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1,3-Dipolar cycloaddition reactions of benzo[*b*]thiophene 1,1-dioxide with azomethine ylides

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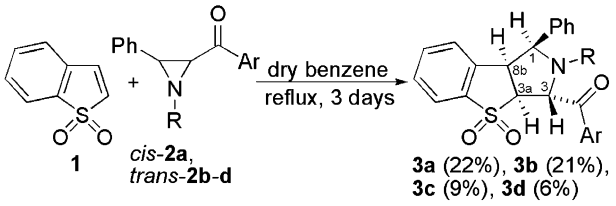
Abstract—New pyrrolo derivatives of benzo[*b*]thiophene 1,1-dioxide have been synthesised via 1,3-dipolar cycloaddition reactions. Reaction of benzo[*b*]thiophene 1,1-dioxide with stabilised azomethine ylides gave products in low yield but high stereoselectivity whereas reaction with non-stabilised azomethine ylides gave high overall yields but low stereoselectivity.

Interest in synthesising new benzo[*b*]thiophene derivatives continues as more of their biological activities, amongst other applications, are discovered.[1] We have been investigating the formation of novel three-ringed heterocycles derived from benzo[*b*]thiophene using cycloaddition strategies, however, benzo[*b*]thiophene itself is not very reactive with dipoles and 2,3-unsubstituted benzo[*b*]thiophene 1-oxide is only stable in dilute solution.[2] We previously reported the stable *N*-tosyl sulfimide derivative of benzo[*b*]thiophene[3] but this sulfimide subsequently was found to have no dipolarophilic activity under a variety of standard reaction conditions. Benzo[*b*]thiophene 1,1-dioxide (**1**), however, is a useful dipolarophile and reactions already reported for this sulfone include the cycloadditions with diazomethane,[4] diphenyl nitrone,[5] nitrile oxides[6] and nitrile imides.[7] These reactions proved to be highly regioselective and in almost all cases, only one regioisomer was isolated where the more nucleophilic terminus of the dipole (oxygen or nitrogen) is attached to the β-carbon of the benzo[*b*]thiophene 1,1-dioxide. Cycloadditions with azomethine ylides are of great interest since a five-membered heterocyclic ring with up to four new chiral centres may be obtained in one step, and to our knowledge, no such reactions with **1** have been reported. Unfortunately, we have been so far unable to find conditions to oxidise the *N*-tosyl sulfimide to the corresponding sulfoximide but were nevertheless still interested in investigating further the 1,3-dipolar cycloadditions of these dipoles with **1**.

Initially, we attempted cycloaddition of **1** with stabilised azomethine ylides. The dipoles were generated through thermal ring-opening of aziridines[8] **2a–d** (Scheme 1). The dipoles proved to be not very reactive, and after exploration of several different solvents and conditions, we found that cycloadducts formed only after three days of heating under reflux in benzene. The cycloadducts were isolated in modest to low yields and only one isomer was isolated in each reaction. Also, unexpectedly, the structures of all the cycloadducts **3a–d**, as suggested by their ^{1}H NMR, were related. Under such conditions, it was expected that the *cis*-aziridine **2a** would give the *trans*-azomethine ylide and *trans*-aziridines **2b–d** would



Scheme 1. 1,3-Dipolar cycloaddition reactions of **1** and azomethine ylides generated from aziridines **2a–d**, affording only one cycloadduct **3a–d**: **a**, R = CH_3, Ar = Ph; **b**, R = CH_3, Ar = 4–$CH_3C_6H_4$; **c**, R = *cyclo*-C_6H_{11}, Ar = Ph; **d**, R = *cyclo*-C_6H_{11}, Ar = 4–$CH_3C_6H_4$.

