EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201200678

# Synthesis and Reactivity of the 3-Substituted Isoindolinone Framework to Assemble Highly Functionalized Related Structures

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**Keywords:** Synthetic methods / Domino reactions / Aldol reactions / Nitrogen heterocycles

An efficient potassium carbonate-catalyzed synthesis of 3-substituted isoindolinones through tandem aldol/cyclization reactions of active methylene compounds with 2-cyanobenzaldehyde is described. The utility of the obtained isoindolinones has been demonstrated through an exploration of the chemical space by employing a series of interesting methodologies that led to diverse, highly functionalized compounds. Among them, a surprisingly straightforward potassium carbonate-catalyzed double tandem reaction led to tricyclic hemiaminal derivatives.

## Introduction

Isoindolinones are interesting heterocyclic compounds due to their presence in many naturally occurring substances (Figure 1)[1a,1b] and because of their extensive use in therapeutic activities[1–4] such as antihypertensive,[1c] antipsychotic[1d–1f] anesthetic,[1g,1h] anxiolytic,[1i] antiviral,[1j–1l] and antileukemic[1m] agents. In particular, some examples of biologically active compounds of general formula **I** that possess anxiolytic, sedative, hypnotic, and muscle relaxant activity, are described in Figure 2.[1n] Therefore, much attention has been devoted to the development of new methods for the synthesis of 3-substituted isoindolinones, which constitute valuable scaffolds in many synthetic routes.[2,3] However, in spite of the considerable interest in the field, construction of this heterocyclic core often requires the use of metal catalysts and/or inflexible multistep syntheses.[1–3]

In this context, as part of our ongoing research on the challenging aldol additions of active methylene compounds,[4] we have recently reported a series of simple methodologies for the synthesis of 3-substituted isoindolinones.[5–7] All these methods are based on the aldol reaction of several classes of readily enolizable 1,3-dicarbonyl compounds with 2-cyanobenzaldehyde in the presence of triethylamine,[5] or by conveniently exploiting electroinitiated[6] or organocatalyzed procedures.[7]

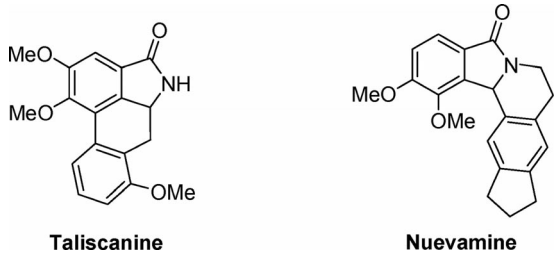


Figure 1. Some naturally occurring isoindolinone substances.

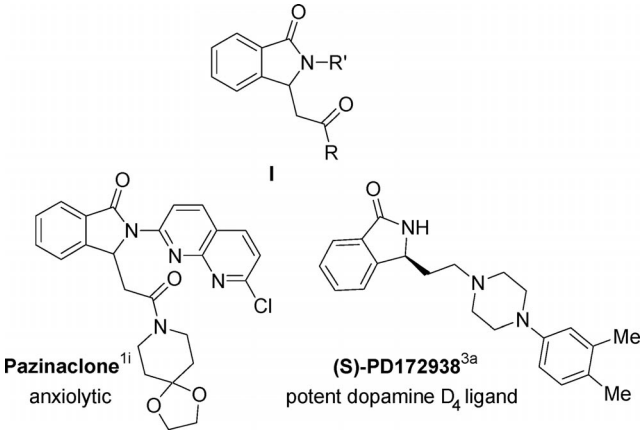


Figure 2. Some biologically active isoindolinone derivatives.

