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# The chemistry of homophthalic acid: a new synthetic strategy for construction of substituted isocoumarin and indole skeletons

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ABSTRACT

Homophthalic acid was reacted with thionylchloride/DMF and chloroethylformate/$NEt_3$ in the presence and absence of $NaN_3$. In all cases completely different isocoumarin derivatives were obtained. These unusual isocoumarin derivatives were isolated and characterized and their formation mechanisms are discussed. The homophthalic acid monomethyl ester was converted into the corresponding isocyanate. Reaction of the isocyanate with different amines produced the urea derivatives. Base-supported condensation reactions of these products gave first an indolinone derivative, which underwent further intermolecular condensation to give substituted indole derivatives. However, when the condensation reaction was carried out in the presence of acetic anhydride, the intermolecular reactions were suppressed. This methodology opens up a new way of synthesizing of various five-membered ring substituted indole derivatives.



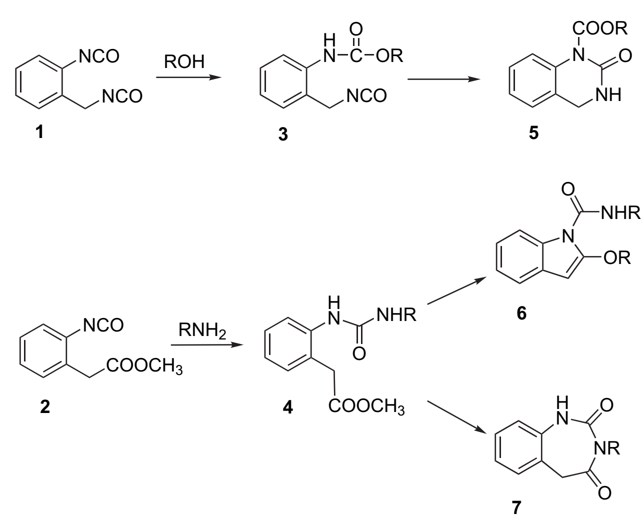
## 1. Introduction

Indole and its derivatives are found abundantly in nature and are known to exhibit potent physiological properties.[1,2] Numerous methods for the preparation of indoles have been developed.[3–7] In some cases, specific substitution patterns have been difficult to obtain by standard indole-forming reactions; thus, new methodologies have emerged. The quinazoline and quinazolinone moities,[8] in particular, are found in a variety of biological active compounds and several approved drugs. Therefore, we were interested in the development of new synthetic methodologies, leading to the synthesis of these class of compounds. The main idea of this work was to synthesize the isocyanate **1** and **2**, which then will be trapped with alcohols or amines to produce the corresponding urethane and urea derivatives, **3** and **4**, which can undergo cyclization to form the corresponding five-, six- and eventually seven-membered ring compounds **6**, **5**, and **7**, respectively (Scheme 1).

## 2. Results and discussion

Our plan for the construction of the desired heterocyclic ring systems involved an intramolecular cyclization reaction of the diisocyanate, which can be generated by the Curtius reaction[9] of the corresponding diazide. Our investigation began with the attempted synthesis of the diazide **9** derived from homophthalic acid **8**. A preliminary communication of this work was published recently.[10] The reaction of the acid **8** with thionyl chloride always produced the lactone **10**.[11]

*N*,*N*-Dimethylchlorosulfitemethaniminium chloride formed from thionyl chloride and dimethyl formamide has been shown as an efficient reagent for the synthesis of acyl azides from carboxylic acids.[12] Therefore, homophthalic acid **8** was reacted with thionyl




**Scheme 1.**

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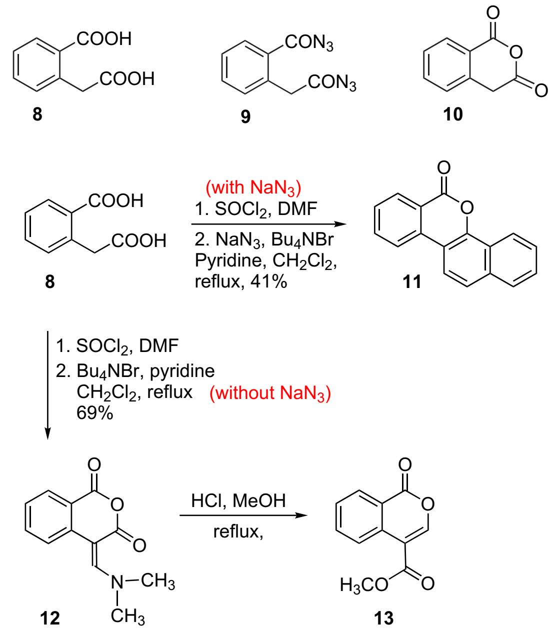



Scheme 2.

chloride, DMF, and sodium azide in the presence of tetrabutylammonium bromide as a catalyst using $CH_2Cl_2$ as the solvent. Unfortunately, the desired diazide **9** was not detected. 6*H*-Dibenzo[*c*,*h*]chromen-6-one[13,14] (**11**) was formed in 41% yield, which was characterized by comparison of its spectral data with those published in the literature (Scheme 2).

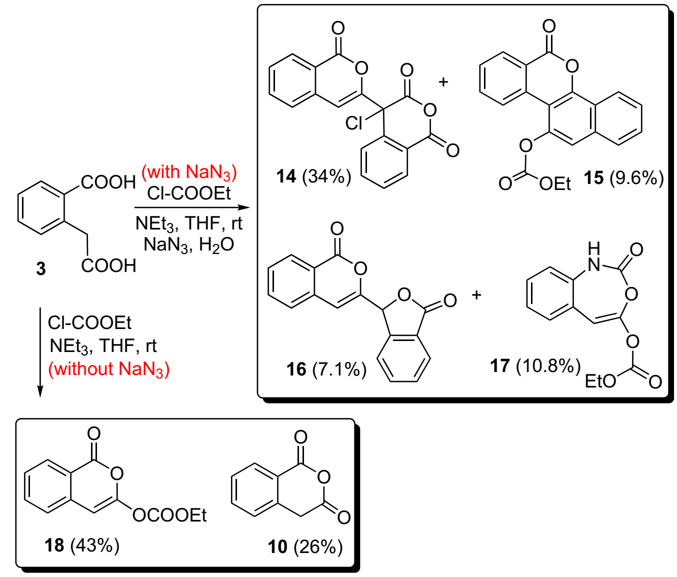
The azide anion was not incorporated in the product **11**. To determine the role of the azide anion in this reaction, the same reaction was run in the absence of $NaN_3$. Instead of the formation of a dibenzochromen-6-one **11**, an aminomethylene compound **12** was formed as the sole product in 69% yield (Scheme 2). The intermediate **12** was identified by comparison of the spectral data with those reported in the literature, which was obtained under Vilsmeier conditions (DMF/$POCl_3$) starting from the homophthalic acid **8**.[15,16] The intermediate **12** was further converted to the isocoumarin derivative **13**[15–18] by the reaction with methanol saturated with hydrogen chloride in 76% yield.

As an alternate method for the formation of acyl azide **9**, homophthalic acid **8** was treated with chloroethylformate in the presence of triethylamine followed by addition of a solution of $NaN_3$ in water. Careful examination of the reaction mixture revealed the formation of four compounds **14**–**17** (Scheme 3), with compound **14** precipitated from the reaction media. The other isomers were separated on a silica gel column eluting with dichloromethane.

Next, homophthalic acid **8** was reacted with chloroethylformate and triethylamine in the absence of $NaN_3$. Surprisingly, none of the products **14**–**17** were formed. Instead the isocoumarin derivative **18**[19] was formed, in 43% yield, as the major product along with anhydride **10** in 26% yield (Scheme 3). The structure of **18** was deduced by NMR spectral data.

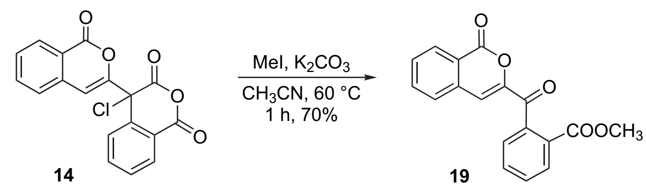
COSY, HMQC, and HMBC experiments allowed for the assignment of the structures **14**–**17**. An HMBC experiment of **14** confirmed this structure, especially by the correlation of the carbon atom bearing the chlorine atom with the double bond proton located in the isocoumarin ring and the α-proton of the other benzene ring. Furthermore the presence of 14 carbon resonances and other spectral data support the formation of an anhydride structure.

For further structural proof, the chlorine compound **14** was treated with $CH_3I$ in the presence of $K_2CO_3$ in acetonitrile. The isocoumarin derivative **19** was isolated as a single compound in 70% yield (Scheme 4). Again, COSY, HMQC, and HMBC experiments are in agreement



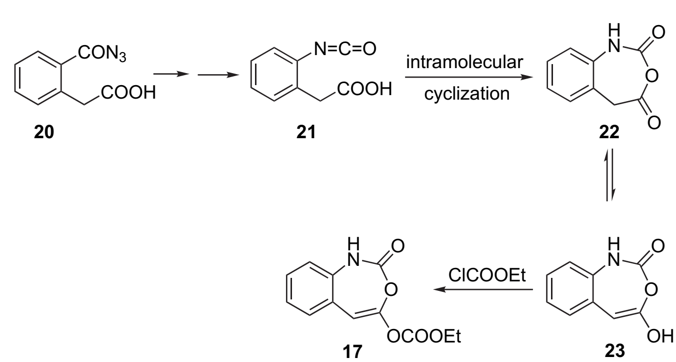

Scheme 3.

with the proposed structure. An HMBC experiment confirmed the presence of a strong correlation between the carbonyl group of the ketone, the double bond proton, and the aromatic proton. Finally, X-ray diffraction analysis of **19** was carried out. The results of this study confirmed unambiguously the proposed structure.[10]