Keywords: 1,3-Dipolar cycloaddition reactions; Benzo[*b*]thiophene 1,1-dioxide; Azomethine ylides; Regio- and stereoselectivity.
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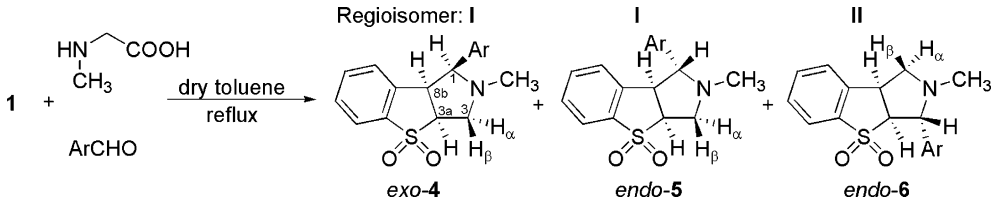


Scheme 2. 1,3-Dipolar cycloaddition reactions of **1** and azomethine ylides generated from sarcosine and an aldehyde (**a**–**e**) (at reflux in toluene, 8 h). Ar: **a** = Ph; **b** = 4-$NO_2C_6H_4$; **c** = 4–$CH_3OC_6H_4$; **d** = 3,5-$(CH_3O)_2C_6H_3$; **e** = 4-BrC_6H_4.

give the *cis*-azomethine ylides, both as a result of conrotatory ring-opening. In theory, the *trans*-ylide can have either (*Z*,*E*) or (*E*,*Z*)-conformation ('*S*' conformations), and the *cis*-ylide (*E*,*E*)- (also called '*W*') or (*Z*,*Z*)-conformation (also called '*U*'). Thus, the same product could arrive, for example, from both the (*E*,*E*)-*endo* and (*Z*,*Z*)-*exo*-approaches.[9] Although not isolated, TLC of the reaction mixtures indicated that with *cis*-aziridines **2c** and **2d**, the same cycloadducts were formed (**3c** and **3d**) as in the reactions with the corresponding *trans*-aziridines **2c** and **2d**. Unreacted **1** was recovered from all the reactions, along with small amounts of by-products that could not be identified. ^{1}H NMR and de-coupling experiments with **3a**–**d** showed that the 3a-H and 8b-H protons were coupled to each other with similar coupling constants ($J = 8.7$ Hz for **3a**). This is similar to that found for 1-H and 8b-H ($J = 8.5$ Hz for **3a**) implying that 1-H, 3a-H and 8b-H are all cis. The signal for 3-H gives a broad singlet and couples to 3a-H only with a very small coupling constant ($J = 1.0$ Hz for 3a-H in **3a**, and not resolved for **3b**–**d**).[10] The small coupling between 3-H and 3a-H indicates, according to the Karplus equation, that the dihedral angle between these two vicinal C–H bonds is probably close to 90°. Using simple molecular modelling (MM2),[11] for all possible isomers, revealed that the structure **3**, where 3-H and 3a-H are trans to each other, is most likely to have this dihedral angle between 90° and 100°. Finally supporting evidence for the assignment of this isomer comes from the aromatic protons and carbons in both the benzo[*b*]thiophene-ring and the C1-phenyl group which correspond very closely to the ^{1}H and ^{13}C NMR spectra in the related cycloadduct **4a** (see below).

The stereochemical structure of products **3a**–**d** could be due to reaction of the *trans*-ylide. It is reasonable to believe that between the two possible *S*-conformations, the dipole adopted the more polar one, where the carbonyl group is on the opposite side from the R substituent on nitrogen, in which case, the products are the result of *endo*-approach in the transition state. Such a dipole is generated via conrotatory ring-opening of *cis*-aziridine-**2a**, while it is possible that *trans*-aziridines-**2b**–**d**, give initially a *cis*-ylide, which isomerised to the *trans*-ylide. Another possible route could involve the generation of a *cis*-dipole from **2b**–**d**, in the more likely *W*-conformation,[12] that would give the products **3b**–**d** via an *endo*-approach and subsequent epimerisation at C-3. At this point the first explanation seems more plausible, when considering the long reaction times needed to generate adducts and also that the *trans*-ylide is known to react faster than its cis-isomer which has more steric compression.[12,13] Lower yields of products **3c** and **3d** (R = cyclohexyl) suggest also that steric effects might be involved in the reactivity of the dipole. Considering the potential regio- and stereoselectivity, it would be worth investigating further the effect of substituents and different reaction conditions also to achieve better yields in these reactions.

Next we decided to use the iminium ion-induced decarboxylative generation of non-stabilised azomethine ylides, using the method often employed by Grigg and co-workers.[14] The dipole is generated from sarcosine and benzaldehyde, followed by in situ cycloaddition to the dipolarophile, and, using this method, three cycloadducts **4a**, **5a** and **6a** were isolated in 38%, 26% and 19% yields, respectively (Scheme 2) from the dipolarophile **1**.[15]

We were able to obtain a single crystal X-ray structure for **5a** (Fig. 1) to determine unequivocally its relative stereo- and regiochemistry (as shown in Scheme 2). Through de-coupling experiments we assigned the signals and coupling constants for protons 1-H, 3-H, 3a-H and 8b-H for all the cycloadducts. The ^{1}H–^{13}C correlation spectrum for **5a** also showed that the ^{13}C signal for C-1 was at δ 76.32, C-3a was at δ 61.69, C-3 at δ 54.83 and the signal for C-8b at δ 54.28. Similarly, the ^{1}H–^{13}C COSY for **4a** showed the corresponding peaks at δ 75.18, 61.09, 56.40 and 50.44, suggesting that **4a** is the C-1 epimer of **5a**. These compounds also showed very similar TLC R_f values compared to that for **6a**. The ^{1}H–^{13}C COSY of **6a** showed that the most down-

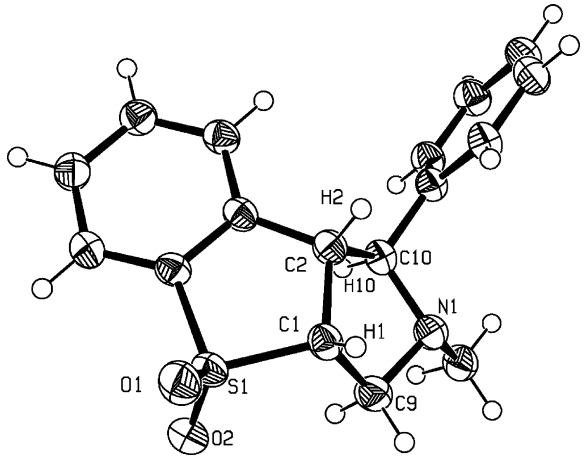
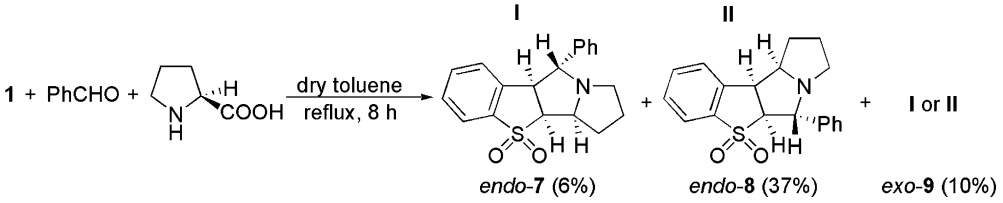


Figure 1. X-ray crystal structure (ORTEP) of **5a**.[15]

Table 1.

Entry	Aldehyde Ar–CHO	Reaction time (h)	Yield[a,b] (%) **4**–**6**	Regioselectivity **I**:**II** (**4** + **5**:**6**)	Stereoselectivity *endo*:*exo* (**5** + **6**:**4**)	Overall yield (%)
a	C_6H_5–	8	38, 26, 19	3.4:1	1.2:1	83
b	4-$NO_2C_6H_4$–	6	44, 16, —	1:0	1:2.8	60[c]
c	4-$MeOC_6H_4$–	6	36, 32, 31	2.2:1	1.8:1	99
d	3,5-$(MeO)_2C_6H_3$–	8	45, 32, 21	3.7:1	1.2:1	98
e	4-BrC_6H_4–	8	41, 27, 17	4:1	1.1:1	85[d]

[a] Isolated and unoptimised yields after silica gel chromatography.
[b] Each isomer was isolated as a racemic mixture.
[c] Also recovered 34% of the starting material **1**.
[d] Also recovered 10% of the starting material **1**.



Scheme 3. 1,3-Dipolar cycloaddition reactions of **1** and azomethine ylides generated from L-proline and benzaldehyde.

field aliphatic signal at δ 71.42, corresponding to C-3a, was coupled to both 8b-H (C-8b at δ 43.87) and to 3-H (C-3 at δ 70.79) and that the latter carbon also bears the phenyl substituent. This indicates that the cycloadduct **6a** is the opposite regioisomer (**II**). The ^{1}H and ^{13}C NMR spectra for **6a** showed signals for the phenyl and *N*-methyl groups to be similar to those in **5a** suggesting a similar stereochemical environment. Thus the phenyl group in **6a** is disposed in an *anti*-relationship to the neighbouring C–S bond. According to Grigg and co-workers, an *anti*-dipole azomethine ylide is generated from sarcosine and benzaldehyde.[14] If that is the case, cycloadducts **5a** and **6a** would result from an *endo*-approach of the dipole, whilst **4a** would be the result of *exo*-cycloaddition. Interestingly, there was no trace of the fourth possible cycloadduct, that is, the *exo*-regioisomer of **II**.

It has already been noted that the main disadvantage of this type of reaction is its low regio- and stereoselectivity.[14,16] Regioisomer **I** seems to be preferred to **II** even though there is very little stereoselectivity (*endo*:*exo* $\sim$ 1:1). Nevertheless, the reaction has synthetic value as the dipole adds in high overall yield. We were therefore interested in possible substituent effects on the reactivity and selectivity of the dipole additions and the results of this study are reported in Table 1. The structures of cycloadducts **4**–**6** from the reactions of **1** with sarcosine and arylaldehydes **b**–**e** (Scheme 2) could be assigned since all ^{1}H NMR data matched those of **4a**, **5a** and **6a**. Again, no traces of the fourth possible cycloadduct in any of the reactions could be found. Also, in the reaction with *p*-nitrobenzaldehyde (entry **b**) the minor isomer (*endo*-**6b**) was not isolated. The same reaction, thus, gave only regioisomer **I**, with the *exo*-stereoisomer being slightly favoured, but the dipole also showed lower reactivity. The highest yields were achieved with the methoxy substituted dipoles (entries **c** and **d**), but with the *endo*-stereoisomer being (slightly) preferred.

When we used L-proline in place of sarcosine to generate the dipole, addition with **1** again gave three products, but in somewhat lower yields (Scheme 3). Comparing their ^{1}H NMR data with those for **4**, **5** and **6**, structures for *endo*-**7** (regioisomer **I**) and *endo*-**8** (**II**) could be proposed, while protons for the opposite stereoisomer *exo*-**9** overlapped and could not be assigned with certainty to regioisomer **I** or **II**. Nonetheless, regioisomer **II** seems to be preferred in this case, with somewhat higher *endo*-selectivity (4:1).

In summary, benzo[*b*]thiophene 1,1-dioxide reacts via 1,3-dipolar cycloadditions with both non-stabilised and stabilised azomethine ylides. Non-stabilised azomethine ylides generated from sarcosine and aldehydes, give higher yields, but with low regio- and stereoselectivity, whilst dipoles generated from aziridines gave only one cycloadduct but in much lower yields.