Interestingly, based also on Ramström's works,[8] it has been demonstrated that these reactions proceed through a tandem aldol addition/cyclization/rearrangement and a final aza-Michael process (Scheme 1). In these studies we have demonstrated that the intramolecular trapping of the aldol adduct **a** is the key requisite that drives these difficult reactions to completion due to the unstable nature of the

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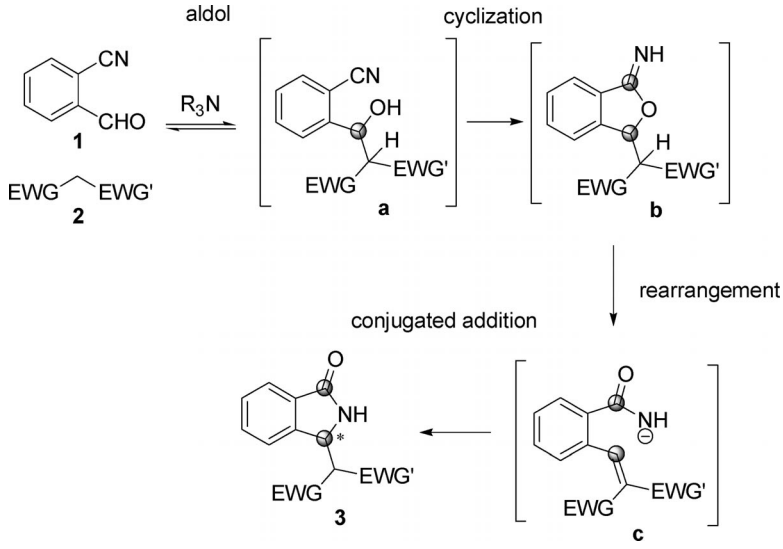
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200678.




Scheme 1.

aldol intermediates **a**.[4,5] All the tandem processes are promoted by weak bases, which both generate the nucleophilic species and deprotonate the intermediate **b**.

The role of the base should not be underestimated and some limitations have been highlighted in the course of these studies:[5] (1) one equivalent of $Et_3N$ is usually required to guarantee reasonable reaction time and high yields; (2) the steric hindrance of both the nucleophile and the base affects the efficiency of the process. For these reasons, considering the convenience of this approach, first we decided to continue the investigation in an effort to overcome these limitations and, at the same time, to develop a more convenient synthesis of 3-substituted isoindolinones. We then broadly tackled the second reactivity with the aim of demonstrating the utility of these isoindolinones in the synthesis of molecules with enhanced molecular diversity, mimicking the structures of valuable compounds already reported in literature. All these aspects are discussed in this article.

## Results and Discussion

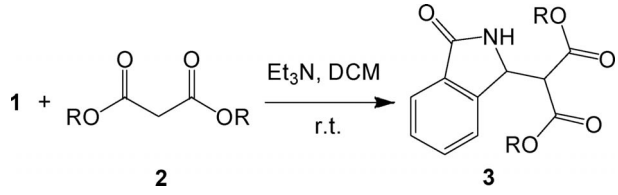
### 2.1 A New Approach to a More Efficient Tandem Reaction

As anticipated in the previous section, the nature of the base plays an important role in the efficiency of the process in terms of catalyst loading and substrate scope (Table 1). In fact, as reported in Table 1, it can be seen that the use of triethylamine (0.2 equiv.) in dichloromethane (Scheme 2) led to only 40% yield after 24 h for the reaction of dimethyl malonate, whereas one equivalent was necessary to obtain high yields (compare in Table 1, entries 1 and 2); moreover, sterically hindered substrates such as di-*tert*-butyl malonate and di-(–)-menthyl malonate proved to be almost completely unreactive and the starting materials were recovered quantitatively after 18 h reaction (Table 1, entries 3 and 4).

Table 1. Isoindolinone synthesis in the presence of $Et_3N$.[a]

| Entry | Nucleophile (R) | $Et_3N$ [equiv.] | *t* [h] | **3** | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | Me | 0.2 | 24 | **3a** | 40 |
| 2 | Me | 1.0 | 18 | **3a** | 87 |
| 3 | *t*Bu | 1.0 | 18 | – | < 10 |
| 4 | (–)-menthyl | 1.0 | 18 | – | no reaction |

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.33 mmol), $Et_3N$ in $CH_2Cl_2$ (2.0 mL). [b] Isolated yield.

