Synthesis of Some Nitrogen Functional Derivatives of 5-substituted-6-azauracil as Biologically Active Compounds

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Abstract

3-Arylhydrazono-2,4-dioxo-4-phenylbutanoates have been prepared by the coupling of benzoylpyruvate with aryldiazonium chlorides. Reactions of the 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates with 1-aminoguanidine, semicarbazide, and thiosemicarbazide gave 5-substituted 2-imino-6-azauracil (**3a**), 6-azauracil (**3b**), and 2-thio-6-azauracil (**3c**), respectively. The analytical data of these compounds - IR, ^{1}H, and ^{13}C NMR spectral data - are reported.

Keywords: Coupling, Benzoylpyruvate, Arylhydrazone, 1,2,4-Triazin-5-one, 6-Azauracil.

Introduction

4-Aryl-2,4-dioxobutyrates are formally derivatives of pyruvic acid and are as such trivially referred to as benzoylpyruvates. Being endowed with multiple functionalities, they are important synthetic precursors, capable of interacting with both electrophilic as well as nucleophilic reagents. In particular, in the latter case they offer a versatile scaffold on which to mould annulated rings carrying distinct structural features. This versatility draws its impetus from the conspicuous qualitative differences between the three carbonyl functionalities, which makes regio- and chemoselective discrimination possible. Through a judicious matching of the applied nucleophilic species, the mode of annulation may be predicted, rendering a powerful tool for the construction of a variety of heterocyclic compounds [1]. Reactions of benzoylpyruvates with *N,N*- and *N,O*-dinucleophiles carrying a two-unit linker lead to formation of heterocyclic compounds [1-10]

It is known that benzoylpyruvate react with aryldiazonium salts to form the corresponding 3-arylhydrazono-

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2,4-dioxo-4-phenylbutanoates [11]. Similarly, 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates with various dinucleophiles carrying a two-unit linker lead to formation of heterocyclic compounds [11-13]. Recently, we report reactions of 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates with *N,N'- N,O-* and *N,S-* dinucleophiles carrying a two-unit linker for the synthesis of the corresponding quinoxaline, 1,4-benzoxazine, 1,4-benzothiazine and pyrazine derivatives [14].

Herein, it is a report of simple reaction between 3-arylhydrazono-2 , 4 - dioxo - 4 - phenylbutanoates and each of 1-aminoguanidine and semicarbazides as *N,N'*-dinucleophiles with a two-unit linker for synthesis of 5-substituted-6-azauracil derivatives. Instead of the well-known title 2,3,4,5-tetrahydro-1,2,4-triazine-3,5-diones, a shorter 6-azauracil is used for ease of referencing. 5-Substituted-6-azauracils represent interesting derivatives of 1,2,4-triazines from point of view of the syntheses of many further derivatives and biologically active compounds [10,15-17]. In recent years, much effort has been done on the synthesis and biological evaluation of 6-azauracil derivatives due to their possible applications. Many 6-azauracils have been demonstrated to exhibit herbicidal, antiviral, antimicrobial, and anti - inflammatory activities. As well as antimalarial, anticancer, and antiulcer activities have been reported [17].

Experimental

Methods

Melting points were measured in open capillaries and are reported uncorrected. Infrared spectra were measured from 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™-500MHz instrument using TMS as an internal standard. Chemical shifts are reported in ppm. Column chromatography was performed on silica gel L 100/250. Thin-layer chromatography was performed on "Silufol-UV 254" plates.

Materials

Ethyl 2,4-dioxo-4-phenylbutanoate (**1**) was prepared from diethyl oxalate and the acetophenone by known methods [18].

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

3 - a r y l h y d r a z o n o - 2 , 4 - d i o x o - 4 - phenylbutanoates (**2a-d**) have been prepared by the coupling of benzoylpyruvate with aryldiazonium chlorides [11].

Reactions of 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (2a-d) with 1-aminoguanidine and semicarbazides. General Procedure

A mixture of **2a** (0.369g, 1.0 mmol) and each of the *1-aminoguanidine, semicarbazide* and

thiosemicarbazide (1.0 mmol) in ethanol (15 ml), in the presence of AcONa (0.082g, 1.0 mmol) was refluxed for 1-2 h. The solid that separated in each case was filtered off, washed with warm water (3´5) and ethanol (3´5) to give **3a-c**, respectively.

