Nucleophilic addition of enaminones to the S-S dimer of 2-aminobenzenethiol

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Abstract
Nucleophilic addition of β-amino α,β-unsaturated ketones and esters to the S-S dimer of 2-aminobenzenethiol which acts as an electrophile, followed by cyclization, lead to 4H-1,4-benzothiazine derivatives.

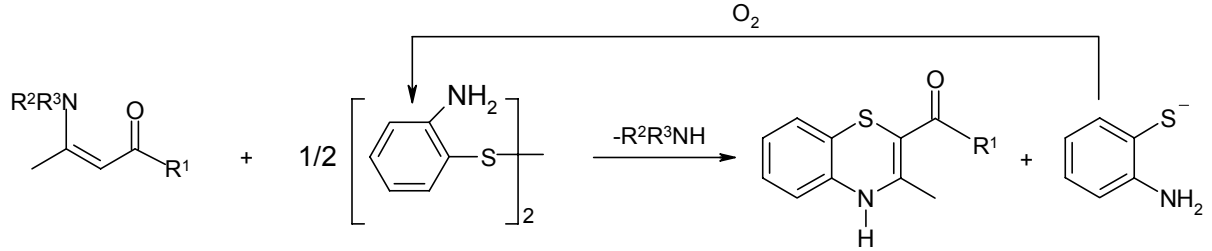
Keywords: Nucleophilic addition, enaminones, 2-aminobenzenethiol, 4*H*-1,4-benzothiazine, disulfides

Introduction

At present the chemistry of enaminones is a developing field of organic synthesis.[1, 2] These compounds are versatile synthetic intermediates that combine the ambident nucleophilicity of enamines with the ambident electrophilicity of enones.[3] There are many reports on functionalization of enaminone in the literature by the introduction of different substituents on the nitrogen, the α-carbon and the β-carbonylic carbon atoms. These derivatives have been extensively used for the preparation of a variety of heterocyclic systems including some natural products and analogues.[4, 5] Recently, β-dimethyl amino-α,β-unsaturated ketones and nitriles have been transformed into pyridine, isoquinoline,[6] pyrazole, isoxazole, pyrimidine[7] and pyranone derivatives.[8] As part of our current studies on the development of new routes to the synthesis of heterocyclic compounds, by using 1,3-bielectrophiles and binucleoplies such as 1,3- dicarbonyl compounds and enaminones,[9-11] we now turn our attention to the reactivity of enaminones by nucleophilic addition of β-amino α,β-unsaturated ketones and esters on the S-S dimer of 2-aminobenzenethiol.

Results and Discussion

Many useful and interesting reactions of disulfides are known.[12,13] Disulfides, especially diaryl disulfides, are very commonly used as electrophiles in the sulfenylation of enolates anions.[14, 15] Sulfenamides and sulfenylimines have been prepared from nucleophilic addition of amines[16] and ketimines[17] to the S-S of disulfide compounds respectively. Enaminones have two electron-deficient centers at C-1 and C-3, while the C-2 and amino functions are electron rich. Thus they can react with both electrophils and nucleophiles. In order to study the reactivity of the enaminones with electrophiles, we have chosen dimer of 2-aminobenzenethiol, which acts as electrophile (sulfur atoms) and nucleophile (amino group) (Scheme 1).