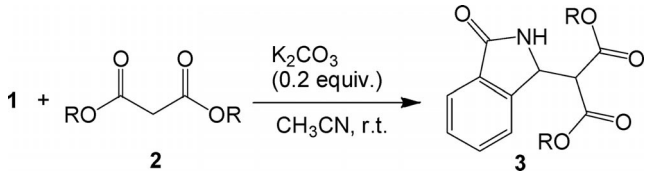



Scheme 2.

Based on these findings, we thought that the fine tuning of both the basicity and the steric bulk of bases such as $K_2CO_3$ could lead to more satisfactory results. In fact, stronger bases can give side reactions, such as Knoevenagel condensation, whereas weaker bases are not able to deprotonate active methylene compounds. More hindered bases such as $iPr_2NEt$ were less reactive. Moreover, the use of $K_2CO_3$ has the added value of low cost, ready availability and reduced environmental impact. Encouraged by these results and considering our recent findings on the synthesis of 3-substituted isobenzofuranones,[9] in preliminary experiments performed with dimethyl malonate as model nucleophile, we tried $K_2CO_3$ under different reaction conditions. First, a stoichiometric amount of base in dichloromethane was used, which gave a low conversion (ca. 20%) in 24 h reaction time. Thus, we decided to change the solvent to acetonitrile, which facilitated higher $K_2CO_3$ solubility. In this way we were pleased to observe that even catalytic

amounts of $K_2CO_3$ (0.2 equiv.) were particularly effective in catalyzing the tandem reaction with a wide range of malonates (Scheme 3, Table 2, entries 1–6). Sterically hindered malonates, such as di-*tert*-butyl malonate and di-(–)-menthyl malonate were also found to be particularly effective and, in both cases, high yields were obtained (Table 2, entries 2 and 3, respectively).




Scheme 3.

Table 2. Isoindolinone synthesis employing a catalytic amount of $K_2CO_3$ (0.2 equiv.).[a]

| Entry | Nucleophile (R) | *t* [h] | **3** | Yield [%][b] |
|---|---|---|---|---|
| 1 | Me | 10 | **3a** | 96 |
| 2 | *t*Bu | 30 | **3b** | 88 |
| 3 | (–)-menthyl | 18 | **3c** | 75 (1:1)[c] |
| 4 | Et | 18 | **3d** | 92 |
| 5 | *i*Pr | 18 | **3e** | 93 |
| 6 | Bn | 18 | **3f** | 89 |

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.33 mmol), $K_2CO_3$ (0.06 mmol), MeCN (0.5 mL). [b] Isolated yield. [c] Diastereomeric ratio was calculated on the basis of $^1$H NMR spectroscopic analysis of the crude product.

The catalytic role of $K_2CO_3$ is evident considering the last two steps of the mechanism depicted in Scheme 1. The iminophthalane intermediate **b** is subjected to base deprotonation to give **c**, whereas after aza-Michael addition, the enolate form of **3** is protonated to again give the base, which can start another catalytic cycle.

On the basis of these results, we then focused our investigation on malonoamide methyl ester derivatives, which are easily obtained in high yields by amine displacement reactions with dimethyl malonate (see the Supporting Information for details). This choice of substrate was made because of the possibility of testing relatively unexplored active methylene compounds and because, at the same time, nitrogen-containing moieties could be introduced into the isoindolinone scaffold, such as piperazines. These moieties have particularly interesting properties and applications also in combination with isoindolinone scaffolds.[3a,3b] Under the optimized reaction conditions, we were pleased to observe good to high yields of the final adducts also for these nucleophiles (Table 3), albeit with rather low diastereoselectivity, as previously reported with nonsymmetric nucleophiles such as β-keto esters.[5]