Synthesis of 6-(1-p-Nitrophenylhydrazono-2-oxo-2-phenylethyl)-3-imino-2,3,4,5-tetrahydro-1,2,4-triazin-5-one (3a)

Yellow powder (Yield 78%), m.p. 245-247°C; IR: 3433, 3265, 3176, 1615 (NH) 1662 (C=O, amide), 1630 (C=O, ketone), 1578, 1558 (C=N), 1493 (C=C), 1527, 1338 (NO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) d: 7.04, 7.20 (2H, 2br.s, 2NH, exchangeable with D_2O), 7.25 (2H, d, $^3J_{HH}$=8.9 Hz, $2CH_{ortho}$ of Ph-NH), 7.56 (2H, t, $^3J_{HH}$=7.4 Hz, $2CH_{meta}$ of Ph-CO), 7.66 (H, t, $^3J_{HH}$=7.4 Hz, CH_{para} of Ph-CO), 7.92 (2H, d, $^3J_{HH}$=7.4 Hz, $2CH_{ortho}$ of Ph-CO), 8.19 (2H, d, $^3J_{HH}$=8.9 Hz, $2CH_{ortho}$ of Ph-NO_2), 11.31, 12.72 (2H, 2br.s, 2NH, exchangeable with D_2O) ppm; ^{13}C NMR (DMSO-d_6) d: 114.6, 126.7, 129.0, 130.9, 133.2, 137.9, 140.0, 141.9 (12C, 2Ph), 150.0, 151.2, 154.8 (3C=N), 157.2 (C=O, amide), 190.9 (COPh) ppm.

Synthesis of 6-(1-p-Nitrophenylhydrazono-2-oxo-2-phenylethyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (3b)

Orange powder (Yield 81%), m.p. 248-250°C; IR: 3385, 3246, 3157,1600 (NH), 1692, 1740 (C=O, amide), 1658 (C=O, ketone), 1545 (C=N), 1500 (C=C), 1521, 1338 (NO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) d: 7.25 (2H, d, $^3J_{HH}$=9.0 Hz, $2CH_{ortho}$ of Ph-NH), 7.58 (2H, t, $^3J_{HH}$=7.5 Hz, $2CH_{meta}$ of Ph-CO), 7.69 (H, t, $^3J_{HH}$=7.5 Hz, CH_{para} of Ph-CO), 7.93 (2H, d, $^3J_{HH}$=7.5 Hz, $2CH_{ortho}$ of Ph-CO), 8.15 (2H, d, $^3J_{HH}$=9.0 Hz, $2CH_{ortho}$ of Ph-NO_2), 11.95, 12.40, 12.69 (3H, 3br.s, 3NH, exchangeable with D_2O) ppm; ^{13}C NMR (DMSO-d_6) d: 118.9, 126.2, 129.2, 130.7, 134.9, 138.3, 140.5, 142.0 (12C, 2Ph), 153.0, 155.2 (2C=N), 158.1, 159.3 (2C=O, amide), 190.4 (C=O, ketone) ppm.

Synthesis of 6-(1-p-Nitrophenylhydrazono-2-oxo-2-phenylethyl)-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazin-5-one (3c)

Red powder (Yield 74%), m.p. 253-255°C; IR: 3392, 3258, 3169, 1607 (NH), 1688 (C=O, amide), 1645 (C=O, ketone), 1549 (C=N), 1483 (C=C), 1532, 1341 (NO_2), 1309 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d_6) d: 7.40 (2H, d, $^3J_{HH}$=8.5 Hz, $2CH_{ortho}$ of Ph-NH), 7.63 (2H, t, $^3J_{HH}$=7.3 Hz, $2CH_{meta}$ of Ph-CO), 7.76 (H, t, $^3J_{HH}$=7.3 Hz, CH_{para} of Ph-CO), 8.02 (2H, d, $^3J_{HH}$=7.3 Hz, $2CH_{ortho}$ of Ph-CO), 8.16 (2H, d, $^3J_{HH}$=8.5 Hz, $2CH_{ortho}$ of Ph-NO_2), 11.14, 12.63, 12.98 (3H, 3br.s, 3NH, exchangeable with D_2O) ppm; ^{13}C NMR (DMSO-d_6) d: 118.9, 126.2, 129.2, 130.7, 134.9, 138.3, 140.5, 142.0 (12C, 2Ph), 152.1, 155.8 (2C=N), 157.9 (C=O, amide), 179.4 (C=S), 190.1 (C=O, ketone) ppm.

Results and Discussion

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

It is known that the ethyl-2,4-dioxo-4-phenylbutanoate (**1**) react with aryldiazonium chlorides in water-methanol medium in presence of AcONa to give the corresponding 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (**2a-d**) (Scheme 1) [11].

