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Synthesis of 3-oxo-4-benzoyl-1-phenylsuccinimide and its reactions with 1,2-dinucleophiles

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Abstract: The base-catalyzed reaction of ethyl benzoylpyruvate (**1**) with phenyl isocyanate yields the 3-oxo-4-benzoyl-1-phenylsuccinimide (**2**). Reactions of compound **2** with hydrazine and phenylhydrazine afforded the corresponding pyridazine-3,6-dione derivatives **3a,b**. The 3-oxo-4-benzoyl-1-phenylsuccinimide (**2**) reacts with 1-aminoguanidine, semicarbazide and thiosemicarbazide to form the corresponding *N*-phenyl maleimide derivatives **4a-c**, respectively. The analytical data of these compounds - IR, ^{1}H, and ^{13}C NMR spectral data are reported.

Keywords: Benzoylpyruvate; Phenyl isocyanate; 3-Oxo-4-benzoyl-1-phenylsuccinimide; Pyridazine-3,6-dione; *N*-Phenyl maleimide; Hydrazone.

Introduction

In recent years *N*-substituted maleimides and 5-ylidenepyrrole-2(5*H*)-ones have received growing attention, since the former have potential utility as fluorescent reagents for labeling different mutant proteins [1] and the latter have interesting features associated with regioselective synthesis when different substituents are bonded to position 3 and 4 of the skeleton [2-4]. Fused or functionalized maleimides are synthetically useful intermediates for the preparation of polycyclic and fused pyridazine derivatives [5,6]. They are also active as dienophiles in Diels-Alder reactions or as 1,3-dipolar reagents [7-9]. A variety of *N*-substituted maleimides provide Michael adducts in excellent yields [10]. Substituted maleimides are a convenient molecular system for the production of thermally cured and/ or photo cured polymers with a wide range of properties and applications. In addition, substituted maleimides are intermediates in the cross linking reactions of PMR-15, a leading candidate for high temperature resins for aerospace applications [11]. Most of the methods reported for the synthesis of maleimides are based on the reaction of the corresponding maleic anhydride with an amine or ammonium acetate [12,13]. Similarly, the reaction of maleamic acid with triethylamine in either toluene or benzene, yielding *N*-maleoylamino esters, can be considered as being in the same class as the previous reaction [14,15]. A series of *N*-substituted maleimides and *N*-substituted succinimides are active as antimicrobial and antibacterial [16,17]. In addition, a series of 1-methyl-3-phenylmaleimide analogues act as inhibitors of enzyme monoamine oxidase B (MAO-B) [18].

Herein, we report a simple reaction between 3-oxo-4-benzoyl-1-phenylsuccinimide (**2**), derived from the addition of ethyl benzoylpyruvate to phenyl isocyanate, and corresponding 1,2-dinucleophiles leading to pyridazine-3,6-dione (**3a,b**) and *N*-phenyl maleimide (**4a-c**) derivatives (Schemes **1**-**3**).

Results and discussion

*1. Synthesis of 3-benzoyl-4-hydroxy-1-phenyl-2,5-dihydro-1H-pyrrole-2,5-dione (**2**)*

In present work, it has been found that treatment of the acidic methylene compound **1** with phenyl isocyanate in boiling toluene containing a catalytic amount of triethylamine afford 3-benzoyl-4-hydroxy-1-phenyl-2,5-dihydro-1H-pyrrole-2,5-dione (**2**) (Scheme **1**).

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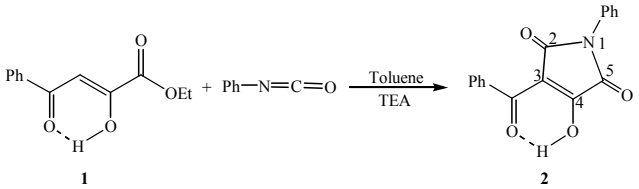
Assignment of the product **2** was based on IR, ^{1}H, and ^{13}C NMR spectral data. The IR spectrum showed absorption bands at 3065, 1750, 1711, 1649 and 1605 cm^{-1} attributable to the enolic OH, two bands for imidic C=O [19], ketonic C=O and C=C, functions, respectively. The low frequency of the ketonic C=O stretching absorption is probably the result of the conjugation of the C=C bond and participation of the C=O group in an intramolecular hydrogen bond with the hydroxyl group of enol fragment. Its ^{1}H NMR spectrum showed a broad singlet at δ 10.70 ppm for the enolic OH proton and multiplet signals integrated for 10 protons at δ 7.30-7.69 ppm (aromatic protons). In the ^{1}H-NMR spectrum of product **2** the resonance signal of a methine proton was absent. The compound **2** could also be readily distinguished using ^{13}C NMR spectroscopy. The ^{13}C NMR spectrum of **2** revealed four signals at δ 170.8, 99.5, 165.0 and 177.6 ppm due to the C^{2}ONPh, =C^3-COPh, =C^4-OH, and C^{5}ONPh carbons, respectively of the maleimide, besides eight signals at δ 126.6-140.7 ppm attributable to the aromatic carbons and a signal at δ 189.6 ppm for the ketonic carbon.