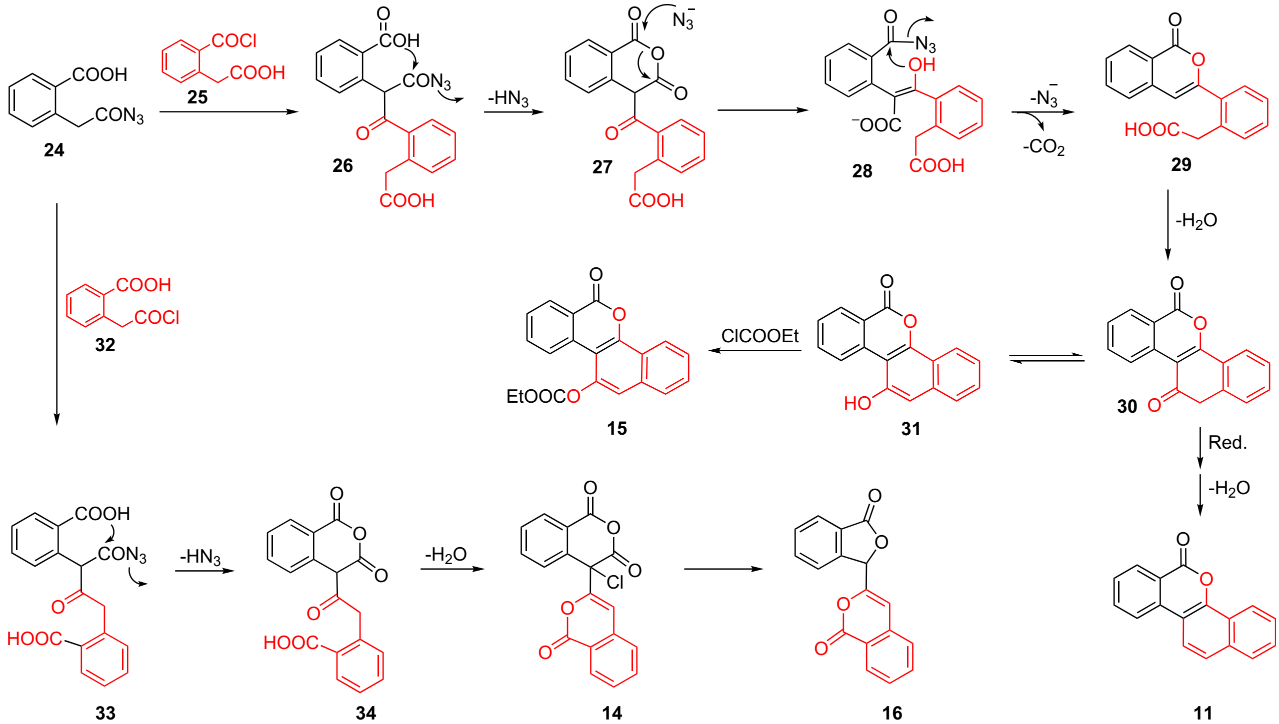



Scheme 4.

The HMBC experiment of **16** revealed a strong correlation ($^3J_{CH}$) between the carbon atom (CH) in the lactone ring with the double bond proton as well as with the α-proton of the second benzene ring. We assume that compound **16** is a secondary product formed from **14** under the reaction conditions. Ring opening of **14** followed by decarboxylation and substitution of the chlorine atom by a carboxylate anion would form the lactone **16**. For the formation of **17** the following mechanism is suggested. The initially formed acyl chloride can react with azide to give the acyl azide **20**, which then rearranges to the corresponding isocyanate **21** followed by trapping of the isocyanate functionality with the acid –OH group. Enolization of the carbonyl group in **22** followed by trapping with chloroethylformate ends up with the formation of compound **17** (Scheme 5).




Scheme 5.




**Scheme 6.**

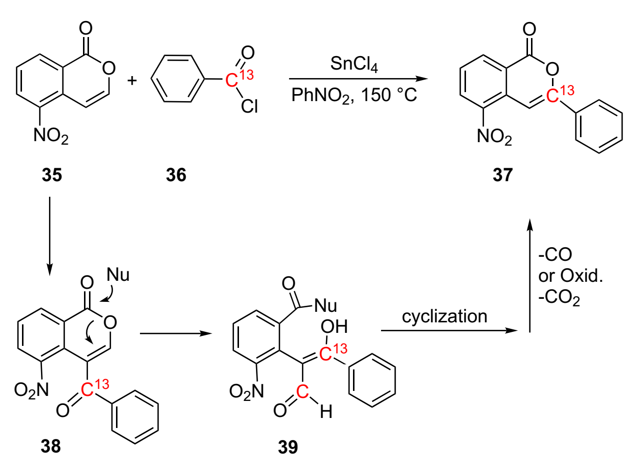
The results of these two attempted azidination reactions (Schemes 2 and 3) show that $NaN_3$ plays an important role in the determination of the mode of the reaction. During attempted azidination reactions it was noticed that intermolecular condensation products such as **11**, **14**, **15**, and **16** were always formed. However, when the reaction was run in the absence of $NaN_3$, only intramolecular cyclization products such as **12** and **18** were produced. In order to have more insight in to the formation mechanism of **11**, **14**–**16**, the azidination reactions were carried out with the anhydride **10** instead of homophthalic acid (**8**). We obtained similar products with similar yields.

A tentative mechanism of the formation of **11**, **14**, **15**, and **16** is outlined in Scheme 6. It is proposed that the first step is the formation of the anhydride **10**, which can be opened up by the azide anion to the corresponding monoazide **24**. Formation of the acyl azide **24** can activate the methylene protons, which might easily undergo intermolecular acylation reactions with **25** as well as with **32**, to give **26** and **33**, respectively. The formed anhydride **27** might undergo again a ring-opening reaction by the attack of the azide anion to produce **28**, which will be in tautomeric equilibrium. Cyclization of **28** followed by decarboxylation then gives **29**. Further cyclization of **29** and reduction of the carbonyl group in **30** with $NaN_3$[20] followed by $H_2O$ elimination results in the formation of **11**. Enolization of the carbonyl group in **30** followed by trapping with ethylchloroformate produces the compound **15**. In addition, it is proposed that **34** is formed from the intermediate **33** as shown in Scheme 6.

Recently, Threadgill et al.[21] have treated 5-nitroisocoumarin with various aromatic acyl chlorides under Friedel–Crafts conditions[22–24] to give 3-aryl-5-nitroisocoumarins rather than the expected 4-acyl-5-nitroisocoumarins. In order to elucidate the mechanism of the reaction, they designed an elegant reaction and reacted nitroisocoumarin **35** with [$^{13}$C]-carbonyl benzoyl chloride (**36**) and determined that the $^{13}$C is located at the C-3 position of the isocoumarin skeleton, indicating that the benzoyl carbon framework is incorporated intact (Scheme 7). For this reaction they have suggested a mechanism where **35** first undergoes an acylation reaction at C-4 position followed by a ring-opening reaction by a nucleophile producing enol **39**. Cyclization of **39** followed by decarbonylation (or oxidation to the carbocyclic acid followed by decarboxylation) forms the $^{13}$C-incorporated isocoumarin derivative **37**. This experimentally well established mechanism strongly supports our suggested mechanism[25] for the formation of the products **11**, **14**–**16**.

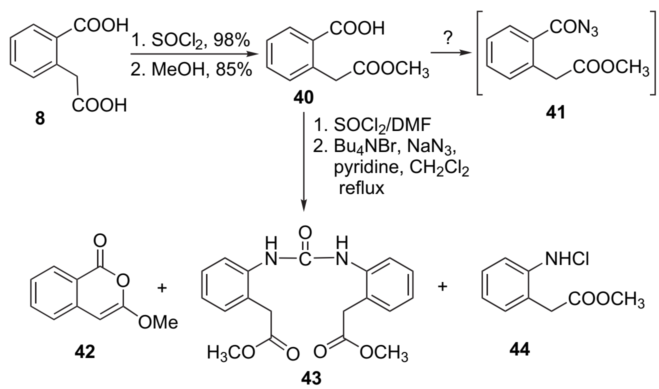
Our initial plan for the construction of quinazoline and quinazolinone moieties involved an intramolecular cyclization of diisocyanate **1**, which could be derived from the diazide **9**. However, the attempted synthesis of diazide **9** failed. The homophthalic acid **8** preferred the cyclization reaction to produce the anhydride **10** from which the isolated products were derived. In order to block the anhydride formation, we decided to synthesize the half ester **40** and generate the isocyanate **2**. In this part, we describe the successful implementation of this strategy.

The starting material, homophthalic acid **8**, was reacted with thionyl chloride to give an anhydride **10** by a ring-closing reaction, which was then treated with methanol to produce the half ester **40** by a regiospecific ring-opening reaction.[26] The half ester **40** was then reacted with thionyl chloride, DMF, and sodium azide in the



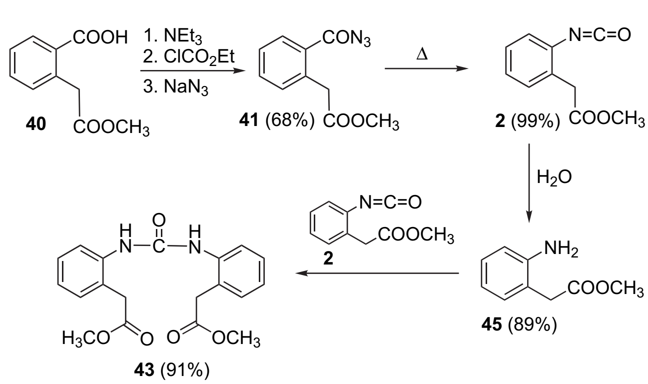

**Scheme 7.**

presence of tetrabutylammonium bromide as a catalyst using $CH_2Cl_2$ as the solvent. Unfortunately, the desired monoazide **41** was not detected. Instead, a mixture of three compounds **42**, **43**, and **44** was obtained in 12, 31, and 25% yields, respectively (Scheme 8). The products **43** and **44** were characterized by NMR spectral data. The high resolution mass spectrum of **43** clearly indicates the formation of a dimeric product. The experimental value of $M^+$=356.1363 is fully in agreement with the theoretical value, $M^+$=356.1372. The 3-methoxy-1*H*-isochromen-1-one (**42**) was characterized by comparison of its spectral data with those published in the literature.[27,28]