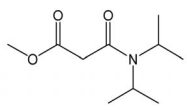
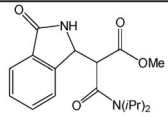
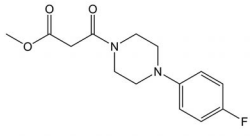
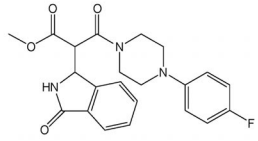
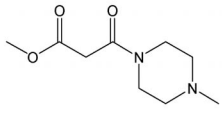
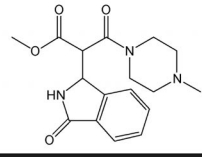
## 2.2 The Second Reactivity of 3-Substituted Isoindolinones

A systematic investigation of the second reactivity of the obtained isoindolinones was then conducted to demonstrate the possibility of using these compounds in an effective synthesis of interesting, highly functionalized molecules that could be suitable for a rational and extensive drug discovery programme. In this investigation, following the Diverse Oriented Synthesis (DOS) approach,[10] we explored the chemical space of isoindolinones reactivity by considering a sequence of two or three organic transformations to enlarge the molecular diversity.[11]

### *2.2.1 Decarboxylation Reactions*

First, we considered the possibility of decarboxylation of the methyl ester derivatives because, in this way, for example, analogues of water-soluble sedative-hypnotic agents can be conveniently obtained from the diastereomeric mixtures

Table 3. Isoindolinone synthesis in the presence of $K_2CO_3$.[a]

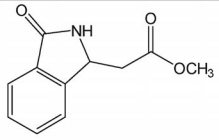
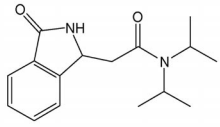
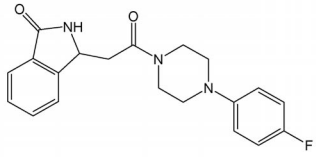
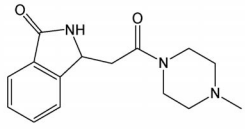
| Entry | Nucleophile | *t* [h] | Product | **3** | Yield [%][b] |
|---|---|---|---|---|---|
| 1 |  | 30 |  | **3g** | 76 (2:1)[c] |
| 2 |  | 24 |  | **3h** | 90 (1.4:1)[c] |
| 3 |  | 18 |  | **3i** | 93 (2.5:1)[c] |

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.33 mmol), $K_2CO_3$ (0.06 mmol), MeCN (0.5 mL). [b] Isolated yield. [c] Diastereomeric ratios were calculated on the basis of $^1$H NMR spectroscopic analysis of the crude product.

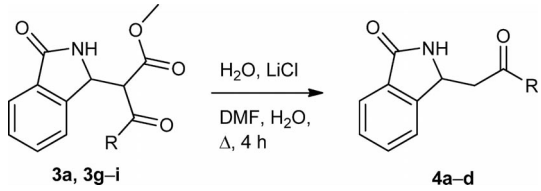
  

of **3g–i** (Table 4).[3a,3b] In this investigation we tried a modification of the known mild methodology developed by Krapcho and co-workers,[12] which employs LiCl/water/*N*,*N*-dimethylformamide (DMF) mixtures. However, by employing the original procedure in the presence of only 1.0 equiv. water,[12] this method did not give any reaction because the limited amount did not allow satisfactory reflux conditions. In fact this mild procedure is reported to work on large amounts of substrate.[12] For this reason, the DMF/$H_2O$ ratio was increased to 5 v/v, which was found to be particularly effective and gave the desired products in high yields also for low amounts of substrate (Scheme 4), and in the presence of other functional groups such as piperazines and amides.

Table 4. LiCl/$H_2O$-promoted decarboxylation.[a]

| Entry | 3: Starting isoindolinone | 4: Final product | | Yield [%][b] |
|---|---|---|---|---|
| 1 | **3a** |  | **4a** | 83 |
| 2 | **3g** |  | **4b** | 89 |
| 3 | **3h** |  | **4c** | 89 |
| 4 | **3i** |  | **4d** | 88 |

[a] Reaction conditions: **3a** and **3g–i** (0.14 mmol), LiCl (0.54 mmol), $H_2O$ (0.4 mL), DMF (2.0 mL), reflