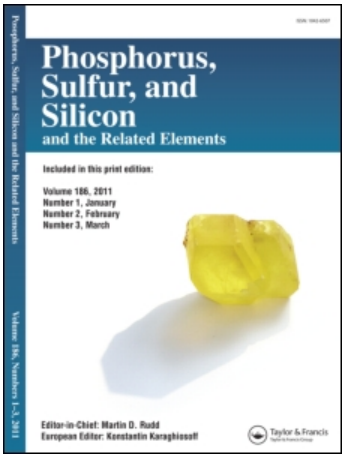

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Conversions of 2-(2-Oxo Cyclohexylcarbonyl)Benzoic Acid Derivatives to Pyrazolo[5], [1], [2], [3], [4], [5], [6], [7], [8], [9], [10]]Isoindole and Pyrimidine Rings

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Conversions of 2-(2-Oxo Cyclohexylcarbonyl)Benzoic Acid Derivatives to Pyrazolo[5,1-a]Isoindole and Pyrimidine Rings

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Phtalic acid derivative of o-methylcarboxybenzoylchloride readily acylates N(1-cyclohexenyl) morpholine and is likely to acylate other enamines along the classic path to 1,3-diketones. It is a convenient route towards o-(1-(1,3-diketone)) derivatives of benzoic acid, which are precursors of o-(heteroaryl)-benzoic acids. Further conversions with hydrazines and amidines lead to pyrazolo[5,1-a]isoindole and pyrimidine rings respectively. The structures of the obtained compounds were confirmed by X-ray structure determinations.

Keywords 1,3-Diketones; enamines; O-acylated enols; pyrazolo[5,1-a]isoindoles; pyrimidines; X ray diffraction analysis

INTRODUCTION

Properly functionalized β-diketones may lead to heterocyclic compounds with desired functional groups. Their applications are numerous, so we limited the examples to very recent results, i.e. the synthesis of fluorescein derivatives,[1] of UVA absorbers,[2] and protein kinase inhibitors (balanol).[3]

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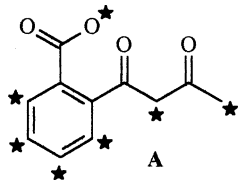
The literature shows a few scattered examples of synthesis of such β-diketones,[4–8] but the reported yield is low. Thus, we decided to test other approaches to obtain compounds possessing the sub-structure presented below as a source of o-(heteroaryl)-benzoic acids, precursors of nitrogen heterocycles.



A

Among the targeted series, pyrazolo[5,1-a]isoindole derivatives are interesting, but not yet extensively covered in the literature in spite of their described biological activity.[9] Thus, reactions with dienophiles seem not to be studied despite unusual results obtained for other isoindole derivatives with bridged nitrogen and azine or azole ring annelated at 1,2 positions. An earlier synthesis of 8-oxo-8H-pyrazolo[5,1-a]isoindole-2,3-dicarboxylic acid dimethyl ester from N-aminophtalimide(2-amino-isoindole-1,3-dione) and dimethylacetylene dicarboxylate ester[10] was reported. The obtained 2-aryl-1,3a-dihydro-pyrazolo[5,1-a]isoindol-8-ones and their dehydrated derivatives 2-aryl-pyrazolo[5,1-a]isoindol-8-ones showed herbicidal and plant growth regulating activity.[11] The synthesis of 2-aryl-8H-pyrazolo[5,1-a]isoindoles start from *o*-(ω-(β-diketone)) derivatives A which were obtained by condensation of phtalic anhydride and arylmethylketones. Chupp et al.[8] suggested a Claisen condensation of aromatic ortho-diesters with methylketones to generate derivatives of A, though this reaction was reported to be limited to electron-deficient and aza-analogs of aromatic ortho-diesters. Additionally, such reactions normally lead to 2-acylindanediones-1,3[12] and the desired compounds A are side products.

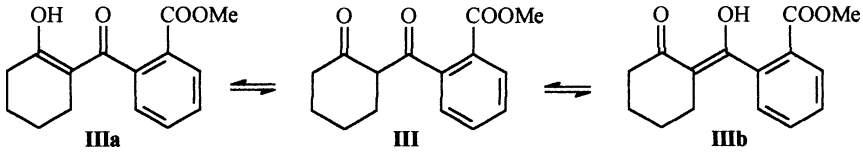
In contrast to "simple" β-diketones, such substrates are scarcely studied due to the lack of efficient synthetic approaches. Thus, the aim of this paper is to attempt to develop new synthetic methods for A and use it as precursor for the synthesis of pyrazolo[5,1-a]isoindoles or to other nitrogen heterocycles, like pyrimidines.

