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A FACILE SYNTHESIS OF THIAAZA- AND THIADIAZA-FLUORENE DERIVATIVES INVOLVING BENZOTHIAZOLE-DMAD ZWITTERION WITH ARYLIDENEMALONONITRILES AND *N*-TOSYLIMINES

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Dedicated to the memory of Professor Ivar Ugi, the great pioneer of isocyanide chemistry.

Abstract – An efficient protocol for the one-pot synthesis of thiaazafluorene and thiadiazafluorene derivatives are described.

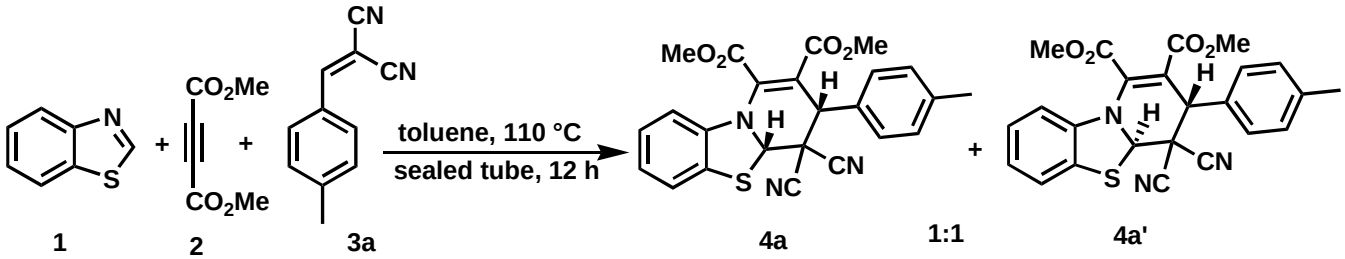
INTRODUCTION

Contemporaneous to his original contributions which led to the development of 1,3-dipolar cycloadditions as the principal protocol for the synthesis of five membered heterocycles,[1] Huisgen also laid the foundation for the related 1,4-dipolar cycloadditions.[2] Inexplicably, the latter, however, did not attract much attention *vis a vis* the 1,3-dipolar cycloadditions. In view of our long-standing interest in the construction of heterocyclic systems utilizing dipolar intermediates,[3] we have investigated the reaction of zwitterionic species derived from DMAD and nucleophilic heterocycles such as pyridine[4] and isoquinoline[5] with a variety of dipolarophiles, *viz*., aldehydes, tosylimines, quinones and electrophilic styrenes. Practically all the zwitterionic intermediates investigated so far were generated by the addition of the nucleophiles having a single heteroatom. Hence it was of interest to undertake an investigation on the reactivity of the zwitterions formed by the addition of nucleophiles with multiple heteroatoms in the ring. In this context, recent studies in our laboratory have shown that, the zwitterion generated by the addition of benzothiazole **1** to DMAD **2**, undergoes a facile reaction with electrophiles like aldehydes to afford oxazinobenzothiazole derivatives in good yields, thereby constituting a novel multicomponent

reaction.[6] Naturally, it was of interest to further explore the reactivity of this zwitterion towards other dipolarophiles. Herein we report the results of our studies on the reaction of the benzothiazole-DMAD zwitterion with arylidenemalononitriles and *N*-tosylimines.

RESULTS AND DISCUSSION

Our investigations were initiated by treating arylidenemalononitrile **3a** with DMAD and benzothiazole **1** in anhydrous toluene in a sealed tube at 110 °C for 12 h. Removal of the solvent under vacuum followed by chromatographic separation of the reaction mixture afforded the diastereomeric mixtures of thiaazafluorene derivative **4a** and **4a′** as a yellow solid in 81% yield (Scheme 1).