**Scheme 8.**

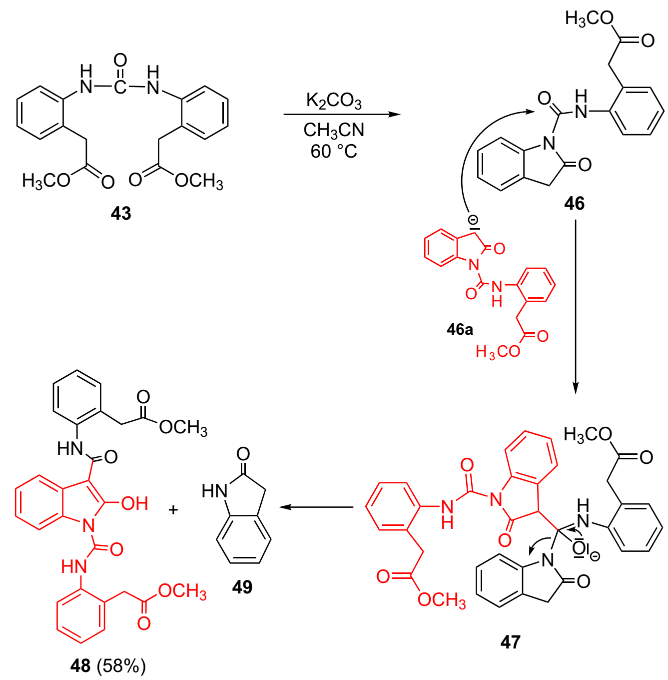
As an alternate method for the formation of acyl azide **41**, homophthalic acid ester **40** was treated with ethylchloroformate in the presence of triethylamine followed by the addition of a solution of $NaN_3$ in water. In contrast to the previous experiment, this azidination method was successful and provided acyl azide **41** in 68% yield (Scheme 9). The azide function provided a convenient handle for the generation of the corresponding isocyanate **2**. Thus, acyl azide **41** was allowed to reflux in benzene under nitrogen atmosphere to effect its quantitative transformation to the corresponding isocyanate **2**.[29] Hydrolysis of this isocyanate **2** with water formed amine **45**.[30] The reaction of amine **45** with isocyanate **2** gave the dimeric product **43** in excellent yield. On the basis of these reactions, the mechanism of formation of **43** obtained from reaction of **40** with DMF/$SOCl_2$ and $NaN_3$ (Scheme 8) was established.




**Scheme 9.**

As a result of this, we redirected our efforts to the ring-closure reaction of **43**, already bearing the necessary functionalities as shown in Scheme 1. The ring-closure reaction of urea derivative **43** was accomplished by treatment with $K_2CO_3$ in acetonitrile at 60 °C (Scheme 10).

Detailed examination of the NMR spectra, including COSY, HMQC, and HMBC and HRMS indicated that the condensation



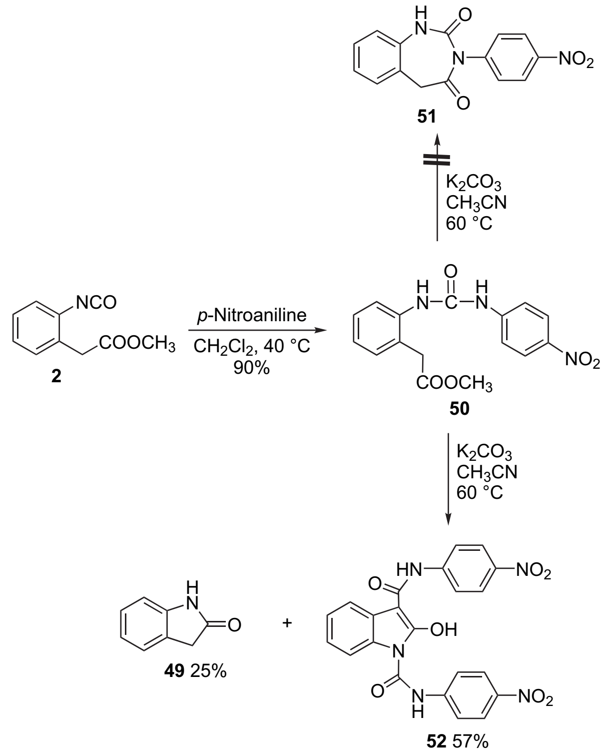

**Scheme 10.**

product **48** was formed as the major product (58% yield) along with the fragmentation product **49**.[31] The formation of a five-membered ring was preferred over the seven-membered ring. Under the reaction conditions, the product **46** undergoes a further condensation reaction with the in situ formed carbanion **46a** and forms the intermediate **47**, whose fragmentation results in the formation of **48** as shown in Scheme 10.

In order to force the system to undergo a regioselective ring-closure reaction to generate a 1,3-benzodiazepine-2,4-dione **7** structure, we decided to increase the acidity of one of the NH groups in **43**. For that purpose, isocyanate **2** was reacted with *p*-nitroaniline to give the urea derivative **50**. The product **50** was subjected to an intramolecular condensation reaction with $K_2CO_3$ to form **51**. Unfortunately, the interference of the other intramolecular process (condensation with the NH-proton attached to the benzene ring) gave the indole derivative **52** resulting from intramolecular condensation followed by intermolecular condensation (Scheme 11).

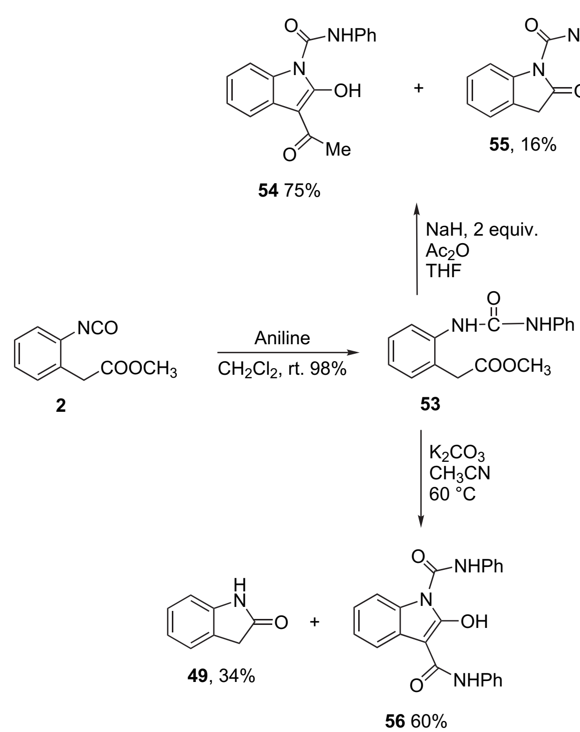
It became apparent that the urea derivatives **43** and **50** undergo first an intramolecular condensation to form a five-membered ring followed by an intermolecular condensation reaction as depicted in Scheme 10. To prevent the intermolecular condensation reaction and as a further support for the formation mechanism of **48** and **52**, we decided to trap the intermediate having the structure of the type **46a**.

To address this question, isocyanate **2** was reacted with aniline to give the urethane **53** in high yield. The reaction of **53** with NaH in the presence of acetic anhydride in THF gave two easily separable products **54** and **55** in yields of 75 and 16%, respectively (Scheme 12). Careful examination of the reaction mixture did not reveal the formation of any trace of the intermolecular condensation products having the structure such as **48**. The exclusive formation of **54** and **55** confirmed our original hypothesis that an intramolecular condensation takes place first. The indolinone derivative **55** undergoes a proton abstraction to form a carbanion having the structure of the type **46a**, which is then trapped by acetic anhydride. On the other hand, the reaction of **53** with $K_2CO_3$ in acetonitrile at 60 °C resulted in the formation of **49** and **56**, as expected.




**Scheme 11.**

In conclusion, the attempted synthesis of a diazide derived from homophthalic acid failed. However, unusual coumarin derivatives were produced instead. The isolated products were completely different, depending on whether the reaction was carried out in the presence or absence of $NaN_3$; in spite of the fact that the $N_3^-$ anion was not incorporated into the molecule. This method opens up a new route for the synthesis of coumarin derivatives. The targeted




**Scheme 12.**

monoazide **41** derived from homophthalic acid was successfully synthesized. The conversion of the monoazide **41** into the corresponding isocyanate **2**, followed by trapping with different amine bases gave the urea derivatives **43**, **50**, and **53**. Base-supported condensation reactions of these products gave first an indolinone structure, which further undergoes intermolecular cyclization to give substituted indole derivatives. However, when the condensation reaction is carried out in the presence of a trapping reagent, the intermolecular reaction can be controlled.

These methodologies open up new ways of synthesizing of various isocoumarins and five-membered ring substituted indole derivatives. Further application and extension of this methodology is currently under investigation.

## 3. Experimental

### 3.1. General

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. IR spectra were recorded on a Perkin–Elmer 980 spectrometer. NMR spectra were recorded on a Bruker instrument at 300 MHz for $^1H$ and 75 MHz for $^{13}C$ NMR. Apparent splitting is given in all cases. Column chromatography was performed on silica gel (60-mesh, Merck). TLC was carried out on Merck 0.2 mm silica gel 60 $F_{254}$ analytical aluminum plates. All substances reported in this paper are in their racemic form.

