the reaction mixture was stirred at room temperature for 24 h. The solvent was then evaporated under reduced pressure and the residue was treated with ethyl acetate to give the title compound as crystals (0.54 g, 60%). − M.p. 145−147 °C (EtOAc). − IR (KBr): $\tilde{\nu}$ = 3260, 2880, 2160, 1650, 1570, 1500, 1240, 1030, 830, 720, 670 cm^{-1}. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (s, 1 H, NH), 7.47−7.18 (m, 12 H, Ar), 6.82 (d, 2 H, Ar), 4.65 (d, *J* = 16.2 Hz, 1 H, C*H*$_2$Ph), 4.53 (d, 1 H, C*H*$_2$Ph), 4.10 (d, *J* = 13.8 Hz, 1 H, CH_2), 3.77 (s, 3 H, OCH_3), 3.42 (d, 1 H, CH_2), 3.25 (s, 3 H, CH_3). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.49 (*C*ONHAr), 160.77 (C-4), 156.76, 138.21, 136.01, 130.29, 129.05, 128.90, 128.49, 127.96, 126.67, 121.70, 114.01 (Ar), 119.34 (CN), 68.74 (C-5), 67.16 (C-2), 60.18 (*C*H$_2$Ph), 55.46 (OCH_3), 45.97 (C-3), 40.45 (CH_3). − $C_{27}H_{25}N_3O_2S$: calcd. C 71.18, H 5.53, N 9.22; found C 71.08, H 5.52, N 9.40.

4-Acetyl-5-[benzyl(methyl)amino]-*N*-(4-nitrophenyl)-2-phenyl-2,3-dihydrothiophene-2-carboxamide (9): To a solution of **1** (0.84 g, 2.0 mmol) in dry CH_2Cl_2 (10 mL) was added methyl vinyl ketone (**5**, 0.14 g, 2.0 mmol) and the reaction mixture was stirred at room temperature for 24 h. The solvent was then evaporated under reduced pressure and the residue was treated with methanol/diethyl ether to give the title compound as crystals (0.75 g, 79%). − M.p. 116−118 °C (MeOH). − IR (KBr): $\tilde{\nu}$ = 3180, 1680, 1580, 1500, 1340, 720, 680 cm^{-1}. − ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.41 (s, 1 H, NH), 8.22 (d, 2 H, Ar), 7.88 (d, 2 H, Ar), 7.55−7.16 (m, 10 H, Ar), 4.61 (d, *J* = 16.3 Hz, 1 H, C*H*$_2$Ph), 4.56 (d, 1 H, C*H*$_2$Ph), 3.86 (d, *J* = 13.8 Hz, 1 H, CH_2), 3.43 (d, 1 H, CH_2), 3.13 (s, 3 H, CH_3). − ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 169.90 (*C*ONHAr), 161.55 (C-4), 144.87, 143.07, 138.72, 136.65, 129.12, 128.90, 128.69, 127.85, 127.14, 126.40, 124.99, 120.22 (Ar), 119.58 (CN), 69.62 (C-5), 65.32 (C-2), 59.17 (*C*H$_2$Ph), 44.80 (C-3), 40.33 (CH_3). − $C_{27}H_{25}N_3O_4S$: calcd. C 66.51, H 5.17, N 8.62; found C 66.38, H 5.24, N 8.51. − HRMS: calcd. for [M + H] 488.164403; found 488.163681.

4-Acetyl-5-[benzyl(methyl)amino]-*N*,2-diphenyl-2,3-dihydrothiophene-2-carboxamide (10): To a solution of **2** (0.74 g, 2.0 mmol) in dry CH_2Cl_2 (10 mL) was added methyl vinyl ketone (**5**, 0.14 g, 2.0 mmol) and the reaction mixture was stirred at room temperature for 24 h. The solvent was then evaporated under reduced pressure and the residue was treated with ethanol/diethyl ether to give the title compound as crystals (0.69 g, 78%). − M.p. 118−120 °C (Et_2O). − IR (KBr): $\tilde{\nu}$ = 3320, 1680, 1590, 1240, 760, 740, 690 cm^{-1}. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (s, 1 H, NH), 7.50−7.09 (m, 15 H, Ar), 4.75 (d, *J* = 16.1 Hz, 1 H, C*H*$_2$Ph), 4.53 (d, 1 H, C*H*$_2$Ph), 4.29 (d, *J* = 13.1 Hz, 1 H, CH_2), 3.52 (d, 1 H, CH_2), 3.07 (s, 3 H, OCH_3), 2.19 (s, 3 H, NCH_3). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.74 (*C*OCH_3), 169.30 (*C*ONHPh), 163.35 (C-4), 138.48, 137.19, 136.42, 128.89, 128.81, 128.23, 127.59, 126.92, 126.83, 124.71, 119.89 (Ar), 105.54 (C-5), 67.57 (C-2), 61.02 (*C*H$_2$Ph), 46.67 (C-3), 44.39 (CO*C*H$_3$), 30.44 (NCH_3). − $C_{27}H_{26}N_2O_2S$: calcd. C 73.27, H 5.92, N 6.33; found C 73.24, H 5.98, N 6.27.

4-Acetyl-5-[benzyl(methyl)amino]-*N*-(4-methoxyphenyl)-2-phenyl-2,3-dihydrothiophene-2-carboxamide (11): To a solution of **3** (0.81 g, 2.0 mmol) in dry CH_2Cl_2 (10 mL) was added methyl vinyl ketone (**5**, 0.14 g, 2.0 mmol) and the reaction mixture was stirred at room temperature for 24 h. The solvent was then evaporated under reduced pressure and the residue was treated with ethanol/diethyl ether/petroleum ether to give the title compound as crystals (0.41 g, 43%). − M.p. 112−114 °C (EtOH/petroleum ether). − IR (KBr): $\tilde{\nu}$ = 3260, 1670, 1600, 1520, 1230, 830, 740, 700 cm^{-1}. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (s, 1 H, NH), 7.50−7.15 (m, 12 H, Ar), 6.78 (d, 2 H, Ar), 4.75 (d, *J* = 16.1 Hz, 1 H, C*H*$_2$Ph), 4.52 (d, 1 H, C*H*$_2$Ph), 4.27 (d, *J* = 13.1 Hz, 1 H, CH_2), 3.76 (d, 1 H, CH_2), 3.07 (s, 3 H, OCH_3), 2.19 (s, 3 H, NCH_3). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.71 (*C*OCH_3), 169.18 (*C*ONHAr), 163.63 (C-4), 156.64, 138.57, 136.39, 130.29, 128.84, 128.71, 128.14, 127.56, 126.89, 126.84, 121.80, 113.88 (Ar), 105.42 (C-5), 67.45 (C-2), 60.95 (*C*H$_2$Ph), 55.40 (ArO*C*H$_3$), 46.60 (C-3), 44.37 (OCH_3), 30.35 (NCH_3). − $C_{28}H_{28}N_2O_3S$: calcd. C 71.16, H 5.97, N 5.93, S 6.79; found C 71.48, H 6.03, N 5.89, S 6.65.

Dimethyl 5-[Benzyl(methyl)amino]-2-phenyl-2-(*N*-phenylcarbamoyl)-2,3-dihydrothiophene-3,4-dicarboxylate (12). − Procedure A: To a

solution of **2** (0.50 g, 1.3 mmol) in dry CH_2Cl_2 (20 mL) was added dimethyl maleate (0.19 g, 1.3 mmol) and the reaction mixture was stirred at room temperature for 10 d. The solvent was then evaporated under reduced pressure and the residue was treated with ethyl acetate/petroleum ether to give the title compound as crystals (0.10 g, 15%). − M.p. 113−115 °C (EtOAc/Et_2O). − IR (KBr): $\tilde{\nu}$ = 3200, 1730, 1650, 1520, 1230, 750, 690 cm^{-1}. − ^1H NMR (400 MHz, $CDCl_3$): δ = 8.29 (s, 1 H, NH), 7.61−7.06 (m, 15 H, Ar), 5.40 (s, 1 H, 4-H), 4.86 (d, *J* = 16.0 Hz, 1 H, CH_2), 4.48 (d, 1 H, CH_2), 3.66 (s, 3 H, CO_2CH_3), 3.25 (s, 3 H, CO_2CH_3), 3.10 (s, 3 H, NCH_3). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.09 (CONH), 168.72 (CO_2CH_3), 164.54 (CO_2CH_3), 163.08 (C-4), 137.31, 136.58, 134.46, 128.82, 128.70, 128.42, 127.60, 126.94, 124.64, 119.88 (Ar), 94.47 (C-5), 69.69 (C-2), 61.05 (CH_2), 59.74 (C-3), 51.53 (CO_2CH_3), 51.08 (CO_2CH_3), 43.59 (NCH_3). − $C_{29}H_{28}N_2O_5S$: calcd. C 67.42, H 5.46, N 5.42, S 6.21; found C 67.58, H 5.51, N 5.39, S 6.08. − **Procedure B:** To a solution of **2** (1.00 g, 2.7 mmol) in dry benzene (30 mL) was added dimethyl maleate (0.39 g, 2.7 mmol) and the reaction mixture was stirred under reflux for 24 h. The solvent was then evaporated under reduced pressure and the residue was treated with ethyl acetate/petroleum ether to give the title compound as crystals (0.46 g, 33%). − M.p. 112−115 °C (EtOAc/Et_2O).

Anhydrides 15 and 16. − Procedure A: To a solution of **14** (1.00 g, 1.9 mmol) in CH_2Cl_2 (20 mL) was added maleic anhydride (0.20 g, 1.9 mmol) and the reaction mixture was left to stand at room temperature for 12 h. The solvent was then evaporated under reduced pressure and the residue was submitted to column chromatography (silica gel, benzene/acetonitrile, 10:1). From a first fraction, compound **15** was crystallized (0.25 g, 22%). − M.p. 187−189 °C. − $[\alpha]_D$ = −181; $[\alpha]_{578}$ = −195; $[\alpha]_{546}$ = −248 (*c* = 0.5, chloroform). − IR (KBr): $\tilde{\nu}$ = 1850, 1775, 1765, 1680 cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 7.47−7.26 (m, 10 H, Ar), 6.08 (d, *J* = 6.5 Hz, 1 H, 1′-H), 5.97 (d, *J* = 2.8 Hz, 1 H, 3′-H), 5.23 (m, 1 H, 5′-H), 5.00 (d, 1 H, 2′-H), 4.58 (dd, 1 H, *J* < 1.0, *J* = 12.2 Hz, 6′a-H), 4.31 (dd, *J* = 9.5 Hz, 1 H, 4′-H), 4.12 (dd, *J* = 4.4 Hz, 1 H, 6′b-H), 2.09 (s, 6 H, OAc), 2.00 (s, 3 H, OAc). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.36, 169.63, 168.14 ($COCH_3$), 161.22 (CO), 160.16 (C-4), 157.14 (CO), 148.28 (C-6a), 135.96 (C-2), 123.06 (C-3), 95.33 (C-1′), 83.83 (C-1), 76.62 (C-4′), 72.11 (C-3′), 66.44 (C-5′), 66.18 (C-2′), 62.77 (C-6′), 20.63, 20.40 ($COCH_3$). − $C_{31}H_{26}N_2O_{11}$: calcd. C 61.79, H 4.35, N 4.65; found C 61.53, H 4.22, N 4.58. − From a second fraction, compound **16** was crystallized (0.37 g, 31%). − M.p. 202−204 °C (EtOH). − $[\alpha]_D$ = +37; $[\alpha]_{578}$ = +40; $[\alpha]_{546}$ = +43 (*c* = 0.5, chloroform). − IR (KBr): $\tilde{\nu}$ = 1845, 1775, 1755, 1745, 1730, 1675, 1655 cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): rotamer a: δ = 7.70−7.18 (m, 10 H, Ar), 6.37 (d, *J* = 2.9 Hz, 1 H, 3′-H), 6.00 (d, *J* = 6.6 Hz, 1 H, 1′-H), 5.31 (m, 1 H, 5′-H), 4.98 (d, 1 H, 2′-H), 4.57 (dd, *J* = 2.5, *J* = 12.3 Hz, 1 H, 6′a-H), 4.49 (dd, *J* = 9.5 Hz, 1 H, 4′-H), 4.12 (dd, *J* = 4.2 Hz, 1 H, 6′b-H), 3.91 (d, 1 H, J_{CH2a} = 22.8 Hz, CH_2), 3.53 (d, 1 H, J_{CH2b} = 22.8 Hz, CH_2), 2.18 (s, 3 H, OAc), 2.15 (s, 3 H, OAc), 2.13 (s, 3 H, OAc); rotamer b: δ = 7.70−7.18 (m, 10 H, Ar), 6.08 (d, *J* = 6.6 Hz, 1 H, 1′-H), 5.85 (d, 1 H, 2′-H), 5.23 (m, 1 H, 5′-H), 5.08 (d, 1 H, 2′-H), 4.55 (dd, *J* = 2.4, *J* = 12.2 Hz, 1 H, 6′a-H), 4.26 (dd, *J* = 3.1, *J* = 9.5 Hz, 1 H, 4′-H), 4.10 (dd, *J* = 5.0 Hz, 1 H, 6′b-H), 3.89 (d, 1 H, J_{CH2a} = 22.8 Hz, CH_2), 3.58 (d, 1 H, J_{CH2b} = 22.8 Hz, CH_2), 2.11 (s, 6 H, OAc), 2.07 (s, 3 H, OAc). − ^{13}C NMR (50 MHz, $CDCl_3$): rotamer a: δ = 177.27 (CS), 170.65, 170.17, 168.72 ($OCOCH_3$), 167.43 (CO), 166.09 (C-1), 164.27 (CO), 147.04 (C-2), 119.53 (C-3), 91.65 (C-1′), 76.63 (C-4′), 72.18 (C-3′), 66.76 (C-5′), 65.98 (C-2′), 63.18 (C-6′), 34.20 (C-4), 20.78 (CH_3); rotamer b: δ = 178.46 (CS), 170.42, 169.75, 168.45 ($OCOCH_3$), 167.55 (CO), 166.84 (C-1), 164.41 (CO), 146.83 (C-2), 118.83 (C-3), 92.45 (C-1′), 76.26 (C-4′), 73.79 (C-3′), 66.76 (C-5′), 66.33 (C-2′), 62.92 (C-6′), 34.20 (C-4), 20.78 (CH_3). − $C_{31}H_{28}N_2O_{11}S$: calcd. C 58.49, H 4.43, N 4.40; found C 58.43, H 4.39, N 4.35. − **Procedure B:** To a suspension of **14** (1.00 g, 1.9 mmol) in toluene (13 mL) was added maleic anhydride (0.20 g, 1.9 mmol) and the reaction mixture was refluxed for 3 h. The solvent was then evaporated under reduced pressure and the residue was treated with ethanol. Compound **16** crystallized (0.60 g, 47%). Compound **15** was detected in the mother liquor by TLC. − **Procedure C:** To a suspension of **14** (1.00 g, 1.9 mmol) in acetic acid (20 mL) was added maleic anhydride (0.20 g, 1.9 mmol) and the reaction mixture was left to stand at room temperature for 48 h. Compound **16** was deposited as a white solid. It was collected by filtration and washed with diethyl ether (0.85 g, 72%).