Scheme 1

The structure of the product was elucidated by spectroscopic techniques. In the IR spectrum, absorption at 2254 cm^{-1} can be attributed to the cyano group and a sharp band at 1745 and 1710 cm^{-1} was assigned to the ester carbonyl group. The ^1H NMR spectrum displayed two methoxy groups as singlets at δ 4.03 and 3.83, the benzylic proton was seen as a singlet at δ 4.50 and the ring junction proton resonated at δ 5.69 as a singlet. In the ^{13}C NMR spectrum, the two cyano groups resonated at δ 111.5 and 111.9. The two ester carbonyls were seen at δ 164.2 and 163.6. All other signals were also in good agreement with the assigned structure. The compound gave satisfactory HRMS analysis also.

The diastereoisomers were separated using HPLC and the stereochemistry of one diastereomers **4a** was established by ^1H nOe difference spectroscopic studies (Figure 1). It was assigned *cis* stereochemistry since selective irradiation of H_a produced enhancements (9%) in the signals corresponding to H_b.

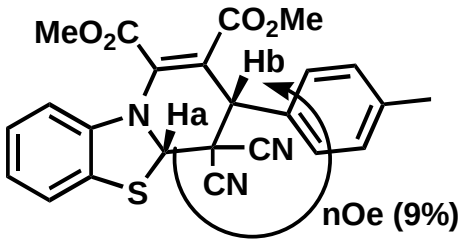
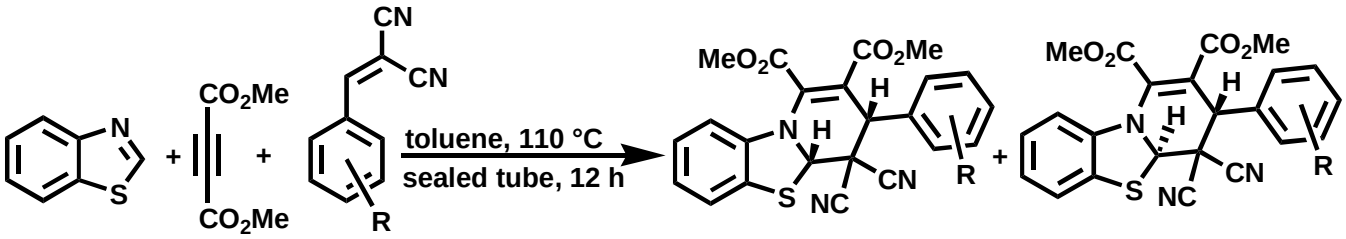


Figure 1. Selected nOe correlations for the diastereoisomer 4a.

To explore the generality and scope of this process, similar substrates were subjected to the reaction under identical conditions. The results obtained are presented in Table.1.

Table 1. Reaction of benzothiazole and DMAD with arylidenemalononitriles

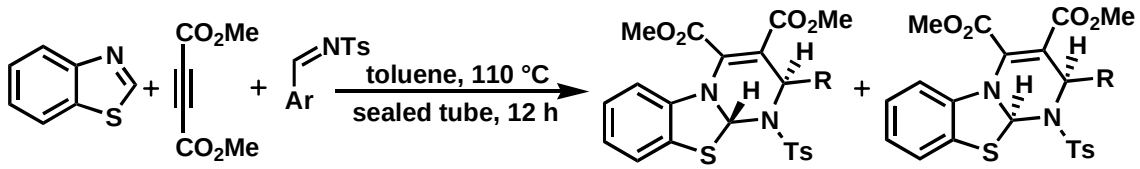


1 2 3b-3g 4b-g 4b'-g'

Entry	Styrene	Product	diastereomeric ratio (cis:trans)	Yield (%)
1	3b = 3-chlorophenyl	4b & b'	6:1	73
2	3c = 3-nitrophenyl	4c & c'	1.8:1	62
3	3d = phenyl	4d &d'	1.2:1	55
4	3e = 4-chlorophenyl	4e & e'	1.7:1	75
5	3f = 4-fluorophenyl	4f & f'	2:1	69
6	3g = 4-methoxyphenyl	4g &g'	1:1	41

In all the cases, the compounds were completely characterized and their structures established by spectroscopic methods.