1 2

Scheme 1

*2. Reactions of the compound **2** with 1,2-dinucleophiles*

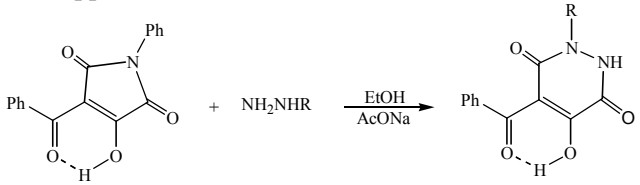
The compound **2** was used as a precursor for synthesis of heterocycles. It has been found that interaction of hydrazine, phenylhydrazine, 1-aminoguanidine, semicarbazide and thiosemicarbazide with **2** generally lead to formation of nucleophile condensation products.

These 1,2-dinucleophiles add to different reaction centers of **2**: either to imidic (atoms C-2 and C-5, see Scheme **2**) or to enolic fragments (atom C-4, see Scheme **3**). The nucleophile condensation pathways and regioselectivity depend on the nucleophile and reaction conditions.

*2.1. Reactions of the compound (**2**) with hydrazines*

It is know that the *N*-alkylphetalimide with hydrazine undergo *Gabriel Synthesis* through the nucleophilic displacement of imidic fragment to give the pyridazine structure [20]. We have found that the compound **2** with hydrazinium sulfate and phenylhydrazine hydrochloride on refluxing in ethanol in the presence of AcONa form the substituted pyridazines-3,6-dione **3a,b** (Scheme **2**).

Structures **3a,b** was assigned on the basis of their IR, ^{1}H, and ^{13}C NMR spectra. For example, the IR spectrum of compound **3b** showed six characteristic absorption bands at 3462, 3056, 1758, 1697, 1640 and 1493 cm^{-1} attributable to the NH, enolic OH, two bands for amimidic C=O, ketonic C=O and C=C, functions, respectively. Its ^{1}H NMR spectrum displayed a broad singlet at δ 3.36 ppm for the NH, OH, and nH_2O protons and multiplet signals integrated for 10 protons at δ 7.30-7.54 ppm (aromatic protons). The ^{13}C NMR spectrum of **3b** revealed four signals at δ 174.4, 164.5, 97.8 and 170.4 ppm due to the CONH, =C-OH, =C-COPh, and CONPh carbons, respectively of the pyridazine, besides eight signals at δ 126.6-141.3 ppm attributable to the aromatic carbons and a signal at δ 187.1 ppm for the ketonic carbon.



2

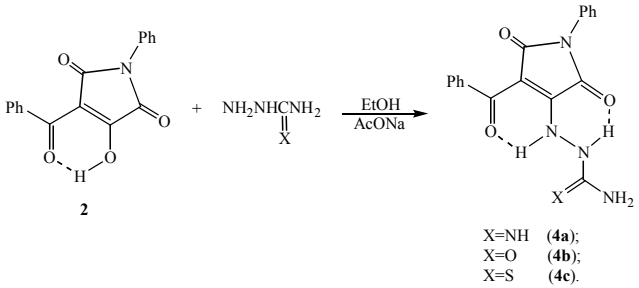
Scheme 2

*2.2. Reactions of the compound **2** with 1-aminoguanidine and semicarbazides*

In our investigation, condensation of the compound **2** with each of 1-aminoguanidine, semicarbazide and thiosemicarbazide in ethanol and in the presence of AcONa yielded the 4-amino-maleimide derivatives **4a-c** (Scheme **3**).

Structures **4a-c** was confirmed according to their IR, ^{1}H and ^{13}C NMR spectral data. The IR and ^{13}C NMR spectra of the isolated products showed the presence of C=N (amidino) in **4a** by absorption band at 1579 cm^{-1} and signal at δ 158.9 ppm, the presence of C=O (semicarbazido) in **4b** by absorption band at 1576 cm^{-1} and signal at δ 157.3 ppm, and the presence of C=S (thiosemicarbazido) in **4c** by absorption band at 1385 cm^{-1} and signal at δ 181.2 ppm. In the ^{1}H NMR spectra of **4a-c** we observed signals for -NH-NH- protons at δ 10.49-10.55 and 11.12-11.41 ppm. The low shielding of the -NH-NH- protons is probably the participation of the C=O groups in an intramolecular hydrogen bond with the NH groups (Scheme **3**). Their ^{1}H NMR spectra displayed signals at δ 7.07, 5.85 and 7.46 ppm due to the protons of NH=C-NH_2, $CONH_2$ and $CSNH_2$ groups, respectively. On shaking the compounds **4a-c**

with D_2O, the broad band signals attributable to NH, NH_2 disappeared.



