Serendipitous synthesis of 1,4-benzothiazin derivatives using 2-[(2-aminophenyl)disulfanyl]aniline

Mohammad Reza Islami[a]*, Fouziyeh Mollazehi[a], Alireza Badiei[b], and Hassan Sheibani[a]

[a] *Department of Chemistry, Shahid Bahonar University of Kerman, Kerman 76619, Iran*
[b] *Department of Chemistry, Faculty of Science, University of Tehran, Tehran, Iran*
E-mail: mrislami@mail.uk.ac.ir

(received 14 Jul 05; accepted 10 Aug 05; published on the web 17 Aug 05)

Abstract

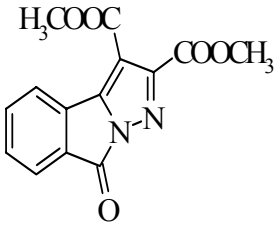
Alkyl-2-(3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yliden)acetates have been synthesized by the condensation of 2-[(2-aminophenyl)disulfanyl]aniline with dialkyl acetylenedicarboxylates in boiling dioxane as solvent in excellent yields.

Keywords: Dialkyl acetylenedicarboxylate, benzothiazin derivatives, disulfides

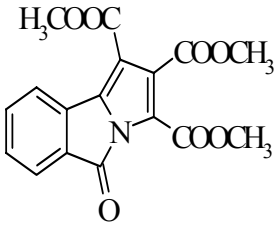
Introduction

We have recently reported a one-pot procedure for the synthesis of heterocyclic compounds such as functionalized pyrazoloisoindole **1** and pyrroloisoindole **2** derivatives from the reaction of electron-deficient acetylenic compounds, N-aminophthalimide or N-hydroxyphthalimide and triphenylphosphine using an intramolecular Wittig reaction.[1,2] With the aim of preparing alkyl (7-oxo-7,8-dihydro-5H-5,8-diaza-13,14-dithiadibezo[a,f]cyclodecen-6-ylidene)acetates **3**, 2-[(2-aminophenyl)disulfanyl]aniline was treated with dialkyl acetylenedicarboxylates in boiling dioxane as solvent in the absence of triphenylphosphine. However, compound **3** was not observed but 1,4-benzothiazin derivatives **4** were isolated from the reaction mixture. The initial synthesis of 1,4-benzothiazin derivatives **4a-b** was done using 2-aminothiophenol, which was condensed with activated acetylenic esters. [3,4] In spite of extensive work in this field, there are no characterization data such as mp and FT-IR, ^{1}H NMR and ^{13}C NMR spectral data for compound **4c** in the literature.[3] Additionally, to the best of our knowledge, the preparation of compounds **4a-c** has not been reported in the literature using 2-[(2-amino phenyl)disulfanyl]aniline **5** as starting material. Further, thiols such as 2-aminothiophenol are easily oxidized to the corresponding disulfides by hydrogen peroxide or oxygen in the air.[5,6] Thus, to regenerate these compounds it is necessary to reduce the disulfides to the thiols by mild reducing agents such as zinc and dilute acid or triphenylphosphine and water.[7,8] Also, aryldisulfides can be added to double bonds by anodic oxidation or copper(II) acetate as oxidation reagent.[9,10] Previously, we

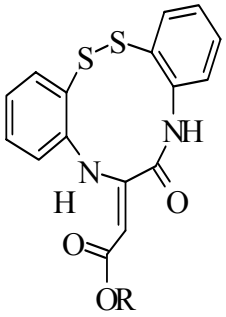
used the disulfide of 2-aminothiophenol as a starting material without using any reducing agent or any oxidising reagent. For these reasons, here, we report a second route to the synthesis of these compounds, which begins with the condensation of 2-[(2-aminophenyl)disulfanyl]aniline **5** and dialkyl acetylenedicarboxylates **6** in boiling dioxane, in excellent yields.