RESULTS AND DISCUSSION

Preparation of the β-Diketone

This study addressed the well-known reaction of acylchlorides (o-methyl carboxybenzoylchloride **I** here) with enamines.

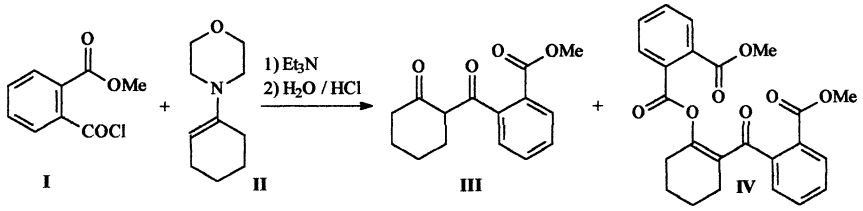
We prepared **I** and reacted it with N-(1-cyclohexenyl)morpholine **II**. Along with the expected β-diketone **III** we isolated with a good yield another compound which was attributed to **IV** (Scheme 2). The separation of the obtained compounds was achieved by crystallization because **III** failed to be distilled in vacuum (at 0.005 torr it distilled with significant decomposition). The structures of **III** and **IV** were established with PMR, C^{13}-NMR and X-ray structural analysis. The β-diketone **III** may exist in the tautomeric forms of Scheme 1 as seen in $CDCl_3$ solution in PMR whereas it adopts the **IIIa** one in the crystal state.



IIIa **III** **IIIb**

SCHEME 1

The use of 50% excess of enamine did not prevent the formation of **IV** and did not reduce its yield significantly. The formation of such compounds during an enamine acylation seems to have not been described earlier in the chemical literature. This is probably due to the distillation generally used in the final step of the previous synthetic method, which leads to the loss of such side compounds.



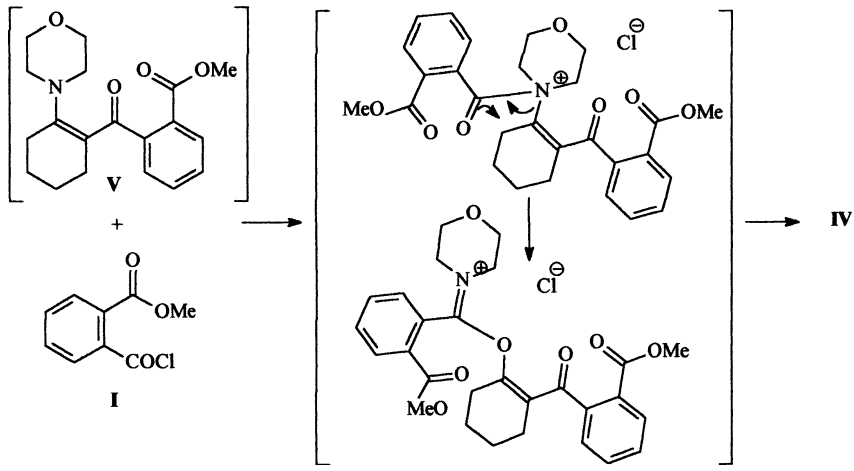
I **II** **III** **IV**

SCHEME 2

We think that **IV** arise from Scheme 3, where **V** is one of the known intermediates of the reaction above (Scheme 2).

If pyridine was used instead of triethylamine then only **IV** was isolated, probably because of the weaker basicity of pyridine, which led to the protonation and thus the deactivation of half of the enamine **II**. This left 50% excess of chloroanhydride **I** in the reaction mixture, which react with the intermediate **V**.

The compound **III** readily formed crystals of diketonates with Cu^{2+} and Fe^{3+} ions of green and red color respectively, but failed to react in

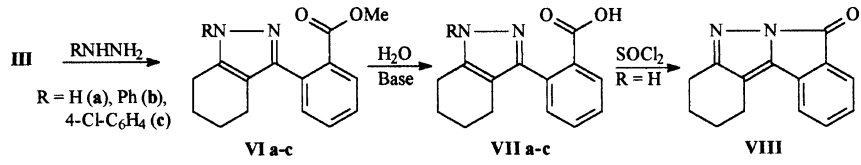


SCHEME 3

similar conditions with Ni^{2+} and Co^{2+}, while reaction with $Ni(OAc)_2$ in presence of ammonia or triethylamine lead to a red solution, probably due to a flat square coordinated Ni diketonate formation.