### 3.2. Synthesis of 6*H*-dibenzo[*c*,*h*]chromen-6-one (11)

In a 25 mL dropping funnel, benzene (10 mL), dimethyl formamide (2 mL, 20.4 mmol), and thionyl chloride (1.6 mL, 22 mmol) were consecutively added. After 3–5 min the two phases were separated and the lower layer was added to a suspension of homophthalic acid **8** (1.8 g, 10 mmol), sodium azide (2.6 g, 40 mmol), tetrabutylammonium bromide (0.6 g, 2 mmol), and pyridine (3.2 mL, 40 mmol) in dichloromethane (50 mL). The mixture was then refluxed overnight and washed with saturated sodium bicarbonate solution (3×50 mL) and water (2×25 mL). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 30 g, $CHCl_3$) to give yellow crystals **11** (0.5 g; mp 182–183 °C, lit. mp 179–180 °C[13]) in 41% yield. The product was crystallized from ethylacetate. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.60 (dd, $J_{7,8}$=7.9 Hz, $J_{7,9}$=1.2 Hz, 1H, H-7), 8.49 (dd, $J_{4,3}$=7.9 Hz, $J_{4,2}$=1.2 Hz, 1H, H-4), 8.21 (br d, $J_{1,2}$=8.1 Hz, 1H, H-1), 8.08 (d, $J_{12,11}$=8.8 Hz, 1H, H-12), 7.89 (ddd, $J_{2,1}$=8.1 Hz, $J_{2,3}$=7.3 Hz, $J_{2,4}$=1.2 Hz, 1H, H-2), 7.87 (dd, $J_{10,9}$=8.1 Hz, $J_{10,8}$=1.4 Hz, 1H, H-10), 7.78 (d, $J_{11,12}$=8.8 Hz, 1H, H-11), 7.65 (ddd, $J_{8,7}$=7.9 Hz, $J_{8,9}$=6.9 Hz, $J_{10,8}$=1.4 Hz, 1H, H-8), 7.63 (dd, $J_{9,10}$=8.1 Hz, $J_{9,8}$=6.9 Hz, 1H, H-9), 7.61 (dd, $J_{3,4}$=7.9 Hz, $J_{3,2}$=7.3 Hz, 1H, H-3); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 161.2 (s, carbonyl), 147.4 (s, C-4b), 135.5 (s, C-10a), 134.9 (d, C-9), 134.3 (s, C-12a), 130.7 (d, C-4), 128.6 (d, C-3), 127.9 (d, C-8), 127.7 (d, C-2), 127.2 (d, C-10), 124.5 (d, C-11), 123.9 (s, C-6a), 122.4 (d, C-7), 122.1 (d, C-1), 121.3 (s, C-10b), 119.2 (d, C-12), 113.1 (s, C-4a).

### 3.3. Synthesis of (4*Z*)-4-[(dimethylamino)methylene]-1*H*-isochromen-1,3(4*H*)-dione (12)

In a 25 mL dropping funnel, benzene (10 mL), dimethyl formamide (2 mL, 20.4 mmol), and thionyl chloride (1.6 mL, 22 mmol) were consecutively added. After 3–5 min the two phases were separated and the lower layer was added to a suspension of homophthalic acid (**8**) (1.8 g, 10 mmol), tetrabutylammonium bromide (0.6 g, 2 mmol), and pyridine (3.2 mL, 40 mmol) in dichloromethane (50 mL). The mixture was then refluxed overnight and washed with aqueous HCl solution (2×50 mL), water (2×50 mL), and aqueous sodium bicarbonate solution (2×50 mL). The organic phase was dried over magnesium sulfate and concentrated by vacuum. The residue was chromatographed (silica gel, 40 g, ethyl acetate) to give the product **12** as yellow solid (1.5 g) in 69% yield (mp 156–157 °C, lit. mp 144–145 °C[15]). The product was crystallized from ethylacetate/hexane (8:2). $^1$H NMR (400 MHz, DMSO-$d_6$, 65 °C) δ 8.34 (br s, 1H, H-1), 7.96 (br d, $J_{5,6}$=7.8 Hz, 1H, H-5), 7.59 (br dd, $J_{6,5}$=7.8 Hz, $J_{6,7}$=7.4 Hz, 1H, H-6), 7.53 (br d, $J_{8,7}$=8.2 Hz, 1H, H-8), 7.18 (dd, $J_{7,8}$=8.2 Hz, $J_{7,6}$=7.4 Hz, 1H, H-7), 3.34 (s, 6H, –$CH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 163.5 (d, C-1), 159.2 (s, C-1, carbonyl), 157.9 (s, C-3, carbonyl), 140.5 (s, C-4a), 135 (d, C-6), 129.9 (d, C-8), 123.7 (d, C-5), 120.7 (d, C-7), 116.4 (s, C-8a), 86.8 (s, C-4), 46.2 (q, –$CH_3$).

### 3.4. Methyl-1-oxo-1*H*-isochromene-4-carboxylate (13)[15]

The product **12** (0.7 g, 3 mmol) was dissolved in 20 mL methanol and dry HCl gas, produced from sulfuric acid and sodium chloride, was passed slowly through this solution. After saturation was complete, it was refluxed for 2 h. The solvent was removed and water was added to the residue, which was then extracted with chloroform (3×10 mL). The combined extracts were dried over magnesium sulfate and the solvent was removed at reduced pressure yielding the product **13**, as a white solid, which was then crystallized from methanol (mp 97–98 °C, lit. mp 97 °C;[15] 0.5 g, 76%). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.66 (br d, $J_{8,7}$=8.0 Hz, 1H, H-8), 8.33 (br d, $J_{5,6}$=7.9 Hz, 1H, H-5), 8.20 (s, 1H, –CH), 7.82 (ddd, $J_{6,5}$=7.9 Hz, $J_{6,7}$=7.5 Hz, $J_{6,8}$=1.2 Hz, 1H, H-6), 7.59 (br dd, $J_{7,8}$=8.0 Hz, $J_{7,6}$=7.5 Hz, 1H, H-7), 3.92 (s, 3H, –$OCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.5 (s, ester carbonyl), 160.7 (s, lactone carbonyl), 152.6 (d, C-3), 135.4 (d, C-6), 133.5 (s, C-4a), 130.0 (d, C-8), 129.0 (d, C-7), 125.4 (d, C-5), 120.5 (s, C-8a), 110.0 (s, C-4), 52.1 (q, –$OCH_3$).

### 3.5. Reaction of homophthalic acid (8) with ethylchloroformate and triethylamine in the presence of $NaN_3$

To a solution of homophthalic acid **8** (10 g, 56 mmol) in 40 mL THF at −5 °C, a solution of triethylamine (12 mL, 87 mmol) in 25 mL THF was added dropwise and the mixture was stirred for 30 min. This was followed by slow addition of a cooled solution of ethylchloroformate (12 mL, 130 mmol) in 25 mL THF and the reaction mixture was stirred at the same temperature, for 30 min. A solution of sodium azide (14 g, 215 mmol) in 50 mL water was then added dropwise and the mixture was left to stir at room temperature overnight. The product **14** (2.5 g), which was precipitated from the reaction medium was separated by filtration and the filtrate was extracted with two portions of ethyl acetate (50 mL). The organic phase was then washed with saturated sodium bicarbonate solution (3×75 mL) and with water (2×50 mL), and dried over magnesium sulfate. By removal of ethyl acetate, under reduced pressure, a mixture of the products **15**, **16**, and **17** (2.95 g) was obtained. When the mixture was dissolved in $CHCl_3$, compound **16** precipitated and was filtered off. The filtrate was concentrated in vacuum and the mixture was chromatographed over silica gel (60 g) eluting with $CH_2Cl_2$. The first fraction was identified as the dibenzochromen-6-one derivative **15**. The compound **17** was isolated as the second fraction.

#### *3.5.1. 4′-Chloro-1H,1′H-3,4′-biisochromen-1,1′,3′(4′H)-trione (**14**)*

Yellow-green solid (3.9 g, 34%), decomposition at 227–228 °C. The product darkens at room temperature. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.03 (br d, $J_{8,7}$=7.7 Hz, 1H, H-8), 7.76 (dd, $J_{8',7'}$=7.8 Hz, $J_{8'6'}$=1.1 Hz, 1H, H-8′), 7.70 (dt, $J_{6,7}$=$J_{6,5}$=8.0 Hz, $J_{6,8}$=1.1 Hz, 1H, H-6), 7.48 (br d, $J_{5,6}$=8.0 Hz, 1H, H-5), 7.41 (br d, $J_{5',6'}$=8.2 Hz, 1H, H-5′), 7.36 (br dd, $J_{7,6}$=8.0 Hz, $J_{7,8}$=7.7 Hz, 1H, H-7), 7.29 (ddd, $J_{6',5'}$=8.2 Hz, $J_{6',7'}$=7.8 Hz, $J_{6',8'}$=1.2 Hz, 1H, H-6′), 6.89 (br s, 1H, H-4), 6.73 (br t, $J_{7',6'}$=$J_{7',8'}$=7.8 Hz, 1H, H-7′); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 165.5 (s, C-1′), 163.6 (s, C-1), 160.6 (s, C-3′), 156.6 (s, C-3), 143.6 (s, C-4a′), 140.4 (s, C-4a), 135.4 (d, C-6), 134.1 (d, C-6′), 129.7 (d, C-8′), 129.1 (d, C-8), 126.5 (d, C-7), 125.8 (d, C-5), 121.1 (d, C-5′), 118.8 (d, C-7′), 118.6 (s, C-8a), 113.5 (s, C-8a′), 103.8 (d, C-4), 80.2 (s, C-4′); IR (KBr, $cm^{-1}$): 1723 (s), 1699 (s), 1628 (s), 1563 (w), 1079 (w). Anal. Calcd for $C_{18}H_9ClO_5$: C, 63.45; H, 2.66. Found: C, 62.73; H, 2.42.

#### *3.5.2. 3-(3-Oxo-1,3-dihydro-2-benzofuran-1-yl)-1H-isochromen-1-one (**16**)*

Yellow-brown solid (550 mg, 7.1%), mp 256–257 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.13 (br d, $J_{8,7}$=8.1 Hz, 1H, H-8), 7.76 (br d, $J_{4',5'}$=7.7 Hz, 1H, H-4), 7.87 (dd, $J_{6,5}$=7.4 Hz, $J_{6,7}$=7.2 Hz, $J_{6,8}$=1.1 Hz, 1H, H-6), 7.83 (dd, $J_{6'5'}$=7.6 Hz, $J_{6',7'}$=7.1 Hz, $J_{6',8'}$=1.1 Hz, 1H, H-6′), 7.73 (br d, $J_{5,6}$=7.4 Hz, 1H, H-5), 7.70 (br d, $J_{5',4'}$=7.7 Hz, $J_{5',6'}$=7.6 Hz, 1H, H-5′), 7.68 (br d, $J_{7',6'}$=7.1 Hz, 1H, H-7′), 7.64 (dd, $J_{7,8}$=8.1 Hz, $J_{7,6}$=7.2 Hz, $J_{7,5}$=1.1 Hz, 1H, H-7), 7.14 (s, 1H, H-4), 6.63 (s, 1H, H-1); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 170.0 (s, C-3), 161.5 (s, C-1), 150.3 (s, C-3a), 146.6 (s, C-7a), 136.5 (s, C-4a), 135.8 (d, C-6), 131.0 (d, C-6′), 130.4 (d, C-5′), 129.7 (d, C-7), 127.6 (d, C-8), 126.0 (d, C-5), 125.8 (d, C-4), 125.6 (s, C-3), 124.0 (d, C-7′), 121.1 (s, C-8a), 107.7 (d, C-4), 79.0 (d, C-1); IR (KBr, $cm^{-1}$): 1770 (s), 1727 (s), 1661 (w), 1381 (w), 1219 (m), 1147 (w); MS: 70 eV, *m*/*z* 279 ($M+H^+$, 41%), 278 (100%), 249 (76%), 145 (60%), 117 (39%), 89 (74%); HRMS calcd for $C_{17}H_{10}$ $O_4$: 278.0579; found: 278.0585. Anal. Calcd for $C^{17}H^{10}O^4$: C, 73.38; H, 3.62. Found: C, 73.24; H, 3.67.

