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REACTIONS OF o-AMINOTHIOPHENOL WITH α,β-UNSATURATED DICARBONYL SYSTEMS. FACILE SYNTHESIS OF BENZOTHIAZINES AND BENZOTHIAZEPINES

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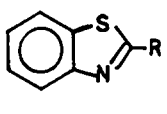
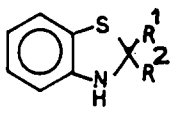
Abstract - When treated with maleanilic/fumaranilic acids or esters or the corresponding imides or isoimides, o-aminothiophenol furnishes benzothiazines, whereas treatment of o-aminothiophenol with acrylic acids/esters furnishes benzothiazepines. The orientational preferences in these Michael-type reactions are discussed.

INTRODUCTION

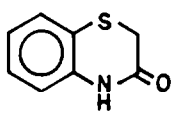
The reactions of the dinucleophile, o-aminothiophenol (o-ATP) with a variety of carbonyl derivatives have been studied extensively. The course of the reaction depends on the conditions of the reaction as well as the nature of the reactants and leads to ring systems such as benzothiazoles (Ia, R=H, alkyl, aryl or aralkyl), benzothiazines (II), benzothiazepines (III) and benzothiazocines (IV). Benzothiazoles (Ia) result from the reaction of o-ATP with aromatic and saturated aliphatic acids[1], acid chlorides [1a,1e,2a,2b], saturated acid anhydrides[1k,1l,3], esters[4], amides[1a] and nitriles[5]. With saturated aldehydes[6] and ketones[7], benzothiazolines (1b) are obtained. These are thermolabile when R^1 and R^2 is alkyl, and on pyrolysis[7a,7c] lead to 1a. Benzothiazines (II), benzothiazepines (III), and benzothiazocines (IV) are obtained when o-ATP reacts with α-halo[8], β-halo[9] and γ-halo[10] carbonyl systems respectively. Besides, benzothiazines are also obtained from reactions of o-ATP with α-nitroketones[11], α-nitroesters[12], α-epoxyketones[13], α-diketones[14], β-diketones[15] and β-ketoesters[16].



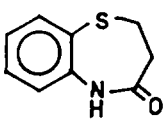
Ia



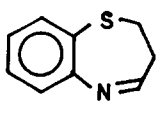
Ib



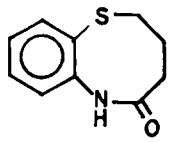
II



IIIa



IIIb



IV

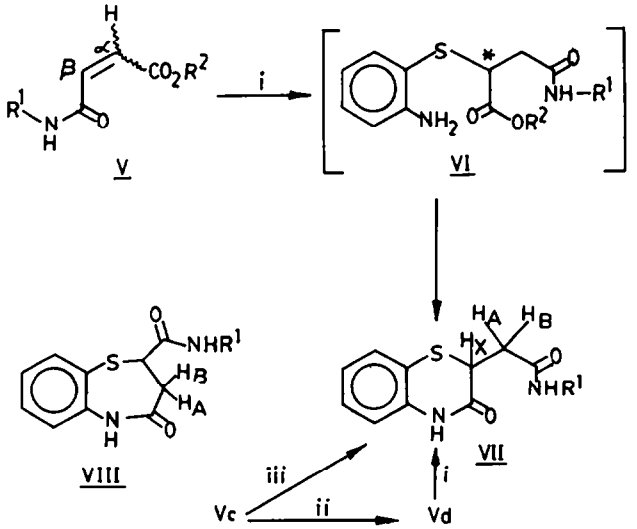
Part X of the series on Reactions of Cyclic Anhydrides. Part IX : Tetrahedron, 39, 1475 (1983).

The reported reactions of α,β-unsaturated carbonyl derivatives with o-ATP display interesting variations. With α,β-unsaturated aldehydes[17] and ketones[9a,9b,18], IIIb are obtained, arising from initial conjugate addition of thiol function, followed by intramolecular azo-methine formation[18a,18g]. The extensively studied reactions of quinones[19] with o-ATP relate to formation of phenothiazines. Acrylic acid derivatives having a carbonyl group as β-substituent (such as COR, -COAr, -COOR, $-CONH_2$ and -CONHR) on reaction with o-ATP afford[8a,20,23c] benzothiazines, whereas propiolic acids/esters on reaction with o-ATP lead to benzothiazoline[21d], benzothiazine[21d] or benzothiazepine[22]. It should however be noticed that acrylic acid chlorides[1j,8a] furnish benzothiazoles with o-ATP and the reaction of cinnamic and β,β-dimethylacrylic acids gives benzothiazoles under strong dehydrating conditions[24].