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10. Data for a typical cycloadduct, **3a**: yellow solid (22%); mp 185 °C; IR (KBr, cm^{-1}): *v* 3051, 1731, 1685, 1447, 1230, 1019; ^{1}H NMR[‡] (400 MHz, $CDCl_3$): δ 8.17–8.14 (m, 2H), 7.70–7.56 (m, 4H), 7.34–7.30 (m, 1H), 7.18–7.03 (m, 4H), 6.95–6.90 (m, 2H), 6.15 (d, $J = 7.8$ Hz, 1H), 5.71 (br s, 1H, 3-H), 4.90 (d, $J = 8.5$ Hz, 1H, 1-H), 4.55 (dd, $J = 8.7$, 8.5 Hz, 1H, 8b-H), 4.04 (dd, $J = 8.7$, 1.0 Hz, 1H, 3a-H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ in the aromatic region (135–120) overlapping signals, 195.03 (C=O), 70.62, 64.90, 50.19, 35.27, 29.76; MS (EI) *m*/*z* (%): M^+ not observed, 298 (76, M^+-PhCO), 217 (9), 178 (10), 105 (49), 91 (28), 77 (100). Anal. Calcd for $C_{24}H_{21}NO_3S$: C, 71.4; H, 5.3; N, 3.5. Found: C, 71.8; H, 5.2; N, 3.5. [‡]The coupling constants were calculated and assigned to protons 1-H, 3-H, 3a-H and 8b-H from decoupling experiments.
11. MM2 is available as a part of *CS Chem3D® Ultra* version 8.0.3, Cambridge Soft Corporations, Cambridge, © 1985–2003. MM2 parameters were provided by N. L. Allinger (MM2 parameters), J. W. Ponder (TINKER parameters) and Cambridge Scientific Computing.
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15. Data for a typical cycloadduct, **4a**: white solid (38%); mp 137 °C; IR (KBr, cm^{-1}): *v* 3064, 2983, 2952, 2774, 1732, 1696, 1598, 1470, 1450, 1373, 1346, 1302, 1253, 1217, 1183, 1150, 1122, 1048, 1016; ^{1}H NMR[§] (400 MHz, $CDCl_3$): δ 7.66 (d, $J = 7.8$ Hz, 1H), 7.32–7.16 (m, 4H), 7.04–6.93 (m, 3H), 5.91 (dd, $J = 7.8$, 0.6 Hz, 1H), 4.27 (dd, $J = 8.2$, 7.9 Hz, 1H, 8b-H), 3.99–3.90 (m, 2H, 3a-H, 3-H$_\beta$), 3.63 (d, $J = 7.9$ Hz, 1H, 1-H), 2.73 (dd, $J = 10.9$, 7.3 Hz, 1H, 3-H$_\alpha$), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.06, 136.44, 135.48, 131.83, 129.19, 128.94, 128.87, 128.23, 128.20, 120.81, 75.18, 61.09, 56.40, 50.44, 39.84; MS (EI) *m*/*z* (%): 299 (3, M^+), 281 (24), 235 (91), 158 (38), 115 (100), 91 (51). Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.2; H, 5.7; N, 4.7; S, 10.7. Found: C, 68.2; H, 5.6; N, 5.0; S, 10.7. Compound **5a**: white solid (26%); mp 148 °C; IR (KBr, cm^{-1}): *v* 2958, 2845, 2814, 2787, 2361, 2342, 1636, 1598, 1475, 1454, 1346, 1301, 1266, 1245, 1198, 1178, 1150, 1127, 1067, 1003; ^{1}H NMR[§] (400 MHz, $CDCl_3$): δ 7.75 (dd, $J = 7.6$, 1.4 Hz, 1H), 7.50–7.34 (m, 7H), 6.79 (dd, $J = 7.6$, 1.1 Hz, 1H), 4.25–4.18 (m, 1H, 3a-H), 4.06 (dd, $J = 9.2$, 9.0 Hz, 1H, 8b-H), 3.78 (dd, $J = 10.6$, 8.6 Hz, 1H, 3-H$_\alpha$), 3.16–3.11 (m, 2H, 1-H, 3-H$_\beta$), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.97, 138.61, 136.68, 133.55, 129.73, 129.05, 128.61, 128.29, 126.66, 122.04, 76.32, 61.69, 54.83, 54.28, 39.36; MS (EI) *m*/*z* (%): 299 (4, M^+), 235 (97), 158 (44), 118 (83), 115 (100), 91 (49). Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.2; H, 5.7; N, 4.7; S, 10.7. Found: C, 67.9; H, 5.8; N, 4.5; S, 10.7. Compound **6a**: white solid (19%); mp 83 °C; ^{1}H NMR[§] (400 MHz, $CDCl_3$): δ 7.71 (d, $J = 7.7$ Hz, 1H), 7.61–7.57 (m, 1H), 7.50–7.47 (m, 3H), 7.39–7.25 (m, 4H), 4.39–4.30 (m, 1H, 8b-H), 3.93–3.90 (m, 2H, 3a-H, 3-H), 3.75 (dd, $J = 9.0$, 8.4 Hz, 1H, 1-H$_\beta$), 2.43 (t, $J = 9.0$ Hz, 1H, 1-H$_\alpha$), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.04, 139.01, 138.10, 134.08, 129.64, 129.02, 128.34, 127.98, 126.83, 122.05, 71.42, 70.79, 62.30, 43.87, 39.55; MS (EI) *m*/*z* (%): 299 (1, M^+), 264 (100), 234 (56), 191 (41), 158 (44), 115 (41). Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.2; H, 5.7; N, 4.7. Found: C, 68.2; H, 6.0; N, 4.7. [§]The coupling constants were calculated and assigned to protons 1-H, 3-H, 3a-H and 8b-H from decoupling experiments and the ^{1}H-^{13}C COSY spectra. Crystallographic data (excluding structure factors) for compound **5a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 606048. These data can be obtained free of charge via www.ccdc.cam.ac.uk/.
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