In view of the success of the above reaction, it was of interest to examine the possibility of intercepting the 1:1 zwitterionic intermediate from benzothiazole and DMAD with *N*-tosylimines. Our preliminary investigations were initiated by the reaction of benzothiazole **1** and DMAD with *N*-tosyl-4-methylbenzaldimine in dry toluene in a sealed tube at 110 °C for 12 h. Removal of the solvent under vacuum followed by column chromatography of the residue on neutral alumina using hexane-ethyl acetate solvent mixtures afforded the product as an inseparable mixture of diastereomers (Scheme 2). The diastereomeric ratio was determined from the ^{1}H NMR spectrum.



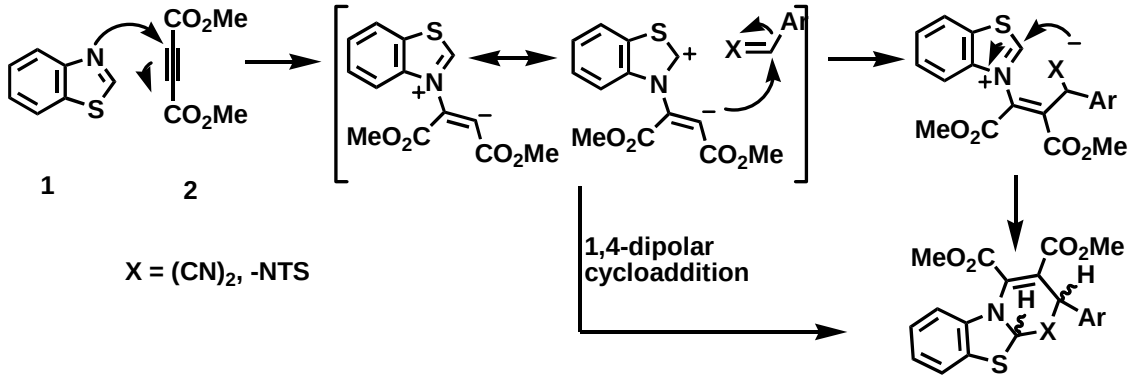
1 2 5a 6a 6a'

5a, Ar = 4-methylphenyl, 6a:6a' - 1:1 (63%)

5b, Ar = phenyl, 6b:6b' - 1:1 (23%)

Scheme 2

The structure of the isomer **6a** was elucidated by spectroscopic techniques. In the IR spectrum, a sharp band at 1735 and 1708 cm^{-1} was assigned to the ester carbonyl group. The ^{1}H NMR spectrum displayed two methoxy groups as singlets at δ 3.77 and 3.62, the benzylic proton was seen as a singlet at δ 5.24 and the ring junction proton resonated at δ 5.96 as a singlet. The methyl protons of p-toluenesulphonyl group displayed as singlet at δ 2.29. In the ^{13}C NMR spectrum, the two ester carbonyls were seen at δ 165.0 and 162.0, while the two methoxy carbons were seen at δ 52.3 and 51.9 respectively. All other signals were also in good agreement with the assigned structure. The compound gave satisfactory HRMS analysis also**.** Mechanistically, the reaction may be considered to involve the initial formation of the 1:1 zwitterionic intermediate between benzothiazole and DMAD, which adds to the electrophilic double bond of the dipolarophiles leading to another dipolar species. Cyclization of the latter leads to the formation of the product. Alternatively, a concerted 1,4-dipolar cycloaddition of the zwitterion to the multiple bond of the dipolarophiles may also be invoked to account for the formation of the product (Scheme 3).