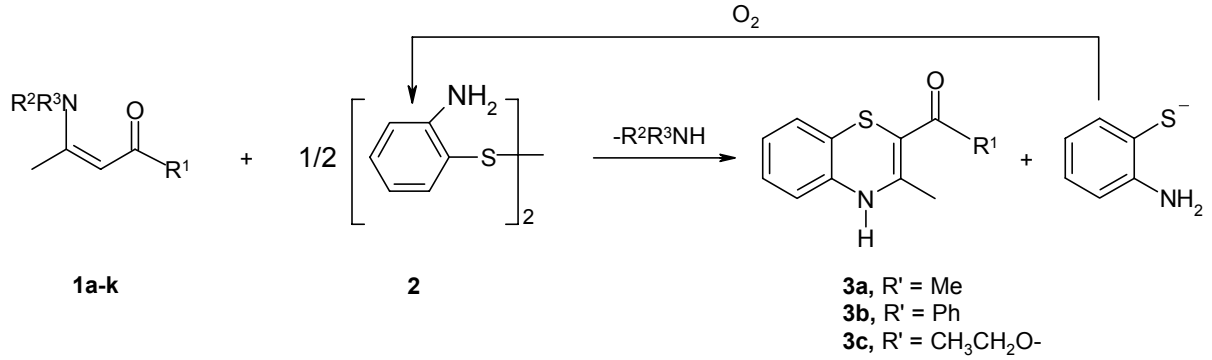
Scheme 1

The reaction of β-amino α,β-unsaturated ketones **1a-g** with compound **2** afforded the 2-acyl-3-methyl-4H-1,4-benzothiazinederivatives **3a, b** in boiling ethanol as solvent in a good to excellent yields. These processes are highly regioselective, and compounds **3a-c** results from the initial attack of the enaminone nucleophilic C atom to the electrophilic S-S dimer of 2-aminobenzenethiol, in keeping with there are reports in the literature which enaminones act as N-nucleophile.[18] Under similar reaction conditions given for β-amino α,β-unsaturated ketones **1a-g,** ethyl-3-methyl-4H-1,4-benzothiazine-2-carboxylate was isolated from the reaction of corresponding β-amino α,β-unsaturated esters **1h-k** with dimer of 2-aminobenzenethiol.

The formation of these compounds was unexpected and it can be considered to proceed by a nucleophilic attack of the C_α of the β-amino α,β-unsaturated esters on the sulfur of dimer of 2-aminobenzenethiol, followed by Michael addition of the 2-amino nitrogen (NH_2) on the C=C double bond.

A possible pathway accounting for the formation of the compounds **3a-c** is depicted in Scheme **2**. On the basis of the well established chemistry of enaminones and diaryl disulfides[1, 19, 20] it is reasonable to assume that compounds **3a-c** result from nucleophilic addition of enaminones on the S-S dimer of 2-aminobenzenethiol which acts as an electrophile, followed by cleavage of disulfide bond to form of an α-(2-amino phenyl sulfonyl)enaminone intermediate

and 2-amino-benzenethionl anion which the thiolate anion is easily oxidized by oxygen (air) to yield the dimer of 2-aminobenzenethionl. Thus only 0.5 equivalents of dimer **2** is needed. Successively, formation of the 2-acyl-3-methyl-4H-1,4-benzothiazines could occur by intermolecular Michael addition of α-(2-amino phenyl sulfonyl)enaminone intermediate, followed by the loss of the aryl or alkyl amino group (Scheme 2).



1a-k **2** **3a,** R' = Me
3b, R' = Ph
3c, R' = CH_3CH_2O-

Scheme 2

1,4-Benzothiazines are usually prepared by the reaction of 2-aminobenzenethiol with α-haloketones or α-haloesters and oxidative cyclocondensation of 2-aminobenzenethiol with 1,3-dicarbonyl compounds[20, 21] 4H-1,4-benzothiazines **3a-c** are known and their melting points and spectral data are in good agreement with those reported in the literature.[22, 23]

It should be stressed that all starting enaminones are readily available.[24, 25] The dimer of 2-aminobenzenethiol is easily obtained in a one pot reaction by oxidizing the alkaline solution of the 2-aminobenzenethionl with hydrogen peroxide.[26]

Although enaminones have three nucleophilic sites of the reaction (nitrogen, C_α and oxygen) and two electrophilic sites (C_β and carbon of carbonyl), the reaction of β-amino α,β-unsaturated ketones and esters on the S-S dimer of 2-aminobenzenethiolo have been produced only one product. These processes are highly regioselective, and the yields of formation of compounds **3a-c** depend on the size of the R^1, R^2 and R^3 (Table **1**).

Table 1. Reaction conditions of enaminones **1a-k** with disulfide **2**

Entry	R^1	R^2	R^3	Solvent	Product	Time (h)	Yield (%)
1a	CH_3-	H	H	Ethanol	3a	12	90
1b	CH_3-	4-MeC_6H_4-	H	Ethanol	3a	20	84
1c	CH_3-	C_6H_5-	H	Toluene	3a	15	75
1d	CH_3-	1-naphtyl	H	Toluene	3a	25	50
1e	CH_3-	- $CH_2CH_2CH_2CH_2$-		Toluene	3a	16	65
1f	C_6H_5-	C_6H_5-	H	Toluene	3b	15	55
1g	C_6H_5-	$(CH_3)_2CHCH_2$-	H	Toluene	3b	12	60
1h	CH_3CH_2O-	C_6H_5-	H	Toluene	3c	15	70
1i	CH_3CH_2O-	$H_2NCH_2CH_2$-	H	Ethanol	3c	12	97
1j	CH_3CH_2O-	$CH_3CH_2CH_2CH_2$-	H	Ethanol	3c	15	91
1K	CH_3CH_2O-	$(CH_3)_2CHCH_2$-	H	Ethanol	3c	15	80