R= NO$_2$ (**2a**);
R=Cl (**2b**);
R=H (**2c**);
R=CH$_3$ (**2d**).
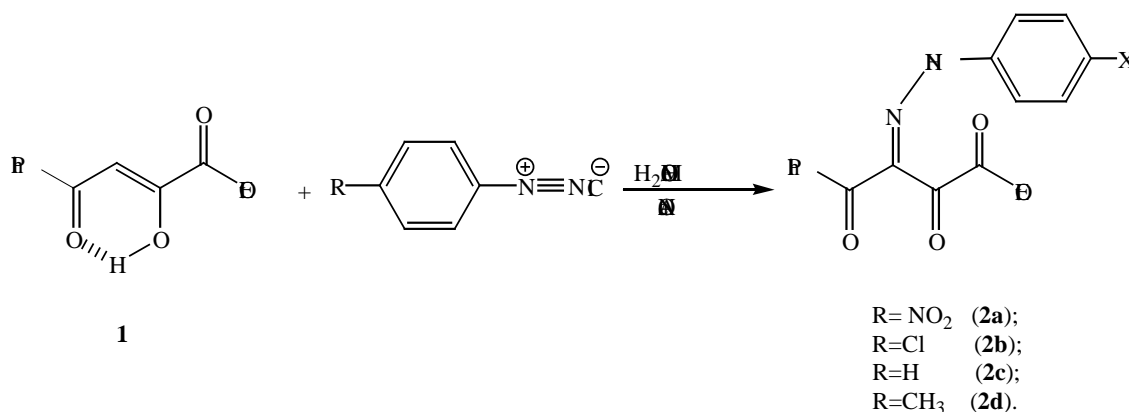
Scheme 1. Preparation of 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates.

Reactions of 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (2a-d) with 1-aminoguanidine and semicarbazides

The ambivalent electrophilic nature of 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (**2a-d**) resides on the presence of three interrelated carbonyl entities, capable of modulating and accentuating the individual electronic character through inductive and tautomeric effects. Embedded within the framework of the 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (**2a-d**) are both the structural features of *a*–keto esters and *b*–diketons (Fig. 1). As a consequence, the chemistry of 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (**2a-d**) may be expected to resonate this dual relationship.
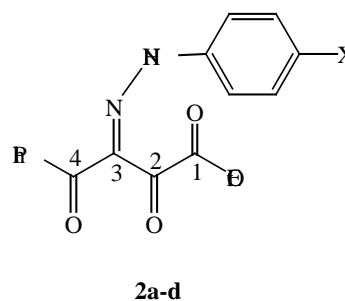

2a-d

Figure 1. Dual nature of 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (**2a-d**).

The selection of potentially applicable *N,N'*-dinucleophiles carrying a two-unit linker is wide in terms of a cyclodehydration sequence on 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (**2a-d**). Considering the acyclic case, the linker may contain both carbon and heteroatom in combination, as well as varying in terms of hybridization, i. e. *C*-sp^3 versus *C*-sp^2. Accordingly, *N,N'*-

dinucleophiles such as ethylene diamines **4**, *a*-amino amides **5** (X=O, S), aminoamidines **6**, semicarbazides **7a** (X=O, S), and aminoguanidines **7b** (X=NH) fall within this category (Figure 2).

For the cyclic *N,N'*-dinucleophiles, carrying a two-unit linker, the number of feasible candidates resonates the acyclic counterpart. In addition, the two amino groups may be joined through an ethene bridge, such as *o*-phenylene diamines **8a** (X=NH) is the case with aromatic systems containing vicinal amines [14].

As in the deliberations for the *N,N'*-dinucleophiles with a two-unit linker, the same general considerations do apply for the *N,O*-, *N,S*-dinucleophiles. In the acyclic *N,O*-, *N,S*-dinucleophiles such as 2-aminoethanols and 2-aminothioethanols, apparently the literature dose not contain any such example. Cyclic *N,O*-, *N,S*-dinucleophiles appended by a two-unit linker are restricted to 2-aminophenols **8b** (X=O) and 2-aminothiophenols **8c** (X=S) [14].
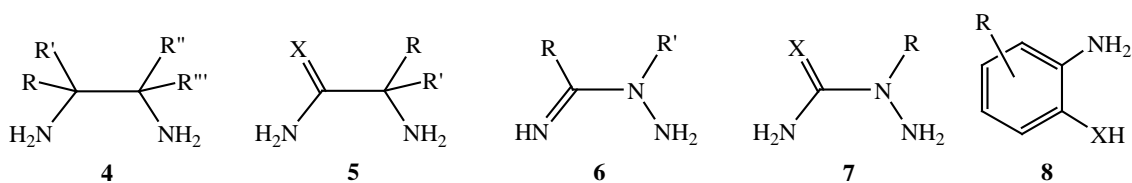

Figure 2. Selection of *N,N'*-dinucleophiles with a two-unit linker.

In contrast to the *N,N'*-dinucleophiles carrying shorter linkers, the product will not be aromatic when condensation involves the *b*–diketo moiety of the 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (**2a-d**). This mode of cyclization will only lead to a labile seven-membered diimine. On the other hand, when condensation takes place across the *a*-keto ester moiety, the resulting annulet may or may not be aromatic.

