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An efficient multicomponent protocol for the stereoselective synthesis of oxazinobenzothiazole derivatives

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Abstract—An easy and efficient protocol for the stereoselective one-pot synthesis of oxazinobenzothiazole derivatives is described.

The reaction of nucleophilic species with acetylenic esters leading to the formation of zwitterions has been known for a long time.[1] These reactive intermediates, however, have only recently received attention from the vantage point of their use in carbon–carbon and carbon–heteroatom bond forming reactions. Extensive work in this area has shown that trapping the zwitterions derived from dimethyl acetylenedicarboxylate (DMAD) and various nucleophiles offers a simple and efficient protocol for the construction of heterocycles.[2] Our recent work in this area has been mainly concerned with the chemistry of zwitterions derived from DMAD and nitrogen heterocycles such as pyridine[3] and isoquinoline.[4] Zwitterions derived from DMAD and nucleophiles with more than one heteroatom have received only scant attention.[5] In view of this, we have undertaken investigations involving the DMAD–benzothiazole zwitterion.

In 1964, Reid et al. reported the reaction of benzothiazole and DMAD in methanol leading to the formation of trimethyl pyrrole[2,1-*b*]benzothiazole-1,2,3-tricarboxylate.[6] Later Acheson and co-workers carried out the reaction in the absence of solvent and observed the formation of 1:2 adduct.[7,8] Ogura et al. have shown that the reaction carried out in methanol at room temperature afforded the 1:2 adduct and also *trans*-dimethyl-4-formyl-2,3-dihydrobenzothiazine-2,3-dicarboxylate.[9] Presumably, all these reactions occur via the intermediacy of zwitterion **1** (Fig. 1). Herein, we report the preliminary investigations of our studies on the trapping of benzothiazole–DMAD zwitterion **1** with aldehydes leading to the one-pot synthesis of oxazinobenzothiazole derivatives.

In a prototype experiment, 4-bromobenzaldehyde **4a** was treated with DMAD **3** and benzothiazole **2** in dry toluene in a sealed tube at 120 °C for 24 h. Removal of the solvent under vacuum followed by column chromatography of the residue on silica gel using hexane–ethyl acetate solvent mixtures afforded product **5a** in 63% yield (Scheme 1).[10]

The structure of **5a** was established by spectroscopic methods. A peak at 1742 cm^{-1} corresponding to the ester carbonyl absorption was observed in the IR spectrum. The ester methyl groups were discernible as two sharp singlets at δ 3.63 and δ 3.71 in the ^1H NMR spectrum. The signal due to the hydrogen on the carbon

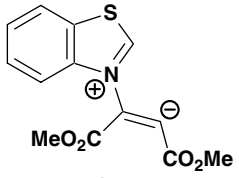

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Figure 1. Benzothiazole–DMAD zwitterion.

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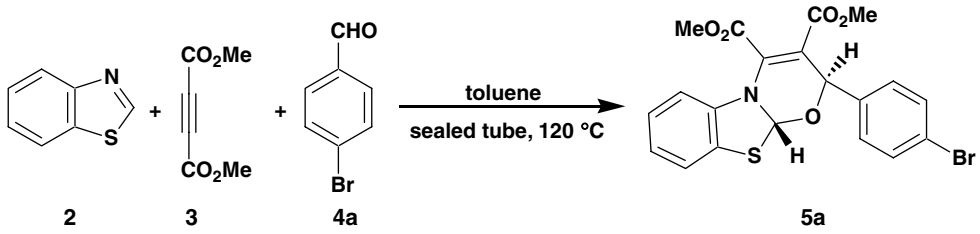


Scheme 1.

linked to the three heteroatoms was observed at δ 5.81. In the ^{13}C NMR, the ester carbonyl signals were visible at δ 162.0 and δ 164.5. The compound gave satisfactory mass spectral data also. Final confirmation of the structure and stereochemistry of the product was obtained from single crystal X-ray analysis (Fig. 2).[11]

Similar results were obtained with various aldehydes showing the generality of the reaction. The results obtained are presented in Table 1.

A tentative mechanistic postulate for the reaction is outlined in Scheme 2. It is conceivable that the reaction in-

