Reactivity of Aryl- and Heteroarylmalonates against *ortho*-Dinucleophiles. Triaryl(heteroaryl)methane Synthesis

Teresa Ramos and Carmen Avendaño*

Departamento de Química Orgánica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain

José Elguero

Instituto de Química Médica, C.S.I.C., Juan de la Cierva 3, 28006 Madrid, Spain

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Condensations of several aryl(heteroaryl)malonates **1** and *ortho*-dinucleophiles are studied as a possible synthetic approach to aryl(heteroaryl)bisheteroarylmethanes **2**.

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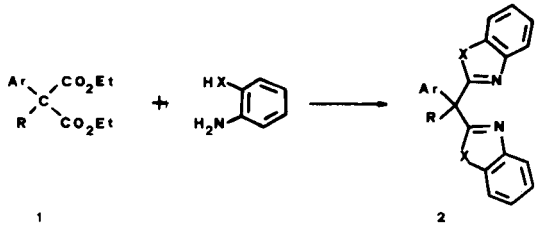
Condensations of diethyl phenylmalonates with *o*-aminothiophenol to give bis-2-benzothiazolylmethane (**2a**, X = S, R = H) [1] and with 2-amino-5-nitrobenzenethiol to give bis(6-nitro-2-benzothiazolyl)phenylmethanes [2] are the only known examples in which aryl-substituted malonic esters have been used to prepare triaryl(heteroaryl)-methanes.

As a part of a program designed to prepare compounds biologically and structurally related to triphenylmethane and cyanine dyes, we have been interested in the study of the reactivity of several aryl- and heteroarylmalonates against *ortho*-dinucleophiles as a method of synthesis of compounds **2** (Scheme 1).

Scheme 1

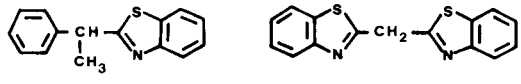


1 2

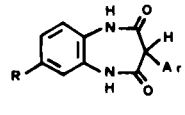
a; Ar=Ph, R=H d; Ar= Ph, R= Me

b; Ar=$C_6H_4NO_2$-p, R=H e; Ar= 2-benzothiazolyl, R=H

c; Ar= 2,4-dinitrophenyl, R=H f; Ar= 2-pyridyl, R=H



3d 3e



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Results and Discussion.

Diethyl aryl(heteroaryl)malonates were prepared following literature procedures (see Experimental). An improved method to achieve diethyl 2-pyridylmalonate in 70% yield by carbethoxylation of ethyl 2-pyridylacetate, is here reported. Other methods give very low yields [3] and/or are much more complicated [4,5].

Diethyl phenylmalonate was used as a model reagent to find the reaction conditions, but the results are largely affected by both, the nature of the *ortho*-dinucleophile and that of the arylmalonic ester (Table 1).

Table 1

Reagents	[a]	Method	Products	Yield (%)
1a	AT	A	**2a**, X = S, R = H	92
	PD	A, B	**4a**, Ar = Ph, R = H	Quant
	Me-PD	B	**4a**, Ar = Ph, R = Me	49
	PD	C	**2a**, X = NH, R = H	62
			4a, Ar = Ph, R = H	32
1b	AT	A	**2b**, X = S, R = H	77
	PD	C	**4b**, Ar = $C_6H_4NO_2$-*p*, R = H	31
1c	AT	A	Carbonization	
	PD	C	Carbonization	
1d	AT	A	**3d**	67
			2-Ethylthioaniline	35
	PD	C	Starting materials	
1e	AT	A	**2e**, X = S, R = H	20
			3e [9]	50
	PD	C	2-Benzimidazolone	
1f	AT	A	**2f**, X = S, R = H	21
	PD	C	2-Benzimidazolone	

[a] AT = *o*-aminothiophenol, PD = *o*-phenylenediamine.

Reactions with *o*-Aminothiophenol: Synthesis of Aryl(heteroaryl)bis(2-benzothiazolyl)methanes **2** (X = S).

The direct condensation of *o*-aminothiophenol with the appropiate carboxylic acid or a reactive carboxylic acid derivative is the most direct route to obtain 2-substituted benzothiazoles although it requires harsh reaction condi-

tions [6]. The polyphosphoric acid-catalyzed condensations (Method A, Table 1) of diethyl arylmalonates **1** proceeded in very good to moderate or poor yields to give products **2a**, **2b**, **2f** and **2e** respectively, but were uneffective with the other malonic esters. The carbonization of the reaction mixture found upon heating with **1c** can be due to the oxidative effect of the *o*-nitro group at elevated temperature [7]. Steric factors explain the failure with diethyl methylphenylmalonate (**1d**). The reaction products in this case were 2-(α-methyl)benzylbenzothiazole (**3d**) and the previously described 2-ethylthioaniline [8]. The former is obviously a monocondensation-decarboxylation product.

The reaction with diethyl 2-benzothiazolylmalonate (**1e**) gave tris(2-benzothiazolyl)methane (**2e**, X = S, R = H) in 20% yield together with the monocondensation-decarboxylation product bis(2-benzothiazolyl)methane (**3e**) [9] in 50% yield.

Reactions with *o*-Phenylenediamine: Synthesis of Aryl(heteroaryl)bis(2-benzimidazolyl)methanes **2** (X = NH).

Only unsubstituted or alkyl-substituted malonates $RCH(COOEt)_2$ (R = H, Me, Et, Bu) have been condensed with *o*-phenylenediamines to give unsubstituted or alkyl-substituted bis-2-benzimidazolylmethanes [10,11]. Analogous condensations with aryl(heteroaryl)malonates **1** were attempted to prepare aryl(heteroaryl)bis(2-benzimidazolyl)methanes **2** (X = NH). Among them, only **2a** (X = NH, R = H) has been apparently obtained by condensation of 2-phenyl-1,1,3,3-tetrafluoro-3-cloropropene and *o*-phenylenediamine [12].

Polyphosphoric acid catalyzed condensations (Method A) of **1a** and *o*-phenylenediamine and 4-methyl-1,2-phenylenediamine gave the corresponding 3-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[b]-1,4-diazepine-2,4-diones **4** which are the 1:1 condensation-products. The 7-unsubstituted compound **4a** (R = H) has been previously prepared by a different approach [13]. The same result was achieved by thermal cyclization in trichlorobenzene as solvent (Method B), but when this procedure was modified by simultaneous distillation of water and alcohol, and a molar ratio malonate:amine 1:3 (Method C), phenylbis(2-benzimidazolyl)methane (**2a**, X = NH, R = H) was obtained in 67% yield together with the above mentioned diazepinedione (Table 1).

Under analogous reaction conditions **1b** gave 3-(*p*-nitrophenyl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*]-1,4-diazepine-2,4-dione (**4b**) exclusively. If the malonic ester is slowly added to the reaction mixture (Method D), 2-benzimidazolone was obtained in quantitative yields as a thermal decomposition product. This was the only product found with malonates **1e** and **1f** while **1d** only gave starting materials and with **1c** carbonization products resulted.

Reactions with *o*-Aminophenol.

Although the condensation of *o*-aminophenol with carboxylic acid derivatives under polyphosphoric acid-catalyzed conditions is a general method to obtain 2-substituted-bezoxazole derivatives, the reaction with diethyl phenylmalonate (**1a**) following the above mentioned method A, was fruitless and starting materials were recovered.

EXPERIMENTAL

All melting points are uncorrected and were measured with a Buchi capillary melting point apparatus. The ^1H nmr spectra were recorded with a Perkin-Elmer R24-B (60 MHz) and ^{13}C nmr with a Varian XL-300 pulsed Fourier transform spectrometer with tetramethylsilane as an internal standard. For bisheteroarylmethanes **3e** and trisaryl(heteroaryl)-methanes **2a-2f**, the ^1H nmr spectra, even at 300 MHz, are extremely complex due to CH/NH tautomerism [14]. The ir spectra were registered with a Perkin-Elmer 457 spectrophotometer, and mass spectra were run on a Hitachi Perkin-Elmer RMU-6MG instrument operating at 70 eV.