Scheme 3

Conclusion

We report a facile route for the formation of pyridazine-3,6-dione and *N*-phenyl maleimide derivatives based on 3-oxo-4-benzoyl-1-phenylsuccinimide.

Experimental

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^{TM}-500MHz instrument using TMS as an internal standard and the chemical shifts are reported in ppm. Thin-layer chromatography was performed on "Silufol-UV 254" plates.

1. Material

Ethyl 2,4-dioxo-4-phenylbutanoate (**1**) was prepared from diethyl oxalate and acetophenone by known methods [21].

*2. Synthesis of 3-benzoyl-4-hydroxy-1-phenyl-2,5-dihydro-1H-pyrrole-2,5-dione (**2**)*

A mixture of compound **1** (2.20 g, 10 mmol) and phenyl isocyanate (1.19 g, 10 mmol) in toluene (25 ml) containing a few drops of TEA was refluxed for 3h. The toluene was evaporated, the residue was recrystallized from isopropyl alcohol, and dried.
Greenish crystal (Yield 53%), m.p. 143-145°C; IR: 3065 (OH, enol), 1750, 1711 (C=O, imide), 1649 (C=O, ketone), 1605 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.30 (2H, d, $^3J_{HH}$=8.7 Hz, $2CH_{ortho}$ of C_6H_5-N), 7.38-7.47 (6H, m, 2Ph), 7.69 (2H, d, $^3J_{HH}$=8.5 Hz, $2CH_{ortho}$ of C_6H_5-CO), 10.70 (1H, br.s, OH) ppm; ^{13}C NMR ($CDCl_3$) δ: 99.5 (=C-COPh), 126.6, 127.0, 127.4, 128.5, 128.6, 130.4 (10C, 2Ph), 132.3 (C_{ipso} of Ph-CO), 140.7 (C_{ipso} of Ph-N), 165.0 (=C-OH), 170.8 (C^2ONPh), 177.6 (C^5ONPh), 189.6 (COPh) ppm.

*3. Reactions of the compound **2** with 1,2-dinucleophiles. General Procedure*

A mixture of **2** (0.292g, 1.0 mmol) and each of the 1,2-dinucleophiles (hydrazinium sulfate, phenylhydrazine hydrochloride, 1-aminoguanidinium hydrogen carbonate, semicarbazide hydrochloride, and thiosemicarbazide) (1.0 mmol) in ethanol (15 ml), in the presence of AcONa (0.082g, 1.0 mmol) was refluxed for 2-4 h. The solid that separated in each case was filtered off and was crystallized from ethanol to give **3a,b** and **4a-d**, respectively.

*4-Benzoyl-5-hydroxy-1,2,3,6-tetrahydropyridazine-3,6-dione (**3a**)*

White crystal (Yield 33%), m.p. 241-243°C; IR: 3437, 3182 (NH), 3066 (OH, enol), 1733 (C=O, amide), 1636 (C=O, ketone), 1606 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 3.38 (br.s, 2NH, OH, nH_2O), 7.32 (2H, t, $^3J_{HH}$=7.6Hz, $2CH_{meta}$ of Ph), 7.40 (1H, t, $^3J_{HH}$=7.3Hz, CH_{para} of Ph), 7.53 (2H, d, $^3J_{HH}$=7.4Hz, $2CH_{ortho}$ of Ph) ppm; ^{13}C NMR (DMSO-d_6) δ: 99.9 (=C-COPh), 127.0, 128.3, 131.1 (5C, Ph), 132.7 (C_{ipso} of Ph), 165.4 (=C-OH), 171.4 (CONH), 177.7 (CONH), 189.8 (COPh) ppm.