We have recently reported[23b,c,d] on the formation of benzothiazines by reaction of o-ATP with maleic/fumaric acids and their esters. As a sequel to this work, we closely examined the reactions of o-ATP with anilic acids and their esters. Earlier, Kirchner and Alexander[20b] have reported reactions of o-ATP with a series of β-aroylacrylic acids, maleamic acids, maleanilic acids and maleic acid monophenylhydrazides. In all these cases, benzothiazine derivatives were the products, apparently resulting from intramolecular Michael-type addition. These structures were deduced by chemical transformations. Conclusive spectral characterisations were, however, not made then. More recently, Augustin and Kohler[26] reported that the reaction of o-ATP with maleanilic esters resulted in merely isomerising the Z-esters to E-isomer without cyclisation, in contrast to the behaviour displayed by the corresponding acids[20b]. Intrigued by the latter observation, we reexamined several of the reactions reported by these two groups and also extended the range of conjugated carbonyl substrates used in earlier studies with a view to scrutinise orientational preferences in Michael-type reactions. The present communication describes our results in this regard.

RESULTS AND DISCUSSION

Equimolar amounts of maleanilic or fumaranilic esters (V, R^1=aryl, R^2=Me) and o-ATP on refluxing in ethanol for 3 hours afforded benzothiazine derivatives (VII, R^1=aryl). The corresponding acids (V, R^1=aryl, R^2=H) on similar reaction in DMF also gave VII (Scheme 1, Table 1). The reaction of o-ATP with maleanilates (Va), monitored by tlc, did not show intermediate formation of fumaranilic ester (Vd). The structure assigned to VIIb (R^1=allyl, ABX pattern : H_A 2.51, dd, J=16, 10 Hz; H_B 2.89, dd, J=16,7 Hz, estimated; H_X 4.00, dd, J=10, 7 Hz) fits in with these data which may not, by themselves, be adequate to uniquely differentiate VIIb and VIII (R^1=allyl).



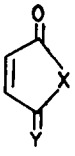
Scheme 1

Va, R^1=alkyl, aryl R^2=H(Z)
Vb, R^1=alkyl, aryl R^2=H(E)
Vc, R^1=2,5-$Cl_2C_6H_3$ R^2=Me(Z)
Vd, R^1=alkyl, aryl R^2=Me(E)

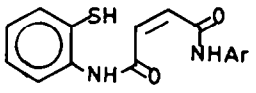
i. o-ATP ii. $(o\text{-}H_2NC_6H_4)_2S_2$
iii. $(o\text{-}H_2NC_6H_4)_2S_2$, Zn/HOAc

In a control experiment, we noticed that methyl 2,5-dichloromaleanilate isomerised to E-ester on reaction with bis (o-aminophenyl) disulphide in ethanol. If the same reaction was carried out under reducing conditions (zinc and acetic acid), it led to VIIn, presumably by initial formation of zinc salt of o-ATP followed by addition of thiolate anion to the olefinic system in maleanilate. Perhaps, in the earlier study[26] o-ATP could have been inadvertently oxidised to the disulphide during the reaction. We further effected the reaction of fumaranilic acid (Vb) and its methyl ester (Vd) with o-ATP to VII under the aforementioned conditions. It therefore appears unlikely that the reported[26] isomerisation of Vc ⟶ Vd with o-ATP could have stopped at that stage short of cyclisation. One more comment on this reaction seems appropriate. It is observed[26] that aniline alone causes isomerisation of maleanilates to fumaranilates, but no intermolecular aminolysis[26,27], whereas thiophenol alone on refluxing with maleanilates in ethanol for 2 hours, adds to the olefinic system to give an isolable adduct[26]. However, the reaction of o-ATP (wherein these nucleophiles are both present together) with maleanilate or fumaranilate under comparable conditions yields the cyclised product VII. Here initial addition of thiol to olefinic system of maleanilate (or fumaranilate) is followed by intramolecular aminolysis at ester carbonyl. It is noteworthy to observe that this Michael-type addition takes place at C_α (by activation due to amido function) rather than at C_β (activation due to ester function). The usually observed order[28] for activation of olefines for Michael-type addition is $COOR > CONR^1R^2$. The reason for such a reversal in orientation of these groups in the present substrates remains obscure as of now.