Experimental Section

General Procedures. Melting points were measured on a calibrated Gallenkamp melting point apparatus. IR spectra were measured on a Mattson 1000 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively. Mass spectra were recorded on a MS-QP2000A Shimadzu mass spectrometer operating at an ionization potential of 70 eV.

1-(3-Methyl-4*H*-1,4-benzothiazin-2-yl)-1-ethenone (3a). Typical procedure
A solution of disulfide **2** (0.24 g, 1 mmol) and enaminone **1a** (0.19 g, 2 mmol) in ethanol or toluene (50 ml) was refluxed with stirring for the hours reported in table **1** (the progress of the reaction being monitored by TLC and was used hexane/ethyl acetate as eluent). The colored product **3a** was precipitated from the reaction mixture by cooling, and the solid was filtered and recrystallized from ethanol. The product **3a** was obtained as red crystals, mp 175-176˚C. IR (KBr) (ν_{max}/ cm^{-1}): 3280, 1617, 1592. ^{1}H NMR (500 MHz, DMSO-d_6): 8.85 (1H, s, NH), 6.91-6.63 (4H, m, Ar), 2.22 (3H, s, CH_3), 2.18 (3H, s, CH_3). ^{13}C NMR (DMSO -d_6): 190.68 (C=O), 153.41 (C_3), 139.36 (C), 127.44, 126.36, 124.99 (3CH), 120.49 (C), 115.43 (CH), 98.15(C_2), 30.24, 21.41 (2CH_3). MS *m/z* (relative intensity) 205 (M^+, 90), 162 (100), 130 (55), 118 (40), 109 (35), 77(18), 65 (20), 43 (32). Anal. Calcd. for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82 %. Found : C, 64..39; H. 5.33; N; 6.81 %.
(3-Methyl-4H-1,4-benzothiazin-2-yl)(phenyl)methanone (3b). Red crystals, mp 183-184˚C. IR (KBr): 3255, 1590 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 9.09 (1H, s, NH), 7.50-6.68 (9H, m, Ar), 1.73 (3H, s, CH_3). ^{13}C NMR (DMSO-d_6): 188.97 (C=O), 154.13 (C3), 140.86, 138.69, 131.02,

128.41, 127.86, 127.06, 126.07, 124.73, 120.31, 115.07, 97.33 (C_2), 21.03 (CH_3). MS *m/z* (relative intensity) 267 (M^+, 25), 162 (18), 105 (100), 77 (60), 51 (15). Anal. Calcd. For $C_{16}H_{113}NOS$: C, 71.88; H, 4.90; N, 5.24 %. Found : C, 71.70; H. 4.92; N; 4.96 %.

Ethyl 3-methyl-4H-1,4-benzothiazine-2-carboxylate (3c). Yellow crystals, mp 142-143˚C . IR(KBr): 3329, 1641, 1592cm^{-1}. ^{1}HNMR (DMSO-d_6): δ 8.63 (1H, s, NH), 6.90-6.57 (4H, m, Ar), 4.03 (2H, q, $^3J_{HH}$ 6.75 HZ, CH_2), 2.18 (3H, s, CH_3), 1.17 (3H, t, $^3J_{HH}$ 6.78 HZ, CH_3). ^{13}C NMR (DMSO-d_6): 163.04(C=O), 152.9 (C_3), 139.20 (C), 127.01, 125.71, 124.15 (3CH), 119.58 (C), 114.72 (CH), 86.00 (C_2), 59.61 (CH_2), 19.73 (CH_3), 14.21 (CH_3). MS *m/z* (relative intensity) 235 (M^+, 100), 207 (20), 162 (98), 130 (25), 118 (24), 109 (23), 77 (14), 65 (15), 45 (15). Anal. Calcd. for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95 %. Found : C, 60.95; H. 5.46; N; 5.92

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