Reaction of III with Hydrazines

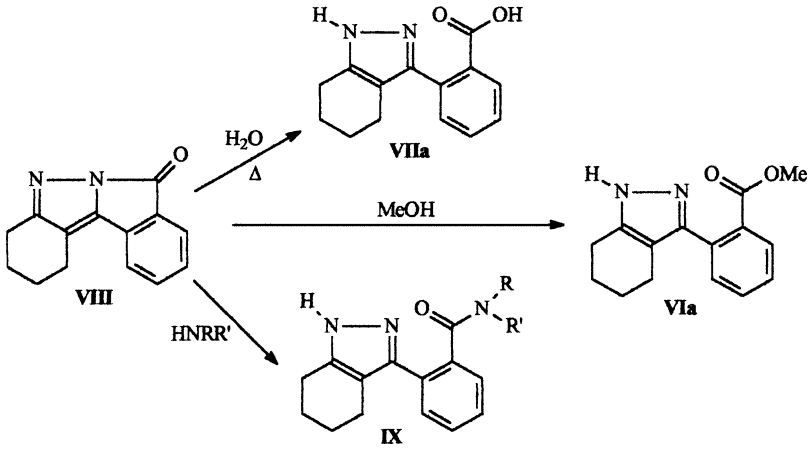
The compound **III** react easily with an equimolecular amount of hydrazine acetate in presence of acetate buffer in water/alcohol solution to give the pyrazole ring **VI** (Scheme 4). But it did not react with phenylhydrazine while boiling in isopropanol for 3 h. The reaction of **III** with arylhydrazines would require harder conditions, thus it was reacted with phenylhydrazine and p-chlorophenylhydrazine in boiling isopropanol/acetic acid yielding then the pyrazoles **VI**. The esters **VI** are easily hydrolyzed into acids **VII**. Moreover, in the case where R=H, the acid reacted with dehydrating agents to give the pyrazoloisoindolone **VIII** which was also identified by X ray structure determination (see below).



SCHEME 4

Reactions of VIII

Compound **VIII**, [5,6,7,8-tetrahydro-9,9a-diaza-indeno[1,2-a]inden-10-one] is a representative of the isoindoloindazole topological system, but its π-electronic system is similar to that of pyrazoloisoindolone, so we treated it as a derivative of the latter. It could be also considered as N-acylpyrazole, so it is expected to react with nucleophiles by a lactame ring cleavage. It reacted with hot water, methanol, and amines giving the corresponding derivatives of the acid **VIIa**, i.e. compounds **VIa**, **VIIa** itself, and **IX** (Scheme 5) respectively.



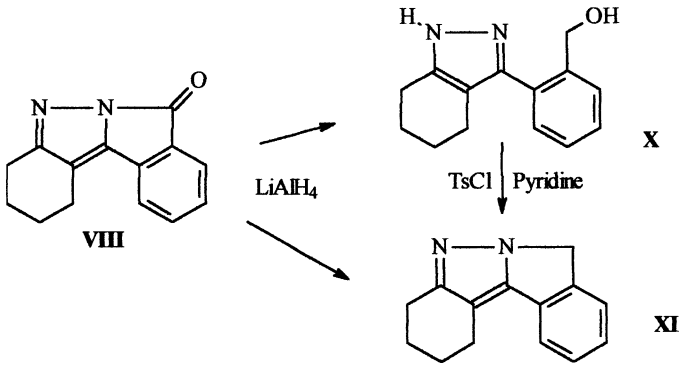
SCHEME 5

We also reacted **VIII** with $LiAlH_4$ in ether to obtain a mixture of two products (Scheme 6). Their PMR-spectrum contain two singlets at 4.51 and 5.16 ppm with an intensity ratio near to 6:1. The mixture is treated by TsCl in pyridine and after work-up a 8H-pyrazoloisoindole derivative like 1,3,4,7-tetrahydro-2H-isoindolo[2,1-b]indazole **XI** is obtained. Its PMR-spectrum contains a unique singlet at 4.51 ppm. A probable explanation is the formation of both isoindole **XI** and a benzyl alcohol derivative **X** corresponding to the singlet at 5.16 ppm. The hydroxy group of **X** activated with TsCl become capable to attack the pyrazole ring, thus forming **XI**.