#### *3.5.3. Ethyl 6-oxo-6H-dibenzo[c,h]chromen-11-yl carbonate (**15**)*

Yellow solid (880 mg, 9.6%), mp 174–175 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.69 (dd, $J_{7,8}$=8.0 Hz, $J_{7,9}$=0.7 Hz, 1H, H-7), 8.5 (dd, $J_{10,9}$=8.1 Hz, $J_{10,8}$=1.5 Hz, 1H, H-10), 7.98 (dd, $J_{4,3}$=8.2 Hz, $J_{4,2}$=0.9 Hz, 1H, H-4), 7.89 (dd, $J_{1,2}$=7.0 Hz, $J_{1,3}$=1.5 Hz, 1H, H-1), 7.86 (ddd, $J_{8,7}$=8.0 Hz, $J_{8,9}$=7.8 Hz, $J_{5,8}$=1.5 Hz, 1H, H-8), 7.55 (s, 1H, H-12), 7.64 (dt, $J_{9,10}$=$J_{9,8}$=8.1 Hz, $J_{7,9}$=1.1 Hz, 1H, H-9), 7.6 (dt, $J_{1,2}$=$J_{2,3}$=7.0 Hz, $J_{2,4}$=1.5 Hz, 1H, H-2), 7.56 (ddd, $J_{3,4}$=8.2 Hz, $J_{3,2}$=7.0 Hz, $J_{3,1}$=1,5 Hz, 1H, H-3), 4.38 (q, *J*=7.0 Hz, 2H, H-1), 1.41 (t, *J*=7.0 Hz, 3H, H-2); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.8 (s, C-6), 152.8 (s, C-13), 148.7 (s, C-11), 144.7 (s, C-4a), 135.5 (d, C-8), 133.7 (s, C-6a), 133.2 (s, C-12a), 131.3 (d, C-10), 129.6 (d, C-9), 128.5 (d, C-2), 127.6 (d, C-1), 126.8 (d, C-3), 126.4 (d, C-7), 125.2 (s, C-4a), 122.5 (s, C-10a), 121.8 (d, C-4), 112.5 (d, C-12), 111.5 (s, C-10b), 66.2 (q, C-19), 14.6 (t, C-20); IR (KBr, $cm^{-1}$): 1753 (s), 1633 (s), 1604 (w), 1464 (w), 1320 (m), 1233 (s); MS: 70 eV, *m*/*z* 334 ($M^+$, 28%), 289 (25%), 262 (100%), 233 (76%), 204 (22%), 176 (27%). Anal. Calcd for $C_{20}H_{14}O_5$: C, 71.85; H, 4.59. Found: C, 71.48; H, 4.36.

#### *3.5.4. Ethyl 2-oxo-1,2-dihydro-3,1-benzoxazepin-4-yl carbonate (**17**)*

Viscous yellow liquid (750 mg, 10.8%). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.43 (br s, 1H, –NH), 7.93 (br d, $J_{6,7}$=7.6 Hz, 1H, H-6), 7.89 (br d, $J_{9,8}$=7.7 Hz, 1H, H-9), 7.76 (br dd, $J_{8,9}$=7.7 Hz, $J_{8,7}$=7.4 Hz, 1H, H-8), 7.63 (br dd, $J_{7,6}$=7.6 Hz, $J_{7,8}$=7.4 Hz, 1H, H-7), 5.93 (s, 1H, H-5), 4.26 (q, *J*=7.1 Hz, 2H, –$CH_2$–), 1.31 (t, *J*=7.1 Hz, 3H, –$CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.9 (s, C-2), 165.2 (s, C-4), 149.9 (s, ester carbonyl), 143.9 (s, C-9a), 135.3 (d, C-8), 130.5 (d, C-7), 125.9 (d, C-6), 124 (s, C-5a), 123.9 (d, C-9), 77.9 (d, C-5), 62.9 (t, –$OCH_2$), 14.1 (q, –$CH_3$); IR (KBr, $cm^{-1}$): 1780 (s), 1721 (s), 1466 (m), 1286 (s), 1185 (m); MS: 70 eV, *m*/*z* 249 ($M^+$, 5%), 145 (6%), 133 (100%), 105 (45%), 89 (10%). Anal. Calcd for $C_{12}H_{11}NO_5$: C, 52.83; H, 4.45; N, 5.62. Found: C, 52.14; H, 4.39; N, 5.31.

### 3.6. Synthesis of methyl 2-[(1-oxo-1*H*-isochromen-3-yl)carbonyl]benzoate (19)

To a suspension of compound **14** (0.48 g, 1.4 mmol) in acetonitrile (15 mL), potassium carbonate (1 g, 7.2 mmol) and methyl iodide (0.2 g, 1.4 mmol) were added. The suspension was stirred at 60 °C and the reaction was complete in 1 h (determined by TLC).

The residue was filtered off to remove the excess potassium carbonate. The filtrate was concentrated by vacuum to give the product **19** (0.3 g, 70%). Yellow crystals from methanol/chloroform (1:1), mp 140–141 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.33 (br d, $J_{8,7}$=7.8 Hz, 1H, H-8), 8.08 (br d, $J_{6',5'}$=7.7 Hz, 1H, H-6′), 7.79 (br t, $J_{6,7}$=$J_{6,5}$=7.8 Hz, 1H, H-6), 7.68 (br t, $J_{4',3'}$=$J_{4',5'}$=7.4 Hz, 1H, H-4′), 7.66 (br dd, $J_{5',6'}$=7.7 Hz, $J_{5',4'}$=7.4 Hz, 1H, H-5′), 7.62 (br t, $J_{7,8}$=$J_{7,6}$=7.8 Hz, 1H, H-7), 7.61 (br d, $J_{5,6}$=7.8 Hz, 1H, H-5), 7.47 (br d, $J_{3',4'}$=7.4 Hz, 1H, H-3′), 7.34 (s, 1H, H-4), 3.80 (s, 3H, –$OCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 189.3 (s, ketone carbonyl), 166.4 (s, ester carbonyl), 160.5 (s, lactone carbonyl), 149.7 (s, C-8a), 139.5 (s, C-2′), 135.2 (s, C-1′), 135.1 (d, C-6), 132.8 (d, C-4′), 130.7 (C-5′), 130.5 (d, C-7), 130.06 (d, C-6′), 130.04 (d, C-8), 129.5 (s, C-3), 128.1 (d, C-3′), 127.9 (d, C-5), 122.8 (s, C-4a), 110.9 (d, C-4), 52.6 (q, –$OCH_3$); IR (KBr, $cm^{-1}$): 3075 (w), 1733 (s), 1681 (w), 1453 (w), 1308 (s), 1284 (s), 1141 (m). Anal. Calcd for $C_{18}H_{12}O_5$: C, 70.13; H, 3.92. Found: C, 69.88; H, 3.96.

### 3.7. Reaction of homophthalic acid (8) with ethylchloroformate and triethylamine in the absence of $NaN_3$

To a solution of homophthalic acid **8** (2.5 g, 14 mmol) in 10 mL THF at −5 °C, triethylamine (3 mL, 22 mmol) in 6 mL THF was added dropwise and the mixture was stirred for 30 min. This was followed by slow addition of a cooled solution of ethylchloroformate (3 mL, 32 mmol) in 6 mL THF and the reaction mixture was stirred at the same temperature for 30 min. The mixture was extracted with two portions of ethyl acetate (15 mL) and the organic phase was then washed with saturated sodium bicarbonate (3×40 mL) and with water (2×25 mL), and dried over magnesium sulfate. Removal of the solvent under vacuum gave a mixture of the compounds **18** and **10** (2.2 g, 3:2), which were separated on silica gel (40 g) column chromatography using ethyl acetate/*n*-hexane (7:3). From the first fraction **18** was isolated (1.40 g, 43%, white crystals from $CHCl_3$, mp 93–94 °C). The second fraction was identified as the anhydride **10** (585 mg, 26%).

#### 3.7.1. *Ethyl 1-oxo-1H-isochromen-3-yl carbonate (**18**)*[19]

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.27 (br d, $J_{8,7}$=8.3 Hz, 1H, H-8), 7.72 (ddd, $J_{6,5}$=7.9 Hz, $J_{6,7}$=7.6 Hz, $J_{6,8}$=0.8 Hz, 1H, H-6), 7.49 (br dd, $J_{7,8}$=8.3 Hz, $J_{7,6}$=7.6 Hz, 1H, H-7), 7.44 (br d, $J_{5,6}$=7.9 Hz, 1H, H-5), 6.27 (s, 1H, –CH), 4.37 (t, $J$=7.1 Hz, 2H, –$OCH_2$), 1.41 (q, $J$=7.1 Hz, 3H, –$CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.6 (s, C-3), 151.0 (s, lactone carbonyl), 150.4 (s, ester carbonyl), 137.4 (s, C-4a), 135.3 (d, C-6), 130.0 (d, C-8), 127.9 (d, C-5), 126.0 (d, C-7), 119.5 (s, C-8a), 93.0 (d, C-4), 66.2 (t, –$OCH_2$), 14.0 (q, –$CH_3$).

