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Reactions of 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates with dinucleophiles

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Abstract: 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates has been prepared by the coupling of benzoyl pyruvic ester with aryldiazonium chlorides. 3-Arylhydrazono-2,4-dioxo-4-phenylbutanoates reacts with 1,2-phenylenediamine, 2-aminophenol, and 2-aminothiophenol, to form the corresponding quinoxaline, 1,4-benzoxazine, and 1,4-benzothiazine derivatives. Interaction of 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates with 2,3-diaminopyridine, 1,2-ethelenediamine, and 1,2-diaminohexane results in pyrazine products. The structure of the resulted products were confirmed by determination of the melting point and spectrophotometric techniques such as IR and ^{1}H NMR and in some cases by using ^{13}C-NMR spectroscopy.

Keywords: *Coupling; Benzoyl pyruvate; Arylhydrazone; Quinoxaline; Benzoxazine; Benzothiazine; Pyrazine*

Introduction

It is known that 1,3-dicarbonyl compounds reactwith aryldiazonium salts to form the corresponding 2-arylhydrazone-1,2,3-tricarbonyl compounds [1,2]. Data on the coupling of fluorine-containing 1,3-dicarbonyl compounds are available [2-4]. Acyl(aroyl)pyruvic esters are known to react with aryldiazonium salts to form the corresponding 3-arylhydrazone-1,2,3,4-triketo esters [5]. Data on the synthesis of arylhydrazones from fluorinated acyl(aroyl) pyruvic esters are available [6-8].

3-Arylhydrazone-1,2,3,4-triketo esters were used as precursors for the synthesis of the following heterocycles and theirreactions with dinuclophiles as substituted analogues were studied [7-15].

This paper describes the synthesis of novel 3-arylhydrazone-1,2,3,4-triketo esters and their heterocyclization reaction products.

Experimental

Melting points were measured in open capillaries and are reported uncorrected. Infrared spectra were obtained by KBr disk using a FT-IR Perkin Elmer GX spectrometer and frequencies are reported in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Ultra Shield TM-500MHz instrument using TMS as an internal standard. Chemical shifts are reported in ppm. Column chromatography was

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performed on silica gel L 100/250. Thin-layer chromatography was performed on "Silufol-UV 254" plates.

Material

Ethyl-2,4-dioxo-4-phenylbutanoate (1) was prepared from diethyl oxalate and the acetophenon by known methods [16].

Synthesis of 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (2a-d)

A solution of the appropriate arylamine (11.0 mmol) in a solution of 1M HCl (60 ml) was diazotized at 0-5˚C by addition of a saturated solution of $NaNO_2$ (11.0 mmol) in 10 ml of water. The solution of aryldiazonium salt was added dropwise to a stirred solution of the dicarbonyl compound (10.0 mmol), NaOAc (5 g) in 1:2 MeOH-water (300 ml) at room temperature. The resulting precipitate was filtered off, washed well with water. Recrystallization from methanol gave compounds 2a-d as yellow precipitates. The yields and melting points of these products were determined (Table 1). The purified products were analyzed by ^{1}H-NMR and IR data (Table 1).

Reaction of 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates with dinucleophiles

3-(1-p-Chlorophenylhydrazono-2-oxo2-phenylethyl) -1,2-dihydroquinoxaline-2-one (3a)

o-Phenylenediamine (0.108 g, 1.0 mmol) was added to a solution of compound 2c (0.358 g, 1.0 mmol) in 20 ml of ethanol. The reaction mixture was refluxed for 1 h. The resulting precipitate was filtered off. Crystallization from ethanol gave 3a (0.25 g, 62%) as an orange powder (m. p. 290˚C (decomposition)). ^{1}H-NMR ($(CD_3)_2SO$) δ: 7.16-7.96 (13H, m, C_6H_5, $2C_6H_4$); 11.47, 12.67 (2H, br.s, NH) ppm. IR: 2920, 1597 (NH); 1674 (C=O, amide); 1656 (C=O, ketone); 1549, 1510 (C=N, C=C) cm^{-1}.