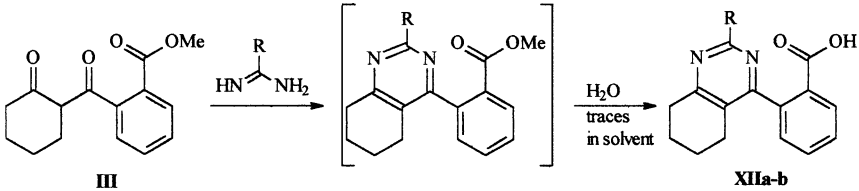
These compounds are novel members of previously known biologically active series.[13]

Reaction of III with Amidines

We studied the reaction of **III** with formamidine and benzamidine which lead to the formation of a pyrimidine ring. Unexpectedly, this formation



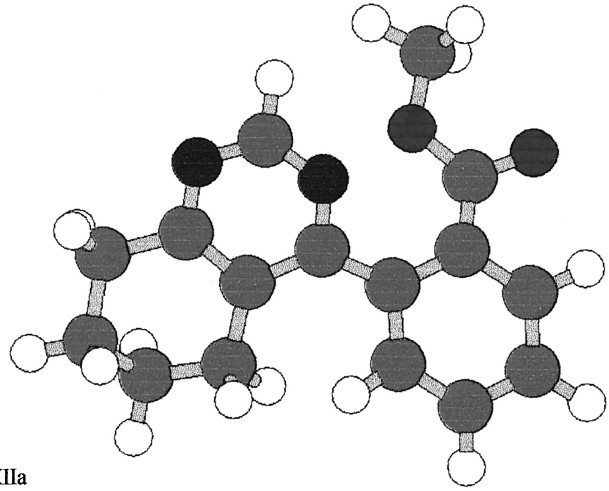
SCHEME 6



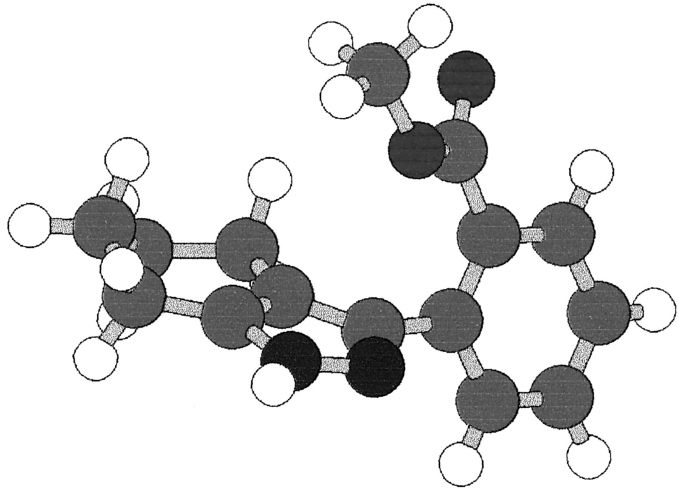
SCHEME 7

is accompanied by a spontaneous hydrolysis of the ester group. Finally, the isolated compound is the acid **XII** (Scheme 7).

The hydrolysis of the intermediate can be explained by a base catalysis by one nitrogen atom of the pyrimidine ring. But the pyrazole ring also has a nitrogen with lone electron pair in similar position and no spontaneous hydrolysis occurs in this case, despite similar reaction conditions. The preparation of 2-pyridin-2-yl-benzoic acid ethyl ester was also reported and the ester group appeared to be stable in similar conditions.[14] To have a better insight of this hydrolysis, we studied the geometric features of the methyl ester of **XIIa** optimized by molecular modeling, and compared it to the results obtained with **VIa**. The molecular mechanics calculations were done with the Hyperchem 5.01 program (1996) from Hypercube Inc. using the MM+ force field, the lowest energy structures were obtained after a molecular dynamics research and the final geometry was checked with a semi-empirical calculation (AM1 hamiltonian). As shown in Figure 1, the most striking difference is the N/OMe distance, which is equal to 2.26 Å for the methyl ester of **XIIa**, and 3.33 Å for **VIa**. The former distance is somewhat shorter (#0.6 Å) than the sum of the Van der Waals radii (O = 1.4 and N = 1.5 Å)



Methyl ester of XIIa



VIa

FIGURE 1 Calculated structures showing the greater distance N-O in **VIa** than in the methyl ester of **XIIa** (3.33 versus 2.26 Å respectively).

indicating a large interaction which may explain in this case the base assistance to the hydrolysis.

X Ray Structural Analysis of Compounds III, IV, and IX

General Features

Reflection data were collected at low temperature using an oil-coated shock-cooled crystal on a Bruker-AXS CCD 1000 diffractometer. The

structures were solved by direct methods (SHELXS-97)[15] and parameters were refined using the least-squares method on F^2.[16]

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 221048, 221047, and 237640 for **III**, **IV** and **VIII** respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax:(+44)-1223-3360-33; E-mail:deposit@ccdc.cam.ac.uk].