### 3.8. Synthesis of 1*H*-isochromen-1,3-(4*H*)-dione (10)

A mixture of homophthalic acid (**8**) (9.3 g, 50 mmol) and thionyl chloride (14.5 mL, 200 mmol) in 150 mL of methylene chloride was refluxed overnight and the solvent and excess thionyl chloride were evaporated under vacuum to give **10** as a yellow solid (8.4 g) in 98% yield, mp 143–144 °C, lit. mp 144–145 °C.[11] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.22 (br d, $J_{8,7}$=7.8 Hz, 1H, H-8), 7.70 (br dd, $J_{7,8}$=7.8 Hz, $J_{7,6}$=7.6 Hz, 1H, H-7), 7.52 (br t, $J_{6,7}$=$J_{6,5}$=7.6 Hz, 1H, H-6), 7.35 (br d, $J_{5,6}$=7.6 Hz, 1H, H-5), 4.14 (s, 2H, –$CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.0 (s, C-3), 161.3 (s, C-1), 135.9 (d, C-6), 134.7 (s, C-4a), 131.3 (d, C-8), 129.1 (d, C-7), 127.9 (d, C-5), 121.9 (s, C-8a), 34.7 (t, –$CH_2$).

### 3.9. 2-(2-Methoxy-2-oxoethyl)benzoic acid (40)

Homophthalic anhydride (**10**) (6 g, 37 mmol) was refluxed in methanol (50 mL) for 2 h. The solvent was concentrated in vacuum to give the pure **40** (pale yellow crystalline compound 6.1 g, 85%; mp 99–101 °C, lit. mp 98 °C).[26] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 11.0 (br s, 1H, –OH), 8.17 (dd, $J_{6,5}$=7.8 Hz, $J_{6,4}$=1.3 Hz, 1H, H-6), 7.56 (dt, $J_{4,5}$=$J_{4,3}$=7.6 Hz, $J_{4,6}$=1.3 Hz, 1H, H-4), 7.43 (dt, $J_{5,6}$=7.8 Hz, $J_{5,4}$=7.6 Hz, $J_{5,3}$=0.9 Hz, 1H, H-5), 7.30 (d, $J_{3,4}$=7.6 Hz, 1H, H-3); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.3 (s, ester carbonyl), 171.9 (s, acid carbonyl), 136.8 (s, C-2), 133.3 (d, C-6), 132.4 (d, C-4), 131.9 (d, C-3), 128.6 (s, C-1), 127.6 (d, C-5), 51.9 (t, –$OCH_3$), 40.6 (t, –$CH_2$).

### 3.10. Reaction of 40 with $SOCl_2$/DMF and $NaN_3$

In a 25 mL dropping funnel, benzene (6 mL), dimethyl formamide (1.18 mL, 11.8 mmol), and thionyl chloride (0.86 mL, 22 mmol), were consecutively added. After 3–5 min two phases were separated and the lower layer was added to a suspension of the half ester **40** (2.3 g, 11.8 mmol), sodium azide (1.5 g, 23.6 mmol), tetrabutylammonium bromide (0.35 g, 1.18 mmol), and pyridine (1.89 mL, 23.6 mmol) in dichloromethane (50 mL). The mixture was then refluxed overnight and washed with saturated sodium bicarbonate solution (3×50 mL) and water (2×25 mL). The organic phase was dried over magnesium sulfate and concentrated under reduced pressure to give 1.5 g of mixture of **42**, **43**, and **44**. The compounds were separated on a silica gel column (40 g) eluting with chloroform/hexane (95:5). The first compound was identified as **42** (0.24 g, 11.5%), the second was the viscous liquid **44** (0.6 g, 25.4%), and the last was **43** (0.65 g, 31.0%).

#### 3.10.1. *3-Methoxy-1H-isochromen-1-one (**42**)*

White crystals, mp 67–68 °C, lit. mp 70–71 °C.[27] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.16 (d, $J_{8,7}$=8.2 Hz, 1H, H-8), 7.60 (br dd, $J_{6,5}$=8.1 Hz, $J_{6,7}$=7.2 Hz, 1H, H-6), 7.30 (d, $J_{5,6}$=8.1 Hz, 1H, H-5), 7.29 (br dd, $J_{7,8}$=8.2 Hz, $J_{7,6}$=7.2 Hz, 1H, H-7), 5.58 (s, 1H, H-4), 3.91 (s, 3H, –$OCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 161.1 (s, C-1), 159.8 (s, C-3), 139.9 (s, C-4a), 135.1 (d, C-6), 129.9 (d, C-8), 125.5 (d, C-5), 124.6 (d, C-7), 117.9 (s, C-8a), 79.1 (d, C-4), 56.0 (q, –$OCH_3$).

#### 3.10.2. *Methyl 2-[2-({[2-(2-methoxy-2-oxoethyl)anilino]carbonyl}-amino)phenyl]acetate (**43**)*

White solids from ethyl acetate/*n*-hexane (7:3), mp 177–178 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.71 (dd, $J_{3,4}$=7.9 Hz, $J_{3,5}$=1.2 Hz, 1H, H-3), 7.40 (br s, 1H, –NH), 7.31 (ddd, $J_{4,3}$=7.9 Hz, $J_{4,5}$=7.5 Hz, $J_{4,6}$=1.5 Hz, 1H, H-4), 7.22 (dd, $J_{6,5}$=7.4 Hz, $J_{6,4}$=1.5 Hz, 1H, H-6), 7.13 (ddd, $J_{5,4}$=7.5 Hz, $J_{5,6}$=7.4 Hz, $J_{5,3}$=1.2 Hz, 1H, H-5), 3.58 (s, 2H, –$CH_2$), 3.54 (s, 3H, –$OCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.5 (s, ester carbonyl), 154.4 (s, amide carbonyl), 137.1 (s, C-2), 131.2 (d, C-6), 128.8 (d, C-4), 127.9 (s, C-1), 126.1 (d, C-5), 125.7 (d, C-3), 52.6 (q, –$OCH_3$), 38.5 (t, –$CH_2$); IR (KBr, $cm^{-1}$): 3332 (s), 3268 (s), 1740 (s), 1638 (s), 1599 (m), 1432 (m), 1168 (s); HRMS calcd for $C_{19}H_{20}N_2O_5$: 356.1363; found: 356.1372. Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.31; H, 5.52; N, 6.84.

#### 3.10.3. *Methyl 2-[2-(chloroamino)phenyl]acetate (**44**)*

Viscous oil (not stable at room temperature). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.45 (br s, –NH), 7.85 (br d, $J_{6,5}$=7.6 Hz, 1H, H-6), 7.33 (br dd, $J_{4,5}$=8.0 Hz, $J_{4,3}$=7.3 Hz, 1H, H-4), 7.20 (br d, $J_{3,4}$=7.3 Hz, 1H, H-3), 7.13 (br dd, $J_{5,4}$=8.0 Hz, $J_{5,6}$=7.6 Hz, 1H, H-5), 3.73 (s, 3H, –$CH_3$), 3.63 (s, 2H, –$CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.9 (s, ester carbonyl), 154.8 (s, C-2), 136 (s, C-1), 130.9 (d, C-6), 128.7 (d, C-4), 125.6 (d, C-5), 123.8 (d, C-3), 52.7 (t, $CH_2$), 38.5 (q, –$OCH_3$).

### 3.11. Methyl 2-[2-(azidocarbonyl)phenyl]acetate (41)

To a solution of half ester **40** (2.4 g, 12 mmol) in 10 mL of THF at −5 °C was added a solution of triethylamine (1.7 mL, 12 mmol) in 6 mL of THF dropwise and the mixture was stirred for 30 min. This was followed by slow addition of a cooled solution of ethylchloroformate (1.6 mL, 14.4 mmol) in 6 mL of THF and the reaction mixture was stirred at the same temperature for 30 min. Then sodium azide (1.6 g, 25 mmol) in 10 mL of water was added dropwise at 0 °C and the mixture was let to stir overnight. The mixture was extracted with two portions of ethyl acetate (15 mL) and the organic phase was washed with saturated sodium bicarbonate (3×40 mL) and with water (2×25 mL), and dried over magnesium sulfate. After the concentration, 1.8 g (68%) of azide **41** (yellow solid, mp 71–73 °C, unstable at room temperature) was obtained. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02 (br d, $J_{6,5}$=7.9 Hz, 1H, H-6), 7.55 (br dd, $J_{4,3}$=7.6 Hz, $J_{4,5}$=7.5 Hz, 1H, H-4), 7.37 (br dd, $J_{5,6}$=7.9 Hz, $J_{5,4}$=7.5 Hz, 1H, H-5), 7.27 (br d, $J_{3,4}$=7.6 Hz, 1H, H-3), 4.05 (s, 2H, –$OCH_2$), 3.71 (s, 3H, –$OCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.2 (s, azide carbonyl), 171.6 (s, ester carbonyl), 136.8 (s, C-2), 133.7 (d, C-4), 132.7 (d, C-6), 131.3 (d, C-5), 129.6 (s, C-1), 127.6 (d, C-3), 51.9 (q, –$OCH_3$), 40.3 (t, –$CH_2$); IR (KBr, cm$^{-1}$): 2280 (s), 2138 (s), 1740 (s), 1691 (s), 1490 (m), 1238 (s), 1169 (s).

### 3.12. Methyl 2-(2-isocyanatophenyl)acetate (2)

The azide **41** (2.0 g, 9 mmol) was refluxed in benzene (25 mL) for 1.5 h and the solvent was evaporated under vacuum to give the isocyanate **2** (1.64 g, 99%), which was not stable at room temperature. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.23 (br d, $J_{3,4}$=7.5 Hz, 1H, H-3), 7.22 (br dd, $J_{4,3}$=7.5 Hz, $J_{4,5}$=6.7 Hz, 1H, H-4), 7.14 (br d, $J_{6,5}$=7.6 Hz, 1H, H-6), 7.12 (br dd, $J_{5,6}$=7.6 Hz, $J_{5,4}$=6.7 Hz, 1H, H-5), 3.69 (s, 3H, –$OCH_3$), 3.66 (s, 2H, –$CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.9 (s, ester carbonyl), 132.9 (s, C-1), 131.0 (d, C-3), 128.9 (s, C-2), 128.4 (d, C-6), 125.9 (d, C-5), 125.8 (s, C-4), 125.0, 52.0 (q, –$OCH_3$), 37.4 (t, –$CH_2$); IR (KBr, cm$^{-1}$): 2280 (s), 2145 (w), 1737 (s), 1591 (m), 1455 (w), 1341 (s), 1223 (s).