3-(1-p-Nitrophenylhydrazono-2-oxo-2-phenylethyl) -7-methyl-1,2-dihydroquinoxaline-2-one (3b)

4-Methyl-1,2-phenylenediamine (0.122 g, 1.0 mmol) was added to a solution of compound 2d (0.369 g, 1.0 mmol) in 20 ml of ethanol. The reaction mixture was refluxed for 30 min. The resulting precipitate was filtered off. Crystallization from ethanol gave 3b (0.30 g, 71%) as a yellow powder (m. p. 298°C (decomposition)). ^{1}H-NMR ($(CD_3)_2SO$) δ: 2.47 (3H,

Table 1 The yields, melting points, IR, and ^{1}H-NMR data for arylhydrazones

Entry	X	Yield (%)	M. p. (°C)	IR (cm^{-1})				^{1}H-NMR ($CDCl_3$, ppm)			
				NH	C=O, CO_2Et	C=O	C=N, C=C	NH	Ar-H	CH_2	CH_3
2a	CH_3	78%	111-113°C	3010, 1595	1733	1638	1517, 1500	14.30 (br.s, 1H)	7.18-7.96 (m,9H)	4.43 (q, 2H)	1.41 (t, 3H)
2b	H	82%	108-110°C	2977, 1595	1743	1638	1525, 1500	14.80 (br.s, 1H)	7.25-7.89 (m,10H)	4.42 (q, 2H)	1.40 (t, 3H)
2c	Cl	87%	128-130°C	3100, 1596	1730	1628	1522, 1500	14.20 (br.s, 1H)	7.26-7.88 (m,9H)	4.42 (q, 2H)	1.39 (t, 3H)
2d	NO_2	89%	141-143°C	3081, 1596	1738	1650	1525, 1500	13.90 (br.s, 1H)	7.47-8.22 (m,9H)	4.38 (q, 2H)	1.38 (t, 3H)

s, CH_3); 7.19-8.20 (12H, m, C_6H_5, C_6H_4, C_6H_3); 11.78, 12.69 (2H, br.s, NH) ppm. IR: 2785, 1596 (NH); 1663 (C=O, amide); 1618 (C=O, ketone); 1542, 1510 (C=N, C=C); 1507, 1336 (NO_2) cm^{-1}.

3-(1-p-Chlorophenylhydrazono-2-oxo-2-phenylethyl) -6-nitro-1,2-dihydroquinoxaline-2-one (3c)

4-Nitro-1,2-phenylenediamine (0.153 g, 1.0 mmol) was added to a solution of compound 2c (0.358 g, 1.0 mmol) in 20 ml of ethanol. The reaction mixture was refluxed for 3 h. The resulting precipitate was filtered off. Crystallization from ethanol gave 3c (0.22 g, 50%) as a red powder (m. p. 295°C (decomposition)). ^{1}H-NMR ($(CD_3)_2SO$) δ: 7.18-8.20 (12H, m, C_6H_5, C_6H_4, C_6H_3); 11.65, 13.02 (2H, br.s, NH) ppm. IR: 2927, 1597 (NH); 1674 (C=O, amide); 1652 (C=O, ketone); 1535, 1510 (C=N, C=C); 1510, 1345 (NO_2) cm^{-1}.

3-(1-p-Chlorophenylhydrazono-2-oxo-2-phenylethyl) -6-methyl-2H-1,4-benzoxazine-2-one (3d)

2-Amino-4-Methyl phenol (0.123 g, 1.0 mmol) was added to a solution of compound 2c (0.358 g, 1.0 mmol) in 20 ml of ethanol. The reaction mixture was refluxed for 2 h. The resulting precipitate was filtered off. Crystallization from ethanol gave 3d (0.28 g, 64%) as a yellow powder (m. p. 248°C (decomposition)). ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s, CH_3); 7.18-8.12 (12H, m, C_6H_5, C_6H_4, C_6H_3); 12.67 (1H, br.s, NH) ppm. IR: 2925, 2854, 1591 (NH); 1745 (C=O, ester); 1662 (C=O, ketone); 1532, 1509 (C=N, C=C) cm^{-1}.

3-(1-p-Nitrophenylhydrazono-2-oxo-2-phenylethyl) -2H-1,4-benzothiazine-2-one (3e)

2-Aminothiophenol (0.125 g, 1.0 mmol) was added to a solution of compound 2d (0.369 g, 1.0 mmol) in 20 ml of ethanol. The reaction mixture was refluxed for 5 h. The resulting precipitate was filtered off. Crystallization from ethanol gave 3e (0.22 g, 52%) as a green powder (m. p. 268°C (decomposition)). ^{1}H-NMR ($CDCl_3$) δ: 7.19-8.20 (13H, m, C_6H_5, C_6H_4, C_6H_4); 12.69 (1H, br.s, NH) ppm. IR: 2928, 1579 (NH); 1673 (C=O, thioester); 1543, 1510 (C=N, C=C); 1494, 1345 (NO_2) cm^{-1}.