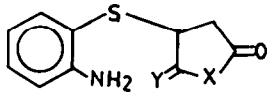
In recent literature, interesting synthetic applications of maleimides[29] and isomaleimides[30] have been reported. However, their reactions with o-ATP have not been explored much[31]. We undertook an investigation of these reactions. We observed that N-arylmaleimides (IXa) or the corresponding N-arylisomaleimides (IXb) afforded benzothiazines (VII) with o-ATP (Table 1). Though these reactions do not seem to offer any special synthetic advantage, the findings help us gain useful insight on the mechanistic pathways for the reactions of unsaturated dicarbonyl systems with o-ATP. In these reactions, two possible pathways can be visualised: (a) initial ring opening of IXa or IXb by amine function of o-ATP followed by thiol addition to give VII (i.e., IXa/IXb ⟶ Xa/Xb ⟶ VII) and (b) initial thiol addition to IXa or IXb followed by intramolecular aminolysis to VII (i.e., IXa/IXb ⟶ XIa/XIb ⟶ VII). But the latter pathway can be ruled out on the basis of reactions of isomaleimides (IXb) with o-ATP, as it will lead to formation of VIII via XIb by intramolecular amine attack at C=O which is more



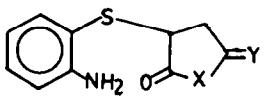
IX



X a,b



XI a,b



XII b

a, X = NAr, Y = O

b, X = O, Y = NAr

nucleophilic. The intermediacy of the alternate thiol-added isosuccinimide XIIb should also be excluded, since nucleophilic addition reactions to isoimides are influenced by carbonyl and not the C=N linkage[32]. Therefore it turns out that the reactions of o-ATP with imides and isoimides should be formulated to proceed by initial aminolysis (with ring opening) to Xa/b followed by a 6-exo-trig cyclisation to yield the observed product. The alternate 7-endo-trig ring closure is also a favoured process by Baldwin rules but this product is seldom encountered in these reactions. This mechanistic scheme is reminiscent of the one advocated by us for reactions of o-ATP with maleic anhydrides[23d].

We have repeated[8a] the reactions of crotonic and cinnamic acids with o-ATP, and spectral characterisations are made to confirm the structure of products. We also examined the reactions of β,β-dimethyl-

Table 1

Benzothiazines From Reaction of Maleanilic/Fumaranilic Acids and Esters (V ⟶ VII)

	V E/Z	V/VII R^1	V R^2	VII Yield %	VII m.p. °C	Analytical / Spectral Data
a	Z	H	H	60	220-1§	VIIa, ir:3400, 3200, 1680, 1650
b	Z	$CH_2CH=CH_2$	H	55	222-5	VIIb, C,60.10;H,5.50;N,11.04%. $C_{13}H_{14}O_2N_2S$ requires C,59.54;H,5.36;N,10.72%. ir: 3310, 3200, 1660, 1640, 1565, 930. pmr ($CDCl_3$/DMSO-d_6): 2.51 (dd,J=16,10 Hz,1H);2.89 (dd,J=16,7 Hz,estimated, 1H); 4.00(dd,J=10,7 Hz,1H);3.85(d,J=5 Hz,2H);5.22 (d,J=16 Hz,1H);5.12(d,J=10 Hz,1H);5.92(m,1H);6.95-7.27(m,4H);7.5(bs,1H);10.25(s,1H)
c	Z	Ph	H	82	248-50§,¶	VIIc, ir: 3330,3200, 1660, 1460
d	Z	4-MeC_6H_4	H	84	212-4¶	VIId, C,65.50,H,4.98%. $C_{17}H_{16}O_2N_2S$ requires C,65.58,H,5.14%.
e	Z	- " -	Me	82	-"-	
f	Z	4-$MeOC_6H_4$	H	80	264-5¶	VIIf, C,62.10,H,4.78%,$C_{17}H_{16}O_3N_2S$ requires C,62.38,H,4.89%.
g	Z	- " -	Me	80	-"-	
h	E	2-ClC_6H_4	H	77	231-2§	VIIo, C,56.12,H,3.65,N,12.20%.$C_{16}H_{13}O_4N_3S$ requires C,55.98,H,3.79,N,12.25%.ir:3350, 3200, 1670, 1460.
i	Z	- " -	Me	83	-"-	
j	Z	3-ClC_6H_4	H	90	228-30§	
k	Z	- " -	Me	92	-"-	
l	E	2,5-$Cl_2C_6H_3$	H	96	258-60	
m	E	- " -	Me	97	-"-	
n	Z	- " -	Me	94	-"-	
o	E	2-$O_2NC_6H_4$	H	88	217-20	
p	Z	- " -	Me	93	-"-	
q	E	- " -	Me	95	-"-	

Cryst.Solvent for VII: a,b,c,f,g,j,k-ethanol/acetone; d,e,h,i,o,p,q-ethanol/DMF; rest, ethanol/acetone/DMF.