The following diethyl arylmalonates were prepared by the literature methods quoted: diethyl *p*-nitrophenylmalonate [15], diethyl 2,4-dinitrophenylmalonate [16], diethyl phenylmethylmalonate [17], and diethyl 2-benzothiazolylmalonate [18,19].

Diethyl 2-Pyridylmalonate.

Sodium metal (1.15 g, 50 mmoles) in small pieces was added to a mechanically stirred solution of ethyl 2-pyridylacetate [20] (8.25 g, 50 mmoles) in diethyl carbonate (100 ml). When the addition of sodium was complete, the mixture was heated close to the boiling point for half an hour, and then allowed to cool. The solid precipitate was filtered and washed with ether, added to "ice-cold" water (100 ml) and neutralized with acetic acid. The malonic ester was extracted with ether and dried over anhydrous sodium sulfate. On evaporation of the ether in vacuum, an oil was obtained (8.5 g, 71%) identified by its spectroscopic data and used with no further purification.

Reactions of Diethyl Arylmalonates with *o*-Aminothiophenol.

Method A.

A mixture of arylmalonate (20 mmoles) and *o*-aminothiophenol (50 mmoles) in polyphosphoric acid (200 ml) was mechanically stirred under a nitrogen stream for 2 hours at 80-90°, 3 hours at 120°, and 1 hour at 140°. The mixture was allowed to cool to 80° and poured into stirred "ice-cold" water. The solid precipitate was filtered, washed with an aqueous solution of potassium carbonate and water and then dried under vacuum over phosphorus pentoxide yielding a crude product. Thus were obtained the following compounds:

Bis(2-benzothiazolyl)phenylmethane (**2a**).

This compound was obtained in 92% yield, mp 146-148° (ethanol/water); ir (potassium bromide): 3360 (NH), 1485, 1450 and 1440 cm^{-1}.

Anal. Calcd. for $C_{21}H_{14}N_2S_2.H_2O$: C, 66.99; H, 4.28; N, 7.44. Found: C, 66.91; H, 4.29; N, 7.50.

Bis(2-benzothiazolyl)-*p*-nitrophenylmethane (**2b**).

This compound was obtained in 77% yield, mp 210-213° (dimethylformamide); ir (potassium bromide): 1600, 1560, 1515 (NO_2) and 1500 cm^{-1}; ms: 403 (M^+, 100).

Anal. Calcd. for $C_{21}H_{13}N_3O_2S_2$: C, 62.51; H, 3.24; N, 10.41. Found: C, 62.15; H, 3.23; N, 10.43.

Tris(2-benzothiazolyl)methane (**2e**).

This compound was obtained in 20% yield, mp 258-260° (ethanol), (literature [21] gives 271° from benzene); ir (potassium bromide): 1500, 1460 and 1435 cm^{-1}.

Bis(2-benzothiazolyl)-2-pyridylmethane (**2f**).

This compound was obtained in 21% yield, mp 138-139° (acetone/water); ir (potassium bromide): 1600, 1580 (pyridine), 1560 and 1545 cm^{-1}.

Anal. Calcd. for $C_{20}H_{13}N_3S_2$: C, 66.83; H, 3.64; N, 11.69. Found: C, 66.55; H, 3.26; N, 11.47.

In the case of malonate **1d**, the aqueous phase was extracted with chloroform, the combined layers were dried and concentrated to give a dark oil from which α-methyl-2-benzylbenzothiazole (**3d**) was obtained by distillation in 67% yield, bp 128-130°/0.2 mm Hg; ir (neat): 1600, 1550, 1510, 1490, 1450 and 1435.