### 3.13. Methyl (2-aminophenyl)acetate (45)

To a solution of isocyanate **2** (1.3 g, 6.8 mmol) in dichloromethane (30 mL), water (0.12 g, 6.8 mmol) was added slowly at room temperature and the mixture was stirred at the same temperature for 30 min. After concentration of the solvent, the compound **45** was purified over a short silica gel column eluting with ethylacetate/hexane (3:1) (0.98 g, 89% yield). The spectroscopic data of **45** was in agreement with those reported in the literature.[30]

#### 3.13.1. *Methyl 2-[2-({[2-(2-methoxy-2-oxoethyl)anilino]-carbonyl}amino)phenyl]acetate (**43**)*

To a solution of isocyanate **2** (1.16 g, 6.05 mmol) in dichloromethane (30 mL) the aniline derivative **45** (1.0 g, 6.05 mmol) was added slowly at room temperature and the mixture was stirred at the same temperature for 1 h. The solvent was concentrated under vacuo and the residue was crystallized from ethyl acetate to give **43** (1.96 g, 91%). The spectral data of the isolated compound was same as previously isolated (Section 3.10).

### 3.14. Reaction of 43 with $K_2CO_3$ in acetonitrile

The urea derivative **43** (0.6 g, 1.7 mmol) was suspended in acetonitrile (20 mL). The suspension was heated to 58–60 °C and at that temperature excess potassium carbonate (1.0 g, 7.2 mmol) was added. After stirring for 1 h, excess potassium carbonate was filtered and the solution was concentrated under reduced pressure. The formed products **48** and **49** were separated by treatment of the mixture with chloroform. The condensation product **48** was insoluble in chloroform whereas **49** was soluble. Evaporation of the solvent followed by column chromatography over silica gel (25 g) eluting with ethyl acetate/*n*-hexane (7:1) provided *1,3-dihydro-2H-indol-2-one (**49**)* in 35% yield (0.08 g). The major product **48** crystallized with methanol/chloroform (3:1). Yellow crystals, mp 205–206 °C (0.25 g, 58%).

#### 3.14.1. *2-Hydroxy-N,N′-methylphenylacetato-1H-indole-1,3-dicarboxamide (**48**)*

$^1$H NMR (400 MHz, acetone-$d_6$) $\delta$ 12.48 (br s, –NH), 10.59 (br s, –NH), 8.38 (dd, $J_{6c,5c}$=7.9 Hz, $J_{6c,4c}$=1.1 Hz, 1H, H-6c), 8.08 (br d, $J_{7,6}$=7.7 Hz, 1H, H-7), 8.04 (br d, $J_{6b,5b}$=8.0 Hz, 1H, H-6b), 7.88 (dd, $J_{4,5}$=7.7 Hz, $J_{4,6}$=1.1 Hz, 1H, H-4), 7.30 (dd, $J_{3b,4b}$=8.4 Hz, $J_{3b,5b}$=1.5 Hz, 1H, H-3a), 7.29 (dd, $J_{5a,6a}$=8.1 Hz, $J_{5a,4a}$=7.7 Hz, 1H, H-5a), 7.20 (dd, $J_{3c,4c}$=7.3 Hz, $J_{3c,5c}$=1.5 Hz, 1H, H-3b), 7.18 (ddd, $J_{5c,4c}$=8.4 Hz, $J_{5c,6c}$=7.7 Hz, $J_{5c,3c}$=1.5 Hz, 1H, H-5b), 7.07 (ddd, $J_{4b,3b}$=8.4 Hz, $J_{4b,5b}$=7.7 Hz, $J_{4b,6b}$=1.1 Hz), 6.96 (dt, $J_{5,4}$=$J_{5,6}$=7.7 Hz, $J_{5,7}$=1.1 Hz, 1H, H-5), 6.90 (ddd, $J_{4c,5c}$=8.4 Hz, $J_{4c,3c}$=7.3 Hz, $J_{4c,6c}$=1.1 Hz, 1H, H-4c), 6.79 (dt, $J_{6,5}$=$J_{6,7}$=7.7 Hz, $J_{6,4}$=1.1 Hz, 1H, H-6), 3.84 (s, 2H, –$CH_2$), 3.81 (s, 2H, –$CH_2$), 3.59 (s, 3H, –$OCH_3$), 3.58 (s, 3H, –$OCH_3$); $^{13}$C NMR (100 MHz, acetone-$d_6$) $\delta$ 171.8 (s, ester carbonyl), 171.7 (s, ester carbonyl), 165.4 (s, carbonyl carbon), 165.1 (s, C-2), 140.1 (s, C-1b), 138.1 (s, C-1c), 131.5 (d, C-3b), 131.1 (d, C-3c), 130.6 (s, C-7a), 130.1 (s, C-3a), 128.3 (d, C-5b), 127.9 (d, C-5c), 126.5 (s, C-2b), 124.1 (d, C-4b), 123.7 (s, C-2c), 123.0 (d, C-4b), 122.7 (d, C-5), 121.8 (d, C-4c), 121.1 (d, C-6c), 118.9 (d, C-6), 117.5 (d, C-4), 114.1 (d, C-7), 86.1 (s, C-3); IR (KBr, cm$^{-1}$): 3321 (m), 1723 (s), 1699 (s), 1563 (s), 1403 (s), 1283 (m), 1133 (s); HRMS calcd for $C_{28}H_{25}N_3O_7$: 515.1693, found: 515.1690.

#### 3.14.2. *1,3-Dihydro-2H-indol-2-one (**49**)*

White solid, mp 118–120 °C, lit. mp 124 °C.[31] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.10 (s, 1H, H-1), 7.25 (d, $J_{7,6}$=7.2 Hz, 1H, H-7), 7.20 (dd, $J_{6,5}$=7.5 Hz, $J_{6,7}$=7.2 Hz, 1H, H-6), 7.0 (t, $J_{5,6}$=7.5 Hz, $J_{5,4}$=7.8 Hz, 1H, H-5), 6.9 (d, $J_{4,5}$=7.8 Hz, 1H, H-4), 3.5 (s, 2H, H-3); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 178.3 (s, C-2), 142.6 (s, C-7a), 129.5 (d, C-6), 127.9 (s, C-3a), 125.3 (d, C-4), 122.4 (d, C-5), 109.9 (d, C-7), 36.34 (t, C-3).

### 3.15. Methyl [2-({[(4-nitrophenyl)amino]carbonyl}amino)-phenyl]acetate (50)

To a solution of isocyanate **2** (0.48 g, 2.5 mmol) in dichloromethane (25 mL), 4-nitroaniline (0.35 g, 2.5 mmol) was added and the mixture was stirred at 35 °C for 3 h. The solvent was removed and the urethane was purified by recrystallization from ethyl acetate (yellow solid, mp 175–176 °C; 0.74 g, 90%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.14 (br d, $J_{3a,2a}$=$J_{5a,6a}$=8.3 Hz, 2H, H-3a and H-5a), 7.67 (br s, –NH), 7.60 (br d, $J_{3,4}$=8.0 Hz, 1H, H-3), 7.56 (br d, $J_{6a,5a}$=$J_{2a,3a}$=8.3 Hz, 2H, H-2a and H6a), 7.37 (br s, 1H, –NH), 7.34 (br dd, $J_{6,5}$=8.0 Hz, $J_{6,4}$=1.6 Hz, 1H, H-6), 7.27–7.21 (m, 2H, H-5 and H-6), 3.71 (s, 2H, –$OCH_2$), 3.69 (s, 3H, –$OCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.3 (s, ester carbonyl), 152.9 (s, amide carbonyl), 145.0 (s, C-1a), 142.6 (s, C-4a), 136.0 (s, C-2), 131.3 (d, C-6), 128.9 (d, C-4), 128.5 (s, C-1), 126.6 (d, C-3), 126.4 (d, C-5), 125.0 (d, C-3a and C-5a), 118.3 (d, C-2a and C-6a), 52.6 (q, –$OCH_3$), 38.0 (t, –$CH_2$); IR (KBr, cm$^{-1}$): 3352 (m), 1735 (s), 1659 (s), 1590 (s), 1563 (s), 1332 (s), 1179 (m). Anal. Calcd for $C_{16}H_9N_3O_3$: C, 58.36; H, 4.59; N, 12.76. Found: C, 58.75; H, 4.61; N, 12.56.

### 3.16. Reaction of 50 with $K_2CO_3$

The urea derivative **50** (0.3 g, 0.9 mmol) was suspended in acetonitrile (10 mL). The mixture was heated to 58–60 °C and at that temperature excess potassium carbonate (1 g, 7.2 mmol) was added. The reaction was completed in 1 h. Excess potassium carbonate was filtered and the solution was concentrated under reduced pressure. The residue was treated with chloroform. 1,3-Dihydro-2*H*-indol-2-one (**49**) was separated as described above (0.03 g, 25%). The major product **52** was recrystallized from methanol/chloroform (3:1) (red-brown solid, mp 266–267 °C; 0.12 g, 57%).

