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, H, and 13C NMR spectral data - are reported.

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

Introduction
4-Aryl-2,4-dioxobutyrate s 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-
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-benzoazaine, 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$^\text{TM}$-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-arylhydrazono-2,4-dioxo-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 (0.082 g, 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 (NO2) cm-1; 1H NMR (DMSO-\(d_6\)) d: 7.04, 7.20 (2H, 2br.s, 2NH, exchangeable with D 2O), 7.25 (2H, d, \(J_{HH}=8.9\) Hz, 2CH\(_{ortho}\) of Ph-NH), 7.56 (2H, t, \(J_{HH}=7.4\) Hz, 2CH\(_{meta}\) of Ph-CO). 7.66 (H, t, \(J_{HH}=7.4\) Hz, CH\(_{meta}\) of Ph-CO), 8.19 (2H, d, \(J_{HH}=8.9\) Hz, 2CH\(_{ortho}\) of Ph-N02), 11.31, 12.72 (2H, 2br.s, 2NH, exchangeable with D\(_2\)O) ppm; 13C 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 (NO2) cm-1; 1H NMR (DMSO-\(d_6\)) d: 7.25 (2H, d, \(J_{HH}=9.0\) Hz, 2CH\(_{ortho}\) of Ph-NH), 7.58 (2H, t, \(J_{HH}=7.5\) Hz, 2CH\(_{meta}\) of Ph-CO), 7.69 (H, t, \(J_{HH}=7.5\) Hz, CH\(_{para}\) of Ph-CO), 7.93 (2H, d, \(J_{HH}=7.5\) Hz, 2CH\(_{ortho}\) of Ph-CO), 8.15 (2H, d, \(J_{HH}=9.0\) Hz, 2CH\(_{ortho}\) of Ph-NO2), 11.95, 12.40, 12.69 (3H, 3br.s, 3NH, exchangeable with D\(_2\)O) ppm; 13C NMR (DMSO-\(d_6\)) d: 118.9, 126.2, 129.2, 130.7, 134.9, 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.

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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].

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 α–keto esters and β–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.

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 does 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].

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.

Figure 2. Selection of $N,N'$-dinucleophiles with a two-unit linker.
Scheme 2. Reaction of 3-arylhydrazone-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 $-\text{NH-C=NH}$, 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 α-keto ester fragment to form cyclocondensation products that were heterocyclic compounds of 5-substituted-6-azauracil derivatives (3a-c).

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References


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