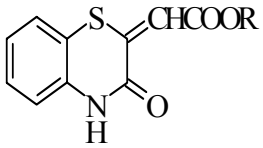
1



2



3

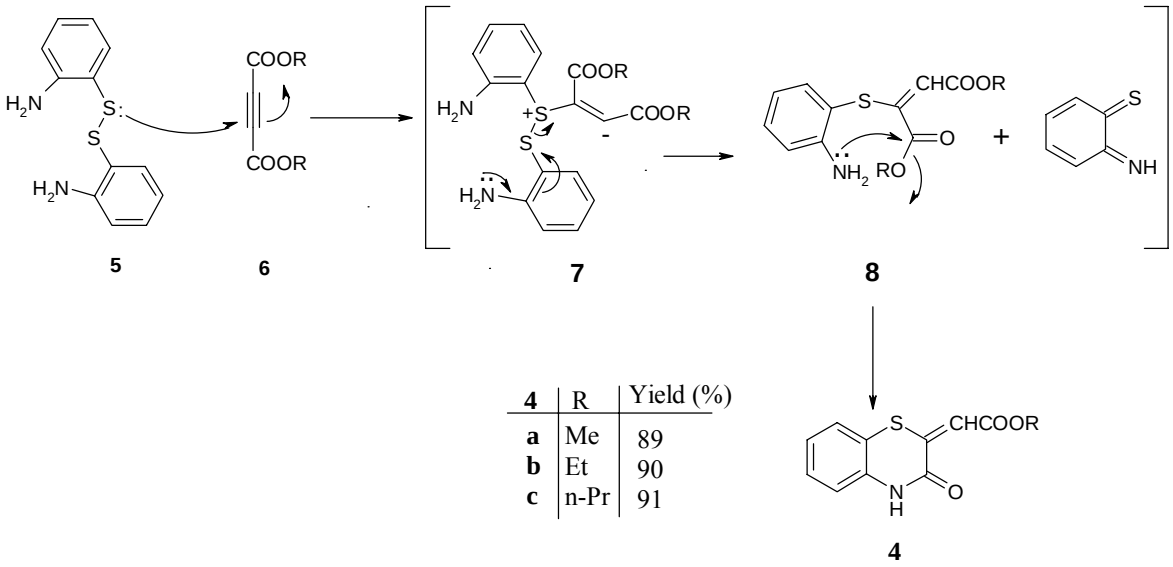


4

Results and Discussion

The structures of compounds **4a-c** were deduced from their IR, ^{1}H NMR and ^{13}C NMR spectra. In the ^{1}H NMR spectrum of **4a,** the signal due to the methoxy group was observed at δ 3.65 ppm as a singlet and the NH proton resonated as a fairly broad signal at δ 11.47 ppm (exchangeable by D_2O). The vinyl CH proton appeared at δ 6.03 ppm as a singlet. The aromatic protons appeared as a multiplet at δ 7.00-7.33 ppm. The ^{13}C NMR spectrum of compound **4a** showed eleven distinct resonances in agreement with the 1,4-benzothiazine structure. The two carbonyl groups along with the methoxy group were observed at δ 165.83, 154.11 and 51.67 ppm, respectively. Other signals due to aromatic rings and the vinyl moiety appeared as characteristic resonance lines with the corresponding chemical shifts (see experimental section). The ^{1}H NMR and ^{13}C NMR spectra of heterocyclic compounds **4b-c** are similar to those of **4a**, except for signals from the ester group which appear as characteristic resonance lines with the corresponding chemical shifts.

The structural assignments made for compounds **4a-c** on the basis of the ^{1}H and ^{13}C NMR spectra were supported by their IR spectra. The carbonyl region of the spectra exhibits one distinct IR absorption band for each compound.



4	R	Yield (%)
a	Me	89
b	Et	90
c	n-Pr	91

4

Although we have not established a mechanism for the formation of compounds **4a-c** in an experimental manner, a reasonable possibility is indicated in Scheme 1. In this mechanism it is assumed that an initial Michael addition of compound **5** to the acetylenic esters leads to intermediate **7**. This 1,3-dipolar intermediate is thermally unstable and rapidly converts to intermediate **8**. The formation of alkyl-2(3-oxo-3,4-dihydro-2H-1,4-benzothiazin-2-yliden)acetates from intermediate **8** in the final step of this mechanism can be considered as a product of a lactamization reaction This process shows that in the first step the sulfur atom acts as a stronger nucleophile than the NH_2 group. The difference in nucleophilic behavior between a nitrogen atom and a sulfur atom has been reported in the literature.[11-13] In this reaction the lower reactivity of the amino group in comparison to the S-S group can be elucidated on the basis of the alpha effect[14,15] on the S-S group. This effect might play an important role in this reaction and causes the sulfur atom to act as an excellent nucleophile. Thus, we found that the preparation of 1,4-benzothiazin derivatives can be successfully carried out as a one-pot process starting with condensation of 2[(2-aminophenyl)disulfanyl]aniline[6] **5** and acetylenic esters **6** in a boiling organic solvent such as dioxane.[16]

Experimental Section

General Procedures. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. NMR spectra were recorded at 500 (^{1}H) and 125.77 (^{13}C) MHz on BRUKER DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively. Chemical shifts are reported (δ) relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. IR spectra were measured on a Mattson 1000 FT-IR spectrophotometer. Dialkyl acetylenedicarboxylate, 2-aminothiophenol, hydrogen peroxide were purchased from Merck Chemical Co. and were used

without further purification. 2-[(2-aminophenyl)disulfanyl]aniline **5** were prepared according to the reported procedure in the literature[6].