§Lit[20b] m.p.VIIa,223-5°;VIIc,250-2°;VIIh,231-2°; VIIj,229-30°.

¶ also prepared by reaction of o-ATP with IXa/b (see Discussion/Experimental).

Table 2

Benzothiazepines Derived from Acrylic Acids/Esters and o-ATP (XIII ⟶ XIV)

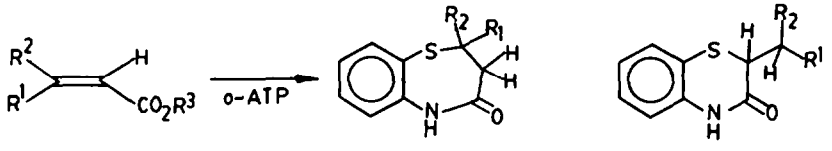
	XIII/XIV R^1	R^2	XIII R^3	XIV Yield %	XIV m.p. (°C)	Analytical/Spectral Data
a	H	Me	H	81	198-9	XIVa, pmr(acetone-d_6):1.39(d,J=8 Hz,3H);2.27 (dd,J=15, 7.5 Hz,1H);2.57(dd,J=15,5.5 Hz,1H);3.86(m,1H);7.14-7.59 (m,4H);8.86(bs,1H).
b	H	Ph	H	72	169-70	XIVb, pmr(acetone-d_6):2.7(m,2H,unresolved);4.95 (dd,J=18,5 Hz,1H);7.2-7.7(m,9H);9.08(bs,1H).
c	Me	Me	H	40	212-15	ms,m/e(%):255(m^+,100),227(10.57),212(14.10),151(41.64), 136(6.88),131(60.90),123(28.38),104(20.02),103(19.09), 96(12.84),77(6.71)
d	Me	Me	Et	55	-"-	XIVc: C,63.61,H,6.40,N,6.91%. $C_{11}H_{13}ONS$ requires C,63.77;H,6.27;N,6.76%. ir:3100, 1680, 1630, 1472, 1422. pmr($CDCl_3$/DMSO-d_6),1.6(s,6H); 2.42 (s,2H);7.1-7.6(m,4H);9.7(bs,1H).

Cryst.Solvent;XIVa,b-ethanol, c,d-ethanol/acetone.

Lit[8a] m.p.XIVa,206°, XIVb,177°.

acrylic acid and its ester with o-ATP. In all these cases, benzothiazepines (XIV) were the products (Scheme 2, Table 2). Here again, the reaction can be envisaged to proceed by either an initial thiol addition followed by aminolysis or by aminolysis followed by thiol addition (6-exo-trig to give XV, or 7-endotrig to give XIV). The observed product is exclusively XIV. Of these mechanistic possibilities, only the former needs to be seriously considered since thiol-added intermediates have been isolated[20c] in reactions of o-ATP with cinnamic acids.

Scheme 2



XIII XIV XV

a, R^1=H, R^2=Me, R^3=H b, R^1=H, R^2=Ph, R^3=H c, R^1=Me, R^2=Me, R^3=H d, R^1=Me, R^2=Me, R^3=Et

In summary, we have shown that (i) maleanilic esters are not isomerised to fumaranilic esters by o-ATP; instead, they as well as the corresponding E-acids and esters, undergo smooth cyclisation to benzothiazine derivatives with o-ATP, thus offering synthetically useful reactions, (ii) imides and isoimides derived from maleanilic acids react with o-ATP to form benzothiazines, (iii) acrylic acid derivatives react with o-ATP to yield generally benzothiazepines and, (iv) the reaction of o-ATP with unsaturated cyclic carbonyl substra tes appears to proceed by an aminolysis/6-exo-trig thiol addition sequence whereas with acyclic unsaturated carbonyl substra tes, thiol addition/aminolysis sequence is preferred.

EXPERIMENTAL

Melting points are uncorrected. IR spectra in nujol were recorded on a Perkin-Elmer R-37 Spectrophotometer (λmax in cm^{-1}). PMR spectra were recorded on a JEOL FX-270 Spectrometer using TMS as an internal standard (chemical shifts are in δ , ppm). Mass spectra were obtained at 70 ev, using a Finnegan 4000 with INCOS data system. All reactions involving o-ATP were conducted in nitrogen atmosphere.