This mode of cyclization leads however to a stable six-membered ring containing a lactam function. 1-Aminoguanidine, semicarbazide and thiosemicarbazide have been reacted with 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates (**2a-d**) and annulation involved the *a*-keto ester moiety (Scheme 2). Reactions involving 1-aminoguanidine, semicarbazide and thiosemicarbazide in ethanol and in the presence of AcONa lead to 5-substituted-6-azauracil derivatives (**3a-c**). An important feature is the generation of a *g*-related diketonoid motif that may be utilized in a second cyclodehydration step.
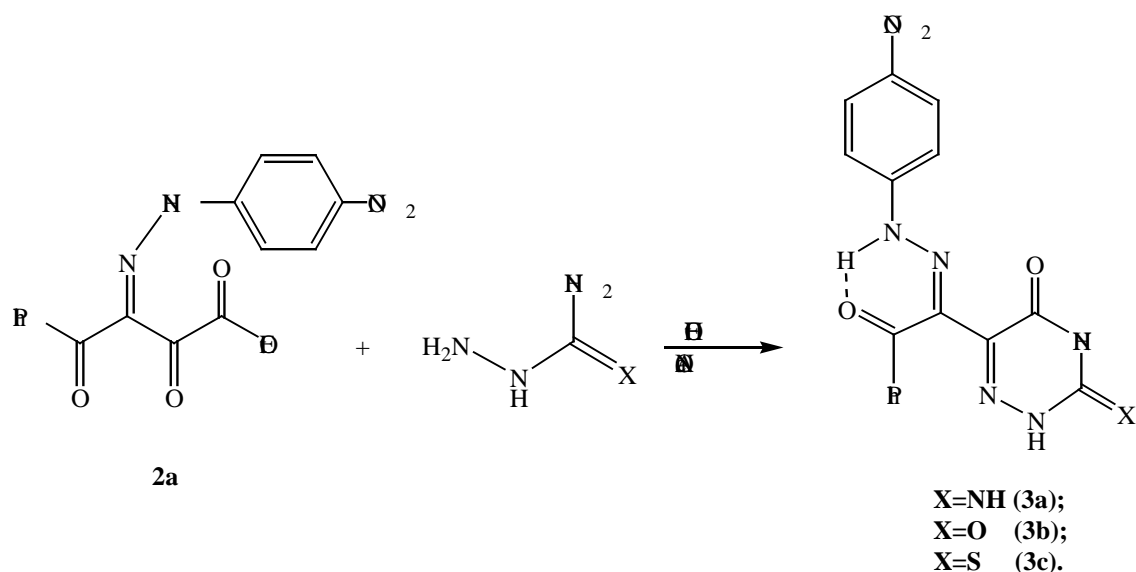
Scheme 2. Reaction of 3-arylhydrazono-2,4-dioxo-4-phenylbutanoates with 1-aminoguanidine and semicarbazides.

Structures **3a-c** was confirmed according to their IR, ^{1}H and ^{13}C NMR spectral data. For example, the IR spectrum of compound **3a** showed eleven characteristic absorption bands at 3433, 3265, 3176, 1615, 1662, 1630, 1578, 1558, 1493, 1527 and 1338 cm^{-1} attributable to the four bands for NH, amidic C=O, ketonic C=O, two bands for C=N, C=C and two bands for NO$_2$ group, functions, respectively. Its ^{1}H NMR spectrum displayed four signals at *d* 7.04, 7.20, 11.31 and 12.72 ppm due to the protons of -NH-C=NH, amidic NH and hydrazonic NH groups, respectively, besides multiplet signals integrated for nine protons at *d* 7.25-8.19 ppm (aromatic protons). The low shielding of the hydrazonic NH proton is the probably participation of the C=O group in an intramolecular hydrogen bond with the NH group. On shaking the compounds **3a** with D$_2$O, the broad band signals at *d* 7.04, 7.20,

11.31 and 12.72 ppm disappeared. The ^{13}C NMR spectrum of **3a** reveled five signals at *d* 150.0, 151.2, 154.8, 157.2 and 190.9 ppm due to the 3C=N, amidic C=O and ketonic C=O carbons, respectively, besides eight signals at *d* 114.6-141.9 ppm attributable to the aromatic carbons.

Conclusion

In the present work, it has been shown that 3-arylhydrazone compounds (**2a-d**) reacted with 1-aminoguanidine and semicarbazides at the *a*-keto ester fragment to form cyclocondensation products that were heterocyclic compounds of 5-substituted-6-azauracil derivatives (**3a-c**).

Acknowledgements

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