1 2

X = $(CN)_2$, -NTS

Scheme 3

In conclusion, we have observed a novel three component condensation reaction that offers an easy and one-pot entry to the synthesis of various thiaazafluorene derivatives *via* the reaction of the zwitterion generated from benzothiazole and DMAD with activated styrenes. In related work, our preliminary

investigations showed that, the benzothiazole-DMAD zwitterion reacts with *N*-tosylimines leading to the synthesis of thiadiazafluorene derivatives

ACKNOWLEDGEMENTS

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7. General procedure for the synthesis of thiaazafluorene derivatives: Benzothiazole (80 mg, 0.59 mmol), DMAD (101 mg, 0.71 mmol) and dicyanostyrene 3a (100mg, 0.59 mmol) were taken in anhydrous toluene (2 mL) in a sealed tube. It was evacuated, sealed and then heated at 110 °C for 12 h. The reaction mixture was cooled and the solvent was removed in vacuo on a rotary evaporator. The residue on purification by column chromatography using neutral alumina and 15% EtOAc-hexane mixture as the eluent, afforded the diastereomeric mixture of the product as a yellow solid in 81% yield. IR υ_{max}: 3015, 2254, 1745, 1710, 1591, 1566, 1492, 1279, 1137, 1056, 987 cm^{-1}. ^1H NMR [300 MHz, $CDCl_3/CCl_4$, 7:3 (v/v)]: δ 7.47-7.55 (m, 2H), 7.20-7.27 (m, 2H), 7.01-7.12 (m,

4H), 5.69 (s, 1H), 4.50 (s, 1H), 4.03 (s, 3H), 3.83 (s, 3H), 2.29 (s, 3H),. ^{13}C NMR (75 MHz) : δ164.2, 163.6, 135.2, 134.3, 130.0, 129.6, 129.3, 128.5, 127.9, 127.6, 127.5, 124.9, 122.8, 111.9, 111.5, 105.7, 105.3, 52.3, 51.9. HRMS (EI) Calcd for $C_{24}H_{19}N_3O_4S$: 445.4915. Found: 445. 4867.

8. General procedure for the synthesis of thiadiaza-fluorene derivatives: Benzothiazole (50 mg, 0.37 mmol), DMAD (53 mg, 0.37 mmol) and *N*-tosyl-4-methylbenzaldimine 5a (121 mg, 0.44 mmol) were taken in anhydrous toluene (2 mL) in a sealed tube. It was evacuated, sealed and then heated at 110 °C for 12 h. The reaction mixture was cooled and the solvent was removed in a rotary evaporator under reduced pressure. The residue on purification by column chromatography using neutral alumina and 15% EtOAc-hexane mixture as eluent afforded the product as an inseparable mixture of diastereomers as a yellow solid in 63% yield. Spectroscopic data for one diastereomer based on comparison of ^{1}H NMR with that in the case of dicyanostyrenes is provided. IR υ_{max}: 3352, 2051, 1735, 1708, 1435, 1315, 1288, 1269, 1226, 1159, 1093, 812 cm^{-1}. ^{1}H NMR [300 MHz, $CDCl_3/CCl_4$, 7:3 (v/v)]: δ 7.72 (d, *J* = 9.0 Hz, 1H), 7.47 (d, *J* = 9.0 Hz, 1H), 7.32-7.25 (m, 3H), 7.19 (d, *J* = 9.0 Hz, 1H), 7.09-7.00 (m, 2H), 6.95-6.93 (m, 2H), 6.87-6.79 (m, 2H), 5.96 (s, 1H), 5.24 (s, 1H), 3.77 (s, 3H), 3.62 (s, 3H), 2.36 (s, 3H), 2.29 (s, 3H). ^{13}C NMR(75 MHz) : δ 165.0, 162.0, 130.2, 129.6, 129.3, 128.5, 127.9, 127.6, 127.5, 124.9, 122.0, 110.0, 105.7, 105.3, 52.3, 51.9, 21.5, 21.2. LRMS (FAB) for $C_{28}H_{26}S_2N_2O_6$: Calculated, 550.65; Found, 550.88.