Methyl-2-(3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yliden)acetate(4a). At ambient temperature dimethyl acetylenedicarboxylate (0.24 mL, 2 mmol) was added dropwise to a stirred solution of 2-[(2-aminophenyl)disulfanyl]aniline (0.50 g, 2 mmol) in dioxane (10 mL). After the addition was complete (approximately 10 min) the mixture was heated under reflux for 4 h. The resulting solid was then filtered off, and crystallized from ethanol. The product was filtered and dried to yield **4a**. The product **4a** was obtained as a yellow powder, m.p 235˚C decomposed, 0.42 g yield 89%. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3196 (NH), 1681 (C=O), 1609 (C=C). ^{1}H NMR: δ 3.65 (3H, s, OCH_3) 6.83(1H, s, vinyl proton), 7.00–7.33 (4H, m, arom), 11.47 (1H, br.s, NH). ^{13}C NMR: δ 51.67 (OCH_3), 113.63 (=CH) 114.96 (C), 117.03, 123.35, 125.14 and 127.15 (4CH), 132.67 and 141.00(2C),154.11 and 165.83 (2C=O).

Ethyl-2-(3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yliden)acetate (4b). Yellow powder, m.p 210˚C decomposed, 0.45 g, yield 90%. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3280 (NH), 1691 (C=O), 1600 (C=C). ^{1}H NMR: δ 1.23 (3H, t, $^3J_{HH}$ 6.3 Hz, CH_3), 4.16(2H, q, $^3J_{HH}$ 6.3 Hz, CH_2) 6.87(1H, s, vinyl proton), 7.04–7.38 (4H, m, arom), 11.49 (1H, br.s, NH). ^{13}C NMR: δ 14.05 (CH_3), 60.34 (OCH_2), 114.01 (=CH) 115.03 (C), 117.01, 123.33, 125.12 and 127.11 (4CH), 132.67 and 140.82 (2C),154.14 and 165.40 (2C=O).

Propyl-2-(3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yliden)acetate (4c). Yellow powder, m.p 185˚C decomposed, 0.48 g yield 91%. IR (KBr) ($\nu_{max,}$ cm^{-1}): 3180 (NH), 1691 (C=O), 1617 (C=C). ^{1}H NMR: δ 0.90 (3H, t, $^3J_{HH}$ 6.0 Hz, CH_3), 1.62 (2H, m, CH_2), 4.08 (2H, t, $^3J_{HH}$ 6.3 Hz, CH_2) 6.89(1H, s, vinyl proton), 7.06–7.38 (4H, m, arom), 11.49 (1H, br.s, NH). ^{13}C NMR: δ 10.11 (CH_3), 21.40 (CH_2), 65.69 (OCH_2), 113.94 (=CH) 114.92 (C), 116.93, 123.26, 125.05 and 127.05 (4CH), 132.59 and 140.72 (2C),154.08 and 165.38 (2C=O).

Acknowledgements

The authors express appreciation to the Shahid Bahonar University of Kerman Faculty Research Committee for its support of this investigation.

References

1. Islami, M. R.; Abedini, J. T.; Fatemi, S. J.; Hassani, Z.; Amiry, A. *Synlett* **2004**, *10*, 1707.
2. Yavari, I.; Islami, M. R. *J. Chem. Res (S)* **1998**, 167.
3. Kalbag, S. M.; Nair, M. D.; Rajagopalan, P.; Talaty, C. N. *Tetrahedron* **1967**, *23*, 1911.
4. Maki, Y.; Suzuki, M. *Chem. Pharm. Bull*. **1972**, *20*, 832.
5. Wallance, T. J.; Schriesheim, A.; Bartok, W. *J. Org. Chem*.**1963**, *28*, 1311.

6. Price, C. C.; Stacy, G. W. *Org. Synth*. **1955**, *3*, 86.
7. Overman, L. E.; Smoot, J.; Overman, J. D. *Synthesis* **1974**, 59.
8. Wardell, J. L. In *The Chemistry of the Thiol group* Pt. 2; Patai Ed.; Wiley: NY, 1974; p 220.
9. Bewick, A.; Coe, D. E.; Mollor, J. M.; Owton, W. M. *J. Chem. Soc., Perkin. 1* **1985**, 1033.
10. Bewick, A.; Mollor, J. M.; Milano, D.; Owton, W. M. *J. Chem. Soc., Perkin. 1* **1985**, 1045.
11. Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc*. **1962**, 84, 16.
12. Wells, P. R. *Chem. Rev*. **1963**, 63, 171.
13. Koskikallio, J. *Acta. Chem. Scand*. **1969**, 23, 1477.
14. Grekov, A. P.; Velselov, V. Y. *Russ. Chem. Rev*. **1978**, 47, 631.
15. Fina, N. J.; Edwards, J. O. *Int. J. Chem. Kint*. **1973**, 5, 1.