3-(1-p-Chlorophenylhydrazono-2-oxo-2-phenylethyl) -1,2-dihydropyrido[2,3-b]pyrazine-2-one (4)

2,3-Diaminopyridine (0.109 g, 1.0 mmol) was added to a solution of compound 2c (0.358 g, 1.0 mmol) in 20 ml of ethanol. The reaction mixture was refluxed for 8 h. The resulting precipitate was filtered off. Crystallization from ethanol gave 4 (0.27 g, 66%) as a yellow powder (m. p. 285°C (decomposition)). ^{1}H-NMR ($(CD_3)_2SO$) δ: 7.14-8.63 (12H, m, C_6H_5, C_6H_4, C_5H_3N); 11.36, 13.15 (2H, br.s, NH) ppm. ^{13}C-NMR δ: 115.81, 120.00, 126.10, 127.17, 128.07, 129.28, 129.86, 132.13, 136.19, 137.12, 137.25, 142.02, 143.95, 151.18, 154.78, 155.11, 189.80 ppm. IR: 2926, 1596 (NH); 1660 (C=O, amide); 1645 (C=O, ketone); 1526, 1510 (C=N, C=C) cm^{-1}.

3-(1-p-Nitrophenylhydrazono-2-oxo-2-phenylethyl) -5,6-dihydropyrazine-2(1H)-one (5)

1,2-Ethylenediamine (0.06 g, 1.0 mmol) was added to a solution of compound 2b (0.324 g, 1.0 mmol) in 20 ml of ethanol. The reaction mixture was refluxed for 1 h. The resulting precipitate was filtered off. Crystallization from isopropyl alcohol gave 5 (0.14 g, 44%) as a yellow powder (m. p. 226°C (decomposition)). ^{1}H-NMR ($(CD_3)_2SO$) δ: 3.40 (2H, br.t, CH_2-NH); 3.96 (2H, br.t, CH_2-N); 6.99-7.91 (10H, m, $2C_6H_5$); 8.56, 12.32 (2H, br.s, NH) ppm. IR: 3334, 2927, 1591 (NH); 1686 (C=O, amide); 1630 (C=O, ketone); 1534, 1505 (C=N, C=C) cm^{-1}.

3-(1-p-Nitrophenylhydrazono-2-oxo-2-phenylethyl) -5,6-dihydrocyclohexano[1,2-b]pyrazine-2(1H)-one (6)

1,2-Diaminocyclohexane (0.114 g, 1.0 mmol) was

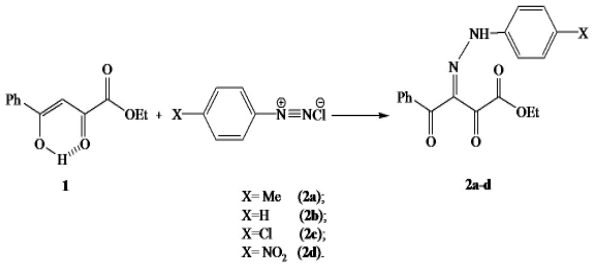
added to a solution of compound 2d (0.369 g, 1.0 mmol) in 20 ml of ethanol. The reaction mixture was refluxed for 1 h. The resulting precipitate was filtered off. Crystallization from isopropyl alcohol gave 6 (0.21 g, 48%) as a clear brown powder (m. p. 249°C (decomposition)). ^{1}H-NMR ($CDCl_3$) δ: 1.40-1.96 (8H, m, $4CH_2$); 2.43 (1H, br.d, CH-NH); 3.42 (1H, br.m, CH-N); 7.16-8.17 (9H, m, C_6H_5, C_6H_4); 6.35, 13.72 (2H, br.s, NH) ppm. IR: 3345, 2928, 2853, 1598 (NH); 1698 (C=O, amide); 1665 (C=O, ketone); 1536, 1505 (C=N, C=C); 1505, 1322 (NO2) cm^{-1}.

Results and discussion

Synthesis of 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates

In present work, it has been found that the ethyl-2,4-dioxo-4-phenylbutanoate (1) reacts with aryldiazonium chlorides in water-methanol medium in presence of NaOAc to give the corresponding 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (2a-d) (Scheme 1).

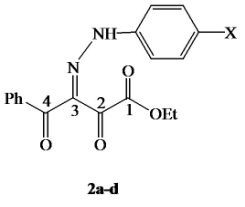
It was proved by IR and ^{1}H-NMR spectroscopies that the obtained compounds 2a-d [7]. In the ^{1}H-NMR spectra of products 2a-d the resonance signal of a methine proton was absent. The IR spectra of 2a-d showed a C=O stretching absorption at 1650-1628 cm^{-1} from the keto groups of 1,3-dicarbonyl fragment. The low frequency of the C=O stretching absorption is probably the result of the conjugation of the C=N bond and participation of the C=O group in an intramolecular hydrogen bond with the amino-group of arylhydrazone fragment.