Imide 17: To a suspension of **14** (1.00 g, 1.9 mmol) in benzene (15 mL) was added *N*-phenylmaleimide (0.34 g, 1.9 mmol) and the reaction mixture was first stirred for 15 min under reflux and then left to stand at room temperature for 24 h. The solvent was subsequently evaporated under reduced pressure. The residue was treated with diethyl ether to yield compound **17** as crystals (0.94 g, 73%). This product was submitted to column chromatography (benzene/acetonitrile, 10:1) and then crystallized from diethyl ether. − M.p. 184−186 °C. − $[\alpha]_D$ = −155; $[\alpha]_{578}$ = −168; $[\alpha]_{546}$ = −214 (*c* = 0.5, chloroform). − IR (KBr): $\tilde{\nu}$ = 1753, 1714, 1660 cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 7.48−7.15 (m, 15 H, Ar), 5.99 (d, 1 H, 3′-H), 5.93 (d, *J* = 6.4 Hz, 1 H, 1′-H), 5.24 (m, 1 H, 5′-H), 4.95 (d, 1 H, 2′-H), 4.60 (dd, 1 H, *J* < 1.0, *J* = 12.4 Hz, 6′a-H), 4.31 (dd, *J* = 2.8, *J* = 9.5 Hz, 1 H, 4′-H), 4.15 (dd, *J* = 4.6 Hz, 1 H, 6′b-H), 2.07 (s, 6 H, OAc), 1.99 (s, 3 H, OAc). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.24, 169.54, 168.04 ($OCOCH_3$), 164.24, 161.52 (CO), 160.60 (C-4), 146.26 (C-6a), 137.26 (C-2), 121.96 (C-3), 95.39 (C-1′), 85.60 (C-1), 76.34 (C-4′), 72.29 (C-3′), 66.47 (C-5′), 65.78 (C-2′), 62.79 (C-6′), 20.55, 20.33 ($OCOCH_3$). − $C_{37}H_{31}N_3O_{10}$: calcd. C 65.58, H 4.61, N 6.20; found C 65.70, H 4.52, N 6.15.