#### 3.16.1. *2-Hydroxy-N,N′-bis(4-nitrophenyl)-1H-indole-1,3-dicarboxamide (**52**)*

$^1$H NMR (400 MHz, acetone-$d_6$) $\delta$ 13.76 (br s, –NH), 11.49 (br s, –NH), 8.30 (br d, $J_{3b,2b}$=$J_{5b,6b}$=8.3 Hz, 2H, H-3b and H-5b), 8.25 (br d, $J_{7,6}$=8.0 Hz, 1H, H-7), 8.20 (br d, $J_{3c,2c}$=$J_{5c,6c}$=8.3 Hz, 1H, H-3c and H-5c), 8.1 (br d, $J_{4,5}$=7.1 Hz, 1H, H-5), 7.99 (m, 4H, H-4b, H-6b, H-4c, and H-6c), 7.05 (br dd, $J_{5,6}$=7.6 Hz, $J_{5,4}$=7.1 Hz, 1H, H-5), 6.99 (br dd, $J_{6,5}$=7.6 Hz, $J_{6,7}$=8.0 Hz, 1H, H-5b); $^{13}$C NMR (100 MHz, acetone-$d_6$) $\delta$ 166.4 (s, carbonyl), 165.5 (s, double bond), 152.7 (s, amide carbonyl), 148.9 (s, C-4c), 146.8 (s, C-1c), 143.3 (s, C-4b), 141.6 (s, C-1b), 131.6 (s, C-6), 130.6 (s, C-7a), 126.9 (s, C-3a), 125.9 (d, C-3c and C-5c), 123.5 (d, C-2c and C-6c), 119.9 (d, C-5), 119.8 (d, C-3b and C-5b), 118.5 (d, C-4), 118.3 (d, C-2b and C-6b), 114.8 (d, C-7), 87.3 (s, C-3); IR (KBr, cm$^{-1}$): 3326 (m), 2909, 1681 (s), 1595 (s), 1504 (s), 1470 (s), 1406 (s), 1328 (m), 1133 (m). Anal. Calcd for $C_{22}H_{15}N_5O_7$: C, 57.27; H, 3.28; N, 15.18. Found: C, 57.45; H, 3.20; N, 14.96.

### 3.17. Methyl {2-[(anilinocarbonyl)amino]phenyl}acetate (53)

To a solution of isocyanate **2** (0.76 g, 4 mmol) in dichloromethane (25 mL), aniline (0.37 g, 4 mmol) was added and the mixture was stirred at room temperature for 2 h. The solvent was removed and the urethane was purified by recrystallization from ethyl acetate (white solid, mp157–158 °C; 1.13 g, 98%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.64 (br d, $J_{3,4}$=7.9 Hz, 1H, H-3), 7.4 (br s, 1H, –NH), 7.25–7.38 (m, 6H, arom.), 7.16 (br dd, $J_{4,3}$=7.9 Hz, $J_{4,5}$=7.5 Hz, 1H, H-4), 7.1 (br t, $J_{5,4}$=$J_{5,6}$=7.3 Hz, 1H, H-5), 6.78 (br s, 1H, –NH), 3.67 (s, 2H, –$CH_2$), 3.63 (s, 3H, –$OCH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.7 (s, ester carbonyl), 153.9 (s, amide carbonyl), 138.3 (s, C-1a), 136.7 (s, C-2), 131.0 (d, C-6), 129.1 (d, C-3a and C-5a), 128.7 (d, C-3), 128.2 (s, C-1), 126.2 (d, C-4), 125.9 (d, C-5), 123.8 (d, C-2a and C-6a), 120.6 (d, C-4a), 52.4 (q, –$OCH_3$), 38.1 (t, –$CH_2$); IR (KBr, cm$^{-1}$): 3319 (m), 1736 (s), 1647 (s), 1455 (m), 965 (m). Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.06; H, 5.70; N, 9.72.

### 3.18. Reaction of 53 with NaH in the presence of $Ac_2O$

To a solution of urethane **53** (0.5 g, 1.8 mmol) in freshly distilled THF (15 mL) at 0 °C, sodium hydride (0.086 g, 3.6 mmol) was added and the resulting mixture was stirred at the same temperature for 30 min. Then acetic anhydride (0.26 g, 2.5 mmol) was added to this solution and stirred at room temperature overnight. The product **54** precipitated from the reaction medium. The precipitate was filtered off and purified by washing with chloroform (0.4 g, 75.5%). The filtrate was concentrated under vacuum to give the crude **55**, which was recrystallized from ethylacetate/hexane (5:2) (0.07 g, 16.0%).

### 3.19. Synthesis of 3-acetyl-2-hydroxy-*N*-phenyl-1*H*-indole-1-carboxamide (54)

White solid, mp 168–169 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.30 (s, 1H, NH), 8.12 (dd, $J_{4,5}$=8.0 Hz, $J_{4,6}$=1.5 Hz, 1H, H-4), 7.83 (br d, $J_{6,7}$=6.6 Hz, 1H, H-7), 7.59 (d, $J_{10,11}$=$J_{14,13}$=7.3 Hz, 2H, H-10 and H-14), 7.35 (br t, $J_{10,11}$=$J_{11,12}$=7.3 Hz, 2H, H-11 and H-14), 7.17 (dt, $J_{6,7}$=$J_{5,6}$=7.3 Hz, $J_{4,6}$=1.5 Hz, 1H, H-6), 7.15 (dt, $J_{4,5}$=$J_{5,6}$=7.3 Hz, $J_{5,7}$=1.4 Hz, 1H, H-5), 7.10 (t, $J_{6,7}$=7.3 Hz, 1H, H-12), 2.65 (s, 3H, –$CH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 176.3 (s, C-15), 170.6 (s, C-2), 150.6 (s, C-8), 138.3 (s, C-9), 135.0 (s, 7a), 129.7 (d, C-11 and C-13), 125.8 (d, C-6), 124.5 (d, C-12), 124.4 (d, C-5), 124.3 (d, C-6), 122.3 (s, 3a), 120.5 (C-10 and C-14), 115.1 (d, H-4), 101.6 (s, C-3), 20.4 (q, C-16); IR (KBr, cm$^{-1}$): 3202 (m), 3144 (m), 1720 (s), 1662 (s), 1589 (s), 1560 (s), 1461 (s), 1375 (m), 1294 (s), 1227 (s); MS: 70 eV, *m*/*z* 294 ($M^+$, 15%), 175 (100%), 157 (49%), 133 (24%), 119 (38%), 91 (25%), 77 (26%). Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.49; H, 4.71; N, 9.84.

#### *3.19.1. 2-Oxo-N-phenylindoline-1-carboxamide (**55**)*

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.59 (br s, 1H, H–NH), 8.24 (br d, $J_{7,6}$=8.2 Hz, 1H, H-7), 7.51 (br d, $J_{2b,3b}$=$J_{6b,5b}$=8.1 Hz, 2H, H-2b and H-6b), 7.28 (m, 3H, H-5, H-3b, and H-5b), 7.22 (br d, $J_{4,5}$=8.1 Hz, 1H, H-4), 7.18 (m, 2H, H-6 and H-4b), 3.7 (s, 2H, –$CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 177.7 (s, C-2), 149.5 (s, carbonyl), 141.6 (s, C-7a), 137.1 (s, 1b), 129.1 (d, C-3b and C-5b), 128.5 (d, C-4), 124.7 (d, C-5), 124.5 (d, C-6), 123.9 (d, C-7), 122.9 (s, C-3a), 120.6 (d, C-2b and C-6b), 116.8 (d, C-4b), 37.1 (t, –$CH_2$).

### 3.20. Reaction of 53 with $K_2CO_3$ in acetonitrile

The urea derivative **53** (2.47 g, 8.7 mmol) was suspended in acetonitrile (20 mL). The suspension was heated to 58–60 °C and at that temperature excess potassium carbonate (4 g, 29 mmol) was added. The reaction was complete in 1 h. Excess potassium carbonate was filtered and the solution was concentrated under reduced pressure. The residue was treated with chloroform to separate the soluble compound **49**. The major compound **56** was recrystallized from methanol/chloroform (3:1).

#### *3.20.1. 2-Hydroxy-N,N′-diphenyl-1H-indole-1,3-dicarboxamide (**56**)*

Purple solid, mp 245–247 °C; 0.98 g, 60%. $^1$H NMR (400 MHz, acetone-$d_6$) $\delta$ 12.94 (br s, 1H, –NH), 10.93 (br s, 1H, –NH), 8.28 (br d, $J_{7,6}$=8.0 Hz, 1H, H-7), 8.09 (br d, $J_{4,5}$=7.6 Hz, 1H, H-4), 7.79 (br d, $J_{6c,5c}$=$J_{2c,3c}$=8.0 Hz, 2H, H-6c and H-2c), 7.74 (br d, $J_{6b,5b}$=$J_{2b,3b}$=8.0 Hz, 2H, H-6b and H-2b), 7.36 (br dd, $J_{5c,6c}$=$J_{3c,2c}$=8.0 Hz, $J_{5c,4c}$=$J_{3c,4c}$=7.7 Hz, 2H, H-5c and H-3c), 7.25 (br dd, $J_{5b,6b}$=$J_{3b,2b}$=8.0 Hz, $J_{5b,4b}$=$J_{3b4b}$=7.7 Hz, 2H, H-5b and H-3b), 7.05 (br t, $J_{4c,5c}$=$J_{4c,3c}$=7.4 Hz, 1H, H-4c), 6.96 (br t, $J_{5,4}$=$J_{5,6}$=7.5 Hz, 1H, H-5), 6.89 (br dd, $J_{4b,5b}$=7.7 Hz, $J_{4b,3b}$=7.7 Hz, 1H, H-4b), 6.88 (br dd, $J_{6,7}$=8.0 Hz, $J_{6,5}$=7.6 Hz, 1H, H-6); $^{13}$C NMR (100 MHz, acetone-$d_6$) $\delta$ 165.4 (s, C-2), 165.2 (s, double bond), 152.3 (s, amide carbonyl), 141.9 (s, C-1b), 139.8 (s, C-1c), 130.7 (s, C-7a), 130.3 (s, C-3a), 128.7 (d, C-3b and C-5b), 128.4 (d, C-3c and C-5c), 122.3 (d, C-6), 121.8 (d, C-5), 120.5 (d, C-4b), 119.4 (d, C-4c), 118.3 (d, C-6b and C-2b), 117.9 (d, C-2c and C-6c), 117.2 (d, C-4), 113.6 (d, C-7), 85.9 (s, C-3). IR (KBr, cm$^{-1}$): 3335 (w), 1691 (s), 1595 (s), 1469 (m), 1437 (s), 1353 (m), 1244 (m), 1134 (m). Anal. Calcd for $C_{22}H_{17}N_3O_3$: C, 71.15; H, 4.61; N, 11.31. Found: C, 71.41; H, 4.33; N, 11.12.

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## Supplementary data

$^1$H and $^{13}$C NMR spectra for all new compounds (74 pages) are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.03.097.

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