*5-Benzoyl-4-hydroxy-1-phenyl-1,2,3,6-tetrahydropyridazine-3,6-dione (**3b**)*

Yellowish crystal (Yield 50%), m.p. 198-200°C; IR: 3462 (NH), 3056 (OH, enol), 1758, 1697 (C=O, amide), 1640 (C=O, ketone), 1606 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 3.36 (br.s, NH, OH, nH_2O), 7.30 (2H, d, $^3J_{HH}$=8.0 Hz, $2CH_{ortho}$ of Ph-N), 7.32-7.45 (6H, m, 2Ph), 7.54 (2H, d, $^3J_{HH}$=7.5 Hz, $2CH_{ortho}$ of Ph-CO) ppm; ^{13}C NMR (DMSO-d_6) δ: 97.8 (=*C*-COPh), 126.6, 126.8, 127.1, 128.3, 128.4, 129.8 (10C, 2Ph), 132.9 (C_{ipso} of Ph-CO), 141.3 (C_{ipso} of Ph-N), 164.5 (=C-OH), 170.4 (CONPh), 174.4 (CONH), 187.1 (COPh) ppm.

*3-Benzoyl-4-(2-amidino)hydrazino-1-phenyl-2,5-dihydro-1H-pyrrole-2,5-dione (**4a**)*

Yellow crystal (Yield 60%), m.p. 199-201°C; IR: 3421, 3341, 3153, 1598 (NH), 1749 and 1707 (C=O, imide), 1622 (C=O, ketone), 1605 (C=C), 1579 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 7.07 (3H, br.s, NH=C-NH_2, exchangeable with D_2O), 7.31 (2H, d, $^3J_{HH}$=7.0 Hz, $2CH_{ortho}$ of Ph-N), 7.34-7.45 (6H, m, 2Ph), 7.56 (2H, d, $^3J_{HH}$=7.0 Hz, $2CH_{ortho}$ of Ph-CO), 10.52, 11.36 (2H, 2br.s, 2NH, exchangeable with D_2O) ppm; ^{13}C NMR (DMSO-d_6) δ: 97.7 (=C-COPh), 126.4, 126.7, 127.0, 128.2, 128.3, 129.7 (10C, 2Ph), 133.0 (C_{ipso} of

Ph-CO), 141.4 (C_{ipso} of Ph-N), 158.9 (C=N), 164.5 (=C-NH), 170.2 (C^2ONPh), 174.2, (C^5ONPh), 186.9 (COPh) ppm.

*3-Benzoyl-4-semicarbazido-1-phenyl-2,5-dihydro-1H-pyrrole-2,5-dione (**4b**)*

Yellow crystal (Yield 66%), m.p. 188-190°C; IR: 3443, 3328, 3288, 1595 (NH), 1759 and 1696 (C=O, imide), 1661 (C=O, ketone), 1610 (C=C), 1576 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 5.85 (2H, br.s, NH_2, exchangeable with D_2O), 7.32 (2H, d, $^3J_{HH}$=7.6 Hz, $2CH_{ortho}$ of Ph-N), 7.41-7.66 (6H, m, 2Ph), 7.71 (2H, d, $^3J_{HH}$=7.8 Hz, $2CH_{ortho}$ of Ph-CO), 10.49, 11.12 (2H, 2br.s, 2NH, exchangeable with D_2O) ppm; ^{13}C NMR ($CDCl_3$) δ: 99.6 (=C-COPh), 125.9, 126.4, 127.3, 128.0, 128.5, 130.7 (10C, 2Ph), 131.7 (C_{ipso} of Ph-CO), 140.0 (C_{ipso} of Ph-N), 157.3 ($CONH_2$), 165.7 (=C-NH), 170.3 (C^2ONPh), 177.8 (C^5ONPh), 190.5 (COPh) ppm.

*3-Benzoyl-4-thiosemicarbazido-1-phenyl-2,5-dihydro-1H-pyrrole-2,5-dione (**4c**)*

Yellow crystal (Yield 75%), m.p. 158-160°C; IR: 3365, 3268, 3176,1597 (NH), 1747 and 1711 (C=O, imide), 1648 (C=O, ketone), 1608 (C=C), 1385 (C=S) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.27 (2H, d, $^3J_{HH}$=8.0 Hz, $2CH_{ortho}$ of Ph-N), 7.46 (2H, br.s, NH_2, exchangeable with D_2O), 7.31-7.44 (6H, m, 2Ph), 7.67 (2H, d, $^3J_{HH}$=7.9 Hz, $2CH_{ortho}$ of Ph-CO), 10.55, 11.41 (2H, 2br.s, 2NH, exchangeable with D_2O) ppm; ^{13}C NMR ($CDCl_3$) δ: 100.0 (=C-COPh), 127.0, 127.4, 127.8, 128.9, 129.0, 130.9 (10C, 2Ph), 132.7 (C_{ipso} of Ph-CO), 141.1 (C_{ipso} of Ph-N), 165.4 (=C-NH), 171.2 (C^2ONPh), 175.8 ($CSNH_2$), 178.0 (C^5ONPh), 190.1 (COPh) ppm.

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