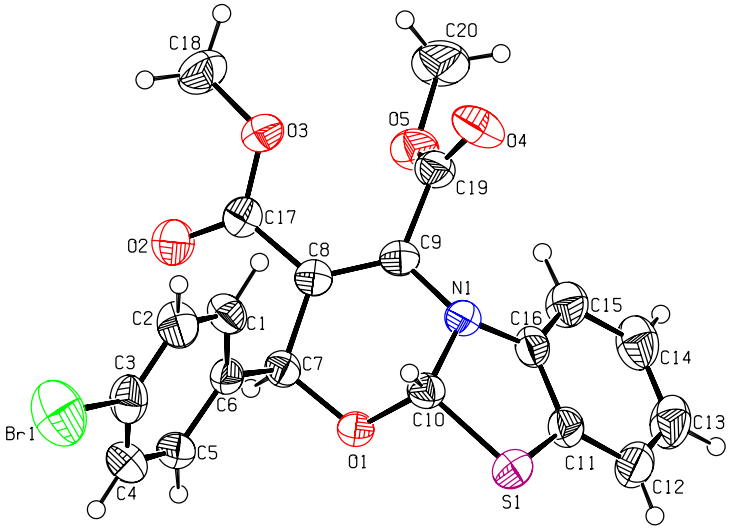
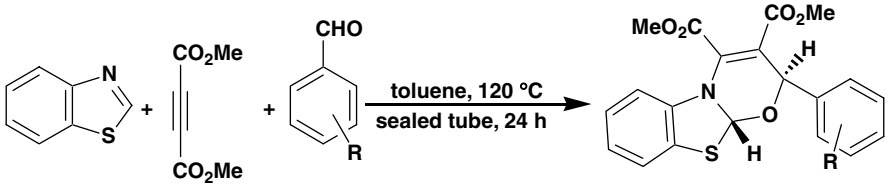
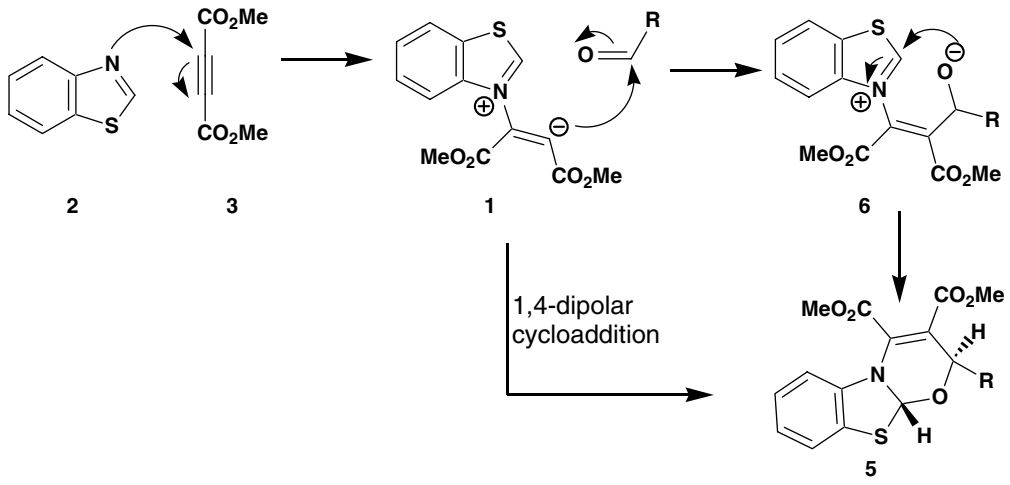


Figure 2. ORTEP diagram for compound **5a**.

Table 1. Reaction of aldehydes with the benzothiazole–DMAD zwitterion



Entry	R-		Product	Yield (%)
1	4-Trifluoromethyl	**4b**	**5b**	69
2	4-Chloro	**4c**	**5c**	58
3	3-Chloro	**4d**	**5d**	55
4	3-Nitro	**4e**	**5e**	56
5	2-Nitro	**4f**	**5f**	59
6	4-Methyl	**4g**	**5g**	44
7	4-Methoxy	**4h**	**5h**	54
8	3,4-Dichloro	**4i**	**5i**	63
9	Hydrogen	**4j**	**5j**	56
10	4-Fluoro	**4k**	**5k**	60
11	Diphenylacetaldehyde	**4l**	**5l**	31



Scheme 2.

volves the initial formation of a 1:1 zwitterionic intermediate **1** between benzothiazole **2** and DMAD **3**, which adds to the aldehyde carbonyl leading to dipolar species **6**. Cyclization of the latter would deliver product **5**. Alternatively, a concerted 1,4-dipolar cycloaddition of the zwitterion to the aldehyde carbonyl may also be invoked to account for the formation of **5**. The stereoselectivity of the reaction is also noteworthy.

In conclusion, a one-pot synthesis of oxazinobenzothiazole derivatives has been achieved by reaction of the benzothiazole–DMAD zwitterion, generated in situ, with aldehydes.

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10. Representative experimental procedure and spectroscopic data for **5a**: 4-Bromobenzaldehyde **4a** (100 mg, 0.5405 mmol), benzothiazole **2** (73 mg, 0.5405 mmol) and DMAD **3** (92 mg, 0.6486 mmol) were taken in dry toluene (2 mL) in a Schlenk tube. The tube was evacuated, sealed and then heated at 120 °C for 24 h. The reaction mixture was cooled and the solvent was removed in vacuo on a rotavapor. The residue, on purification by column chromatography on a silica gel (100–200 mesh) column using 15% ethyl acetate–hexane solvent mixture, afforded the product **5a** (158 mg, 63%) which was recrystallized from dichloromethane–hexane (1:1) mixture. White crystalline solid. Mp 166–168 °C. IR (KBr) ν_{max}: 1742, 1707, 1616, 1581, 1470, 1437, 1304, 1223, 1198, 995 cm^{-1}. ^1H NMR: δ 7.53–7.50 (m, 2H), 7.25–7.22 (m, 2H), 7.18–7.15 (m, 1H), 7.06–6.92 (m, 3H), 6.13 (s, 1H), 5.81 (s, 1H), 3.71 (s, 3H), 3.63 (s, 3H). ^{13}C NMR: δ 164.5, 162.0, 149.1, 138.7, 138.5, 131.1, 129.8, 129.7, 123.6, 122.3, 122.1, 121.2, 117.9, 111.4, 104.5, 73.9, 53.4, 50.8. HRMS (EI) for $C_{20}H_{16}BrNSO_5$ Calcd 462.3148; found: 462.3193.
11. CCDC file No. 635830 contains the supplementary crystallographic data for compound **5a**.