*Crystal data for **III**:* $C_{15}H_{16}O_4$, M = 260.28, monoclinic, $P2_1/n$, a = 8.511(2) Å, b = 14.594(3) Å, c = 10.489(2) Å, β = 92.847 (4)°, V = 1301.1(4)Å^3, Z = 4, ρ_{calcd} = 1.329 Mgm^{-3}, *F (000)* = 552, λ = 0.71073 Å, T = 173(2)K, μ (Mo_{Ka}) = 0.096 mm^{-1}, crystal dimensions 0.3 × 0.4 × 0.5 mm^3, 7520 reflections (2671 independent, R_{int} = 0.0333) were collected, R_1 (for I > 2σ(I)) = 0.0404 and wR_2 (all data) = 0.1085 with $R_1 = \Sigma|F_o| - |F_c|/\Sigma|F_o|$ and $wR_2 = w(\Sigma w\,(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2)^{0.5}$.

The most interesting results on this structure (Figure 2) is that it adopts the **IIIa** configuration in the solid state (see Scheme 1). Thus, the enolic form on the cyclohexyl ring render the C12-C11-C10-C15 moiety planar, the C10-C11 bond shorter (1.363 Å as compared to C9-C11 = 1.437 Å) meanwhile the C10-O4 bond correspond to a single one (1.331 Å). The enolic H form a strong H-bond with O1 (distance O1-O4 only 2.497 Å) with an angle of 153°. Additionally, the C9-C11 bond (1.437 Å) is intermediate between the double C10-C11 (1.363 Å) and the single C9-C6 (1.505 Å) ones.

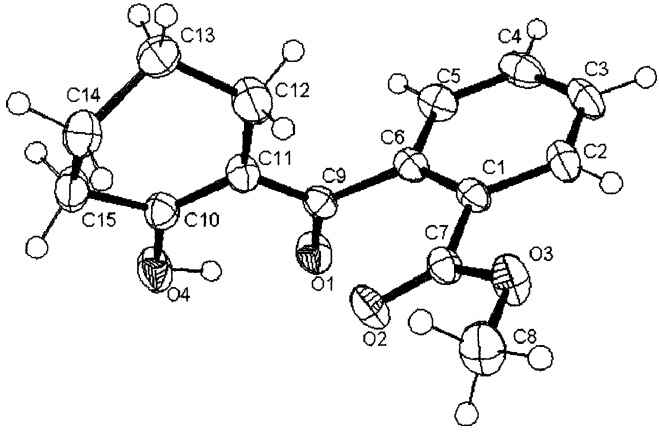


FIGURE 2 ORTEP III for Windows[17] drawing of the X Ray structure of **III**.

Crystal data for ***IV****:* $C_{24}H_{22}O_7$, M = 422.42, monoclinic, $P2_1/n$, a = 8.4305(5) Å, b = 22.693(1) Å, c = 11.0423(7) Å, β = 101.032 (1)°, V = 2073.5(2) Å^3, Z = 4, ρ_{calcd} = 1.353 Mgm^{-3}, F *(000)* = 888, λ = 0.71073 Å, T = 173(2) K, μ (Mo_{Ka}) = 0.100 mm^{-1}, crystal dimensions 0.5 × 0.5 × 0.7 mm^3, 12200 reflections (4246 independent) were collected, R_1 (for I > 4σ(I)) = 0.0336 and wR_2 = 0.0899 (all data) with $R_1 = \Sigma|F_o| - |F_c|/\Sigma|F_o|$ and $wR_2 = (\Sigma w\ (F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2)^{0.5}$.

Concerning this structure, it is interesting to notice that its configuration confirms the synthetic pathway whereas in the crystal the compact arrangement is due to strong inter- and intramolecular interactions. The intermolecular ones are mainly due in part to O1-H1 interactions (2.491 Å, −0.23 Å % sum VdW) and to O6-H11(2.517 Å) between different neighboring asymmetric units, creating a polymeric network in the crystal. Other noticeable intermolecular interactions are observed with O4–H8 (2.625 Å) and O6–H24B (2.521 Å).

Concerning the intramolecular interactions and the geometrical features of **IV**, one may consider that it is an enol ester of **III** with the orthomethylester benzoic acid. The position of the two terminal aromatic methylester groups is interesting, one (C16-O3-C23) is nearly perpendicular to the aromatic plane (dihedral angle C11-C9-C16-O3 = 92.8°) whereas the other lies in quite a plane (dihedral angle C15-C4-C7-O5 = −15.9°). This is due to the strong internal interaction between O4 and C10 and C21, 2.787 and 2.713 Å respectively, i.e. −0.43 and −0.51 Å % sum VdW, and also with O1-C16, 2.683 Å, −0.53 Å % sum VdW (Figure 3).