Anal. Calcd. for $C_{15}H_{13}NS$: C, 75.28; H, 5.47; N, 5.85. Found: C, 74.93; H, 5.48; N, 5.84.

The aqueous phase was partially concentrated, neutralized with sodium bicarbonate, extracted with chloroform and dried over magnesium sulfate. After eliminating the solvent a dark oil was obtained and distilled giving *o*-ethylthioaniline in 35% yield from *o*-aminothiophenol, bp 54-55°/0.02 mm Hg.

Reactions of Diethyl Arylmalonates with *o*-Phenylenediamines.

Method A.

It is analogous to that employed for *o*-aminothiophenol.

Method B.

o-Phenylenediamine (20 mmoles) in 15 ml of 1,2,4-trichlorobenzene was heated to 170-180°, and then, arylmalonate (10 mmoles) was added during 20 minutes, heating to 190-195° for two hours. After cooling, the solid obtained was filtered, washed with benzene and petroleum ether.

Method C.

o-Phenylenediamine (30 mmoles) in 8 ml of 1,2,4-trichlorobenzene was heated to 180-185°, and then, diethyl arylmalonate (10 mmoles) was added dropwise if it is a liquid or in the minimum volume of solvent when solid, over a period of two hours while the ethanol and water formed in the reaction were destilled off. After cooling, the solid obtained was filtered, washed with benzene and a little ethanol.

Method D.

It is analogous to procedure C but the reaction time was reduced to half an hour.

The following products were obtained: 3-Phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]-1,4-diazepine-2,4-dione, (**4a**, Ar = Ph, R = H) [13].

This compound was obtained in quantitative yield following methods A and B, and in 32% yield following method C, by washing the crude product with diluted hydrochloric acid.

7-Methyl-3-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[b]-1,4-diazepine-2,4-dione, (**4a**, Ar = Ph, R = Me).

This compound was obtained in 49% yield following procedure B, mp 292-294° (acetonitrile); ir (potassium bromide): 3180, 3090, 1710 and 1660 cm^{-1}; nmr (deuteriodimethylsulfoxide): δ 2.3 (s, CH_3, 3H), 4.45 (s, CH, 1H), 7.0-7.3 (m, aromatic, 8H), 10.45 (s, NH, 2H).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.14; H, 5.38; N, 10.67.

3-*p*-Nitrophenyl-2,3,4,5-tetrahydro-1*H*-benzo[b]-1,4-diazepine-2,4-dione (**4b**).

This compound was obtained following procedure C in 31% yield, mp 288-289° (dimethylsulfoxide/water); ir (potassium bromide): 3190, 3160, 3060, 1695 and 1660 cm^{-1}; nmr (deuteriodimethylsulfoxide): δ 4.8 (s, CH, 1H), 7.2 (s, aromatic, 4H), 7.6-8.2 (*p*-system, aromatic, 4H), 10.7 (s, NH, 2H); ^{13}C nmr (deuteriodimethylsulfoxide): δ 54.0, 121.8, 122.5, 125.3, 129.9, 133.4, 140.7, 146.9 and 165.0.

Anal. Calcd. for $C_{15}H_{11}N_3O_4$: C, 60.61; H, 3.73; N, 14.13. Found: C, 60.55; H, 3.96; N, 13.95.

Phenylbis(2-benzimidazolyl)methane, (**2a**, X = NH, R = H).

This compound was obtained following method C in 62% yield by neutralization with potassium carbonate the acidic solution of the crude product after separation of **4a** (Ar = Ph, R = H) by filtration, mp 278-280° (ethanol/water); ir (potassium bromide): 3300-2400, 1620, 1585, 1505, 1490, 1435 and 1420 cm^{-1}; ms: 324 (M^+, 100).

Anal. Calcd. for $C_{21}H_{16}N_4$: C, 77.75; H, 4.97; N, 17.27. Found: C, 77.54; H, 4.62; N, 16.93.

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