Scheme 1

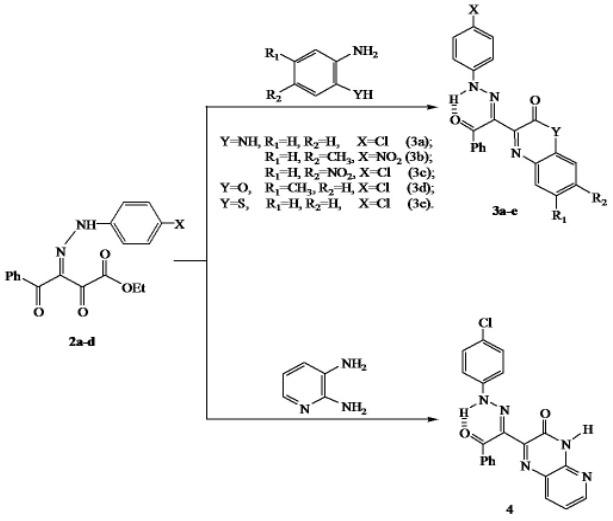
Reactions of 3-arylhydrazono-2,4-dioxo-4-phenyl-butanoates with dinucleophiles

The arylhydrazones 2a-d were used as precursors for synthesis of heterocycles. It has been found that interaction of 1,2-phenylenediamine, 2-aminophenol, 2-aminothiophenol, 2,3-diaminopyridine, 1,2-ethelenediamine, and 1,2-diaminohexane with 2a-d generally lead to formation of nucleophile cycloco densation products. These dinucleophiles cycloadd to reaction centers of 2a-d to α-ketoesteric fragment (atoms C-1 and C-2, see Scheme 2). The nucleophile cyclocondensation pathways and regioselectivity depend on the nucleophile and reaction conditions.



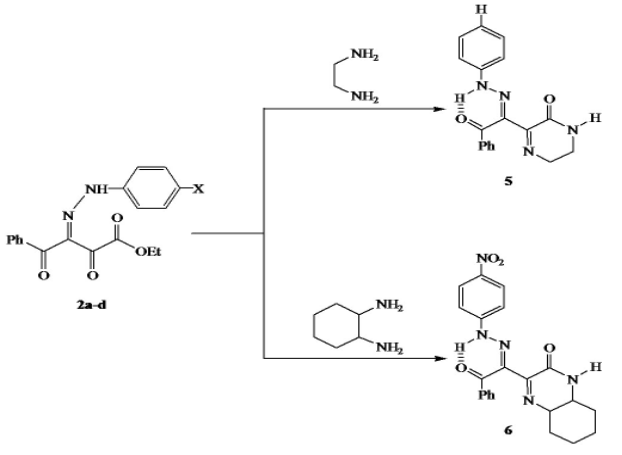
Scheme 2

Arylhydrazones 2c,d react with 1,2-phenylenediamine, 4-methyl-1,2-phenylenediamine, and4-nitro-1,2-phenylenediamine on boiling in ethanol to give quinoxaline derivatives 3a-c (Scheme 2). Similarly, compound 2c reacts with each of4-methyl-2-aminophenol, 2-aminothiophenol, and 2,3-diaminopyridine on boiling ethanol to yield the substituted 2H-1,4-benzoxazine-2-one 3d, 2H-1,4-benzothiazine-2-one derivative 3e and pyrido[2,3-b]pyriazine derivative 4, respectively (Scheme 3).



Scheme 3

Arylhydrazones 2b,d react with 1,2-ethylenediamine and 1,2-diaminocyclohexane on boiling in ethanol to give 5,6-dihydropyrazine-2(1H)-one derivative 5 and 5,6-dihydrocyclohexano[1,2-b]pyrazine-2(1H)-one derivative 6, respectively (Scheme 4).



Scheme 4

Conclusion

3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (2a-d) reacts with diamines (1,2-phenylenediamine, 2-aminophenol, 2-aminothiophenol, 2,3-diaminopyridine, 1,2-ethelenediamine, and 1,2-diaminohexane) at the α-dicarbonyl fragment to form the corresponding quinoxaline, benzoxazine, benzothiazine, and pyriazine similarly to α–diketones and α–ketoesters.

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