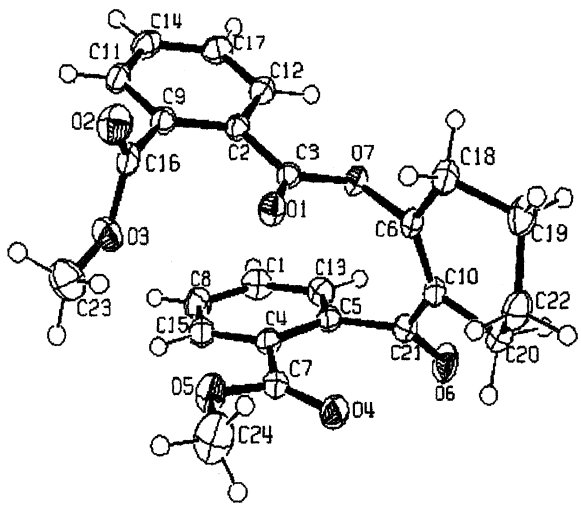


FIGURE 3 ORTEP III for Windows drawing of the X Ray structure of **IV**.

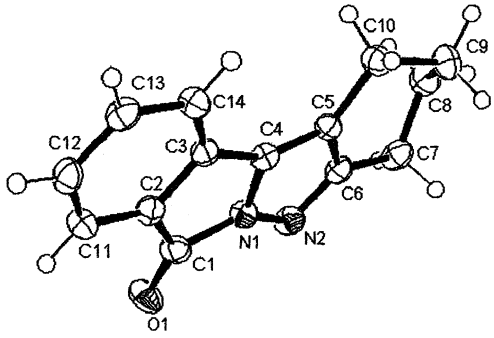


FIGURE 4 ORTEP III for Windows drawing of the X Ray structure of **VIII**.

*Crystal data for **VIII**:* $C_{14}H_{12}N_2O$, M = 224.26, monoclinic, $P2_1/c$, a = 10.90(2) Å, b = 13.92(3) Å, c = 7.37(1) Å, β = 106.97 (5)°, V = 1070(3) Å^3, Z = 4, ρ_{calcd} = 1.392 Mgm^{-3}, *F(000)* = 472, λ = 0.71073 Å, T = 193(2)K, μ (Mo_{Ka}) = 0.090 mm^{-1}, crystal size 0.2 × 0.5 × 0.7 mm^3, 6191 reflections (2156 independent) were collected., R_1(for $I > 4\sigma(I)$) = 0.0494 and wR_2 = 0.1062 (all data) with $R_1 = \Sigma|F_o| - |F_c|/\Sigma|F_o|$ and $wR_2 = (\Sigma w\,(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2)^{0.5}$ (Figure 4).

The structure is entirely planar with the exception of the cyclohexyl ring which present a C7-C8-C9 flap. The C8 atom lies at 0.5 Å over the mean plane formed by the 16 heavy atoms whereas the C9 one is under the plane (−0.265 Å). The other atoms do not deviate for more than 0.09 Å. The C4-C5 bond (1.367 Å) and the C6-N2 one (1.334 Å) are slightly longer than expected for formal double bonds (1.34 and 1.32 Å respectively)[18] whereas N1-N2 (1.374 Å) is relatively short, this may be due to a delocalization over the five membered diaza cycle. This is also observable for C5-C6 (1.437 Å) shorter than a formal C-C single bond (1.46 Å) in this environment.

Concerning the intermolecular interactions, only a weak non classical H bond between H11 and O1 is noticeable (2.70 Å) and in the packing, the planes of alternated molecules (with respect of the C=O orientation) are separated by about 3.6 Å.

CONCLUSIONS

The reaction of o-methylcarboxybenzoylchloride **II** with enamines is a convenient route toward β-diketones like o-(ω-(β-diketone)) derivatives of benzoic acid, which might give rise to heterocycles with o-carboxylphenyle radical in corresponding position. Prepared in this manner 2-(2-oxocyclohexylcarbonyl)benzoic acid methyl ester

was studied and its reactions with hydrazines and amidines yielded pyrazole and pyrimidine rings respectively. The obtained derivative of o-pyrazolobenzoic acid was turned into pyrazolo[5,1-a]isoindole derivatives.

Experimental

Preparation of 2-Chlorocarbonyl-benzoic Acid Methyl Ester I

90 g (0.5 m) of o-methylcarboxybenzoic acid were dissolved in 100 mL of toluene and the obtained solution was filtered from traces of phtalic acid. 50 mL (∼50% excess) of thionyl chloride and then one droplet of DMFA were added to the toluene solution. Vigorous endothermic reaction followed by intensive emission of gases started. When the emission almost stopped, reaction mixture was placed in a bath at 60°C for an hour. When reaction was completed, all the volatile part was thoroughly removed with a rotary evaporator at 60–80°C thus leaving **I** as viscous yellow oil (100%) which was then used in reaction with enamine.