General Procedure for Reaction of Maleanilic and Fumaranilic acids/esters with o-ATP : In a typical experiment, 2,5-dichloromaleanilic acid (0.65g; 0.0025m) was dissolved in DMF (6 ml.). To the warm solution was added a solution of o-ATP (0.31g; 0.0025m) in 2 ml DMF. The solution was refluxed for 3 hours. The cooled reaction mixture was poured onto crushed ice. The solid that separated was filtered and recrystallised; m.p.258-60°, yield 0.75g (83%); lit[20b] m.p. 261-65°.

The reaction of o-ATP with anilic esters was carried out as above except that ethanol was used as solvent in place of DMF. Data regarding reactions of o-ATP with several other maleanilic and fumaranilic acids and esters are assembled in Table 1.

Isomerisation of Methyl 2,5-Dichloromaleanilate with Bis (o-aminophenyl) disulphide : A solution of methyl 2,5-dichloromaleanilate (1.36g; 0.005m) and bis (o-aminophenyl) disulphide (1.24g; 0.005m) in 25 ml ethanol was refluxed for 3 hours. The cooled reaction mixture was poured onto crushed ice. The solid that separated was filtered and recrystallised from boiling ethanol, m.p.165-66°, yield, 72% Lit[20b] m.p. 166-67°.

Reaction of Bis(o-aminophenyl) disulphide with Methyl 2,5-Dichloromaleanilate under Reducing Conditions: To methyl 2,5-dichloromaleanilate (1.36g; 0.005m) and bis(o-aminophenyl) disulphide (0.61g; 0.0025m) in acetic acid (15 ml) was added zinc dust (1.0g). The solution was heated under reflux for 2 hours. The hot reaction mixture was filtered to remove zinc. The cooled filtrate was poured onto crushed ice. The solid that separated was filtered to give the same product as was obtained by reaction of this ester with o-ATP, m.p. 260-61°, yield, 1.2g (67%).

General Procedure for Reaction of Maleimides and Isomaleimides with o-ATP : Solution of equimolar amounts of maleimides or isomaleimides and o-ATP in DMF was stirred at room temperature for 3 hours. The solution was poured onto crushed ice. The solid that separated was filtered and washed repeatedly with dilute HCl to remove any of the disulphide derived from o-ATP.

Reaction of Crotonic acid with o-ATP : Crotonic acid (4.3g; 0.05m) in 15 ml diglyme was added to a solution of o-ATP (6.25g; 0.05m) in 15 ml diglyme and mixture refluxed for 3 hours. The cooled reaction mixture was poured onto crushed ice, the solid filtered and taken in aqueous HCl (2N, 20ml) to remove any of the unreacted o-ATP. The product was filtered, washed with water and then with saturated aqueous $NaHCO_3$ (50 ml) to remove any of the unreacted acid. The material was recrystallised from boiling ethanol to give 7.8g (81%) yield, m.p. 198-99°, Lit[8a] m.p. 205-06°.

Reaction of Cinnamic acid with o-ATP : Cinnamic acid (7.4g; 0.05m) in diglyme (20 ml) was added to a solution of o-ATP (6.25g; 0.05m) in 10 ml diglyme. The reaction mixture was refluxed for 4 hours. Aqueous work-up as described above afforded 8.9g (72%) of product melting at 169-70°. Lit[8a]. m.p.177°.

Reaction of β,β-Dimethylacrylic acid with o-ATP : β,β -Dimethylacrylic acid (1.0g; 0.01m) in digol (10ml) was added to a solution of o-ATP (1.25g; 0.01m) in 5 ml digol. The mixture was refluxed for 4 hours. Aqueous work-up afforded 0.82g (40%) of product melting at 212-15°. The yield was only 10% with a shorter reflux time (2 hours).

Reaction of Ethyl β, β -Dimethylacrylate with o-ATP : A solution of ethyl β,β -dimethylacrylate (1.28g; 0.01m) in DMF (5 ml) was added to a solution of o-ATP (1.25g; 0.01m) in DMF (3 ml.). The reaction mixture was refluxed for 5 hours. Aqueous work-up afforded the same product as was obtained from reaction of the corresponding acid with o-ATP. Yield, 55%.

The analytical data for all compounds derived from substituted acrylic acids and o-ATP are assembled in Table 2.

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