Nitrile 18: A suspension of **14** (1.00 g, 1.9 mmol) in acrylonitrile (9.82 mL) was stirred under reflux for 3 h. The solvent was then evaporated under reduced pressure and the oily residue was treated with iced water, yielding compound **18** (1.00 g, 94%). The product was purified first by column chromatography (benzene/acetonitrile, 5:1) and then by thin-layer preparative chromatography (benzene/acetonitrile, 10:1). − M.p. 132−134 °C (diethyl ether). − $[\alpha]_D$ = −64; $[\alpha]_{578}$ = −69; $[\alpha]_{546}$ = −86 (*c* = 0.5, chloroform). − IR (KBr): $\tilde{\nu}$ = 2231, 1753, 1660 cm^{-1}. − ^1H NMR (200 MHz, $CDCl_3$): δ = 7.60−7.31 (m, 10 H, Ar), 7.38 (s, 1 H, 2′-H), 6.00 (d, 1 H, *J* < 1.0 Hz, 3′-H), 5.99 (d, *J* = 6.4 Hz, 1 H, 1′-H), 5.21 (m, 1 H, 5′-H), 4.98 (d, 1 H, 2′-H), 4.56 (dd, 1 H, *J* < 1.0, *J* = 12.3 Hz, 6′a-H), 4.26 (dd, 1 H, *J* < 1.0, *J* = 8.9 Hz, 4′-H), 4.10 (dd, *J* = 4.4 Hz, 1 H, 6′b-H), 2.09 (s, 6 H, OAc), 1.99 (s, 3 H, OAc). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.03, 169.36, 167.99 ($OCOCH_3$), 158.11 (C-4), 151.84 (C-6a), 140.31 (C-2), 120.95 (C-3), 114.51 (C-1), 94.45 (C-1′), 76.07 (C-4′), 72.00 (C-3′), 65.68 (C-2′), 66.27 (C-5′), 62.57 (C-6′), 20.38, 20.21 (CH_3). − $C_{30}H_{27}N_3O_8$: calcd. C 64.63, H 4.88, N 7.54; found C 64.47, H 4.95, N 7.60.

Ketone 19: To a solution of **14** (1.00 g, 1.9 mmol) in CH_2Cl_2 (20 mL) was added methyl vinyl ketone (5.89 g, 84.0 mmol) and the reaction mixture was stirred under reflux for 3 h. The solvent was then evaporated under reduced pressure and the oily residue was treated with iced water, which resulted in the crystallization of compound **19** (0.71 g, 93%). − M.p. 165−167 °C (diethyl ether/petroleum ether). − $[\alpha]_D$ = −69; $[\alpha]_{578}$ = −78; $[\alpha]_{546}$ = −110 (*c* = 0.5,

chloroform). – IR (KBr): $\tilde{\nu}$ = 1750, 1610, 1500, 1220, 1040 cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 7.54–6.91 (m, 10 H, Ar), 5.84–5.81 (m, 2 H, 1′-H, 3′-H), 5.27–5.23 (m, 1 H, 5′-H), 4.74 (d, *J* = 5.9 Hz, 1 H, 2′-H), 4.53 (dd, *J* = 2.1, *J* = 12.3 Hz, 1 H, 6′a-H), 4.31 (dd, *J* = 5.0 Hz, 1 H, 6′b-H), 4.22 (dd, *J* = 2.9, *J* = 9.4 Hz, 1 H, 4′-H), 3.47 (d, *J* = 16.4 Hz, 1 H, 2b-H), 3.03 (d, 1 H, 2a-H), 2.71 (m, 2 H, CH_2), 2.62 (m, 2 H, CH_2), 2.11 (s, 3 H, CH_3), 2.10 (s, 3 H, CH_3), 2.08 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 2.04 (s, 3 H, CH_3). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.33, 193.08, 170.48, 169.72, 168.57, 168.08 (CO), 146.25 (C-6), 143.30, 137.21, 129.60, 128.68, 128.03, 127.50, 125.75, 121.32 (Ar), 96.36 (C-5b), 93.23 (C-1), 76.28 (C-4′), 72.92 (C-3′), 66.91 (C-5′), 63.33 (C-5a), 63.17 (C-6′), 56.83 (C-3), 42.82 (CH_2COCH_3), 35.92 (C-2), 29.67 ($COCH_3$), 28.74 ($COCH_3$), 23.77 (CH_2S), 20.74 ($OCOCH_3$), 20.59 (2 C, $OCOCH_3$). – $C_{35}H_{38}N_2O_{10}S$: calcd. C 61.93, H 5.64, N 4.13, S 4.72; found C 61.68, H 5.87, N 4.18, S 4.79.

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