Synthesis of 2-(2-Oxo-cyclohexanecarbonyl)-benzoic Acid Methyl Ester III and Phthalic Acid 1-[2-(2-Methoxycarbonylbenzoyl)-cyclohex-1-enyl] Ester 2-Methyl Ester IV

Acylation of enamine with the chloranhydride[19]*.* Freshly distilled enamine **II** (85 mL, slightly more than 0.5 mol) was placed in a round flask, dry toluene (200 mL) and triethylamine (85 mL, 20% excess) were added and the flask was placed in a bath at 35°C with magnetic stirring. A solution of freshly prepared chloranhydride in dry toluene (100 mL) was placed in a dropper funnel and all the system was connected to atmosphere through a desiccating system. The chloranhydride solution was added slowly with intensive stirring of the reaction mixture, which first became yellow and then, when approximately 2/3 of chloranhydride was added, sharply changed to red. A precipitate (triethylamine hydrochloride) was formed during the addition. The reaction mixture was stirred at 35°C for an hour and then let to stand overnight at room temperature. Then 100 mL of 10% aqueous solution of HCl was slowly added to the red reaction mixture and all was refluxed for 30 min and cooled. The red colored toluene layer was separated, and the aqueous layer was extracted twice with toluene (100 mL), the last extraction gave a clear toluene layer. All toluene fractions were gathered, washed successively with water, 5% sodium bicarbonate, water and then dried over Na_2SO_4. Toluene was removed with a rotary evaporator giving a

crude mixture of **III**, **IV**, and tracks of cyclohexanone in form of red viscous oil.

Separation of III and IV by Column Chromatography

3 g of the crude mixture was passed through 100 mL of silica gel 40–100 mesh with chloroform as eluent. Fractions containing **IV** and **V** were collected successively. After evaporation of chloroform pure **III** and **IV** were obtained. **III** formed big white crystals of slight green shade, **IV** formed big white crystals of slight yellow shade.

Separation of III and IV by Crystallization

Several crystals of **III** were added into a crude mixture of products, which then was put in a refrigerator for a week. This lead to crystallization of **III**. Remaining oil was decanted from crystals of **III**, which then were washed with several small portions of toluene (this did not lead to a noticeable dissolving). Remaining oil and toluene layer were joined, toluene was removed with a rotary evaporator, seed crystals of **IV** were added to the resulting oil and all was put again in a refrigerator for a week. This, in turn, lead to crystallization of **IV**. Obtained crystals of **IV** were separated from remaining small quantities of oil and, like **III**, washed with several small portions of toluene. Obtained samples **III** and **IV** were pure, according to TLC.

Reaction of III with Hydrazine: Preparation of 2-(4,5,6,7-Tetrahydro-1(2)H-indazol-3-yl)-benzoic Acid Methyl Ester VI

Hydrazine sulfate (8 g, 0.06 mol) and sodium acetate trihydrate (32 g, 0.24 mol) were dissolved in 100 mL of hot water and the resulting solution was added to a solution of **III** (10.4 g, 0.04 mol) in i-PrOH (100 mL). The resulting mixture was refluxed for 2 hours, cooled and carefully poured into 100 mL of water with 100 mL of saturated solution of sodium bicarbonate. White precipitate was formed. It was filtered off, carefully washed with several portions of saturated sodium bicarbonate solution, water, small quantity of cooled methanol and crystallized from methanol yielding white crystals of **VIa–c** (8.1 g, 78%).

Reaction of III with Phenylhydrazine

III and freshly distilled phenylhydrazine were heated in isopropanol for 3 hours. Then, the reaction mixture was poured into water. Dark-red oil was formed, separated, extensively washed with water, and then triturated with MeOH to give **XIb**.

Reaction of III with p-Chlorphenylhydrazine: Preparation of 2-[1-(4-Chloro-phenyl)-4,5,6,7-tetrahydro-1H-indazol-3-yl]-benzoic Acid Methyl Ester and 2-[1-(4-Chloro-phenyl)-4,5,6,7-tetrahydro-1H-indazol-3-yl]-benzoic Acid XIc

III and p-chlorphenylhydrazine were heated in 50 mL of i-PrOH and 20 mL of acetic acid for 2 hours. Then the reaction mixture was poured into water and treated with an excess of $NaHCO_3$ yielding a brownish precipitate. The precipitate was collected and crystallized from MeOH thus giving a white crystalline substance. The mother liquor after crystallisation was evaporated giving an additional quantity of pyrazole **VI** in form of brownish solid. This sample was heated with aqueous solution of KOH for 30 minutes until dissolved and formed deep red solution. The solution was treated with charcoal, filtered and acidified giving light brown solid, which appeared to be **VII**.

Reaction of III with Formamidine Acetate

Formamidine acetate (1.7 g) was added to a solution prepared by dissolving 0.4 g Na in 10 mL of MeOH. Solution of **III** (2.68 g) in 20 mL of i-PrOH was added and the resulting mixture was kept at room temperature for a week. TCL showed the absence of the starting **III**. Dark-colored reaction mixture was poured into water, a viscous dark oil was separated and treated with MeOH. The resulting precipitate was crystallised from MeOH, giving brownish crystals of **XIa**.

Reaction of III with Benzamidine Hydrochloride

Reaction **III** (2.2 g) was dissolved in 20 mL of warm MeOH, giving a clear solution. Benzamidine hydrochloride (2 g m.p. 72–76°C) was dissolved in 15 mL of warm MeOH. The solution of benzamidine was added to the solution of **I**. The resulting solution immediately became dark-red. Dry triethylamine (1.2 mL) was added and the obtained reaction mixture was refluxed for 2 hours, and then let to stand for 3 days. White precipitate was formed and TLC showed absence of **I** in the reaction mixture. Dilution of the reaction mixture with water led to more white precipitate. Obtained precipitate was filtered, washed consequently with water, MeOH and small quantities of EtOAc. Then the precipitate was diluted in minimal quantities of DMFA and the obtained solution was poured into excess of 5% water solution of KOH, giving a suspension, which was filtered and the filtrate acidified with HCl to pH ~6, giving a white precipitate, which was filtered and dried. m = 2.4 g. TLC showed that the obtained product was a pure individual compound.

Hydrolysis of 2-(4,5,6,7-Tetrahydro-1(2)H-indazol-3-yl)-benzoic Acid Methyl Eester VI to 2-(4,5,6,7-Tetrahydro-1(2)H-indazol-3-yl)-benzoic Acid VII

Ester **VI** (7.69 g, 0.03 mol) was dissolved in 100 mL of methanol and KOH (2.24 g, pellets) in 10 mL of water was added to the solution. The mixture was heated under reflux for 30 min at 80°C (oil bath temperature), then cooled and diluted with 200 mL of water. Obtained dark-red solution was treated with charcoal, filtered and acidified, thus giving a white precipitate of acid **VIIa**. The product was filtered off, carefully washed with water and methanol and crystallized from methanol to give a white solid. **VIIa–c** was almost insoluble in acetone and chloroform; but is easily dissolved in mineral acids and bases.

Cyclization of 2-(4,5,6,7-Tetrahydro-1(2)H-indazol-3-yl)-benzoic Acid VII into 1,3,4,7-Tetrahydro-2H-isoindolo [2,1-b]indazol-7-one VIII

Acid **VIIa** was stirred with $SOCl_2$ in dioxane at room temperature for one hour and then heated for 30 min and cooled. The acid substrate gradually dissolved and after a short period, a yellow solid started to precipitate. Finally, the reaction mixture was diluted with excess water, which resulted in intensive precipitation of yellow solid, which was filtered, washed with water, triturated with a diluted solution of $NaHCO_3$, washed with water again and dried. It moderately dissolved in chloroform, dioxane, DMFA, ethanol. Solution in ethanol turned from yellow to colorless after standing for some hours. It did not dissolve in water or diluted mineral acids.

Hydrolysis of 1,3,4,7-Tetrahydro-2H-isoindolo [2,1-b]indazol-7-one VIII

A sample of **VIII** was boiled with an excess of water. The main part was dissolved after 15 min. Cooling the reaction mixture gave a white precipitate which, according to TLC was identical to **VIIa**.

Reaction of VIII with Methanol

A sample of **VIII** was dissolved in hot methanol, giving a yellow solution, which was then heated to boiling till yellow colour disappeared. TLC of the resulting solution showed only the presence of **VIa**.

Reaction of VIII with Amines

A sample of **VIII** was placed in a flask with 10 mL of dioxane. An equimolecular amount of amine was added. The mixture was stirred till all the solids dissolved and the yellow color disappeared. If reaction was slow, the reaction mixture was heated till the yellow color disappeared.

When the reaction is completed, water was added to reaction mixture, thus precipitating the amide **IX**, which was then filtered off, washed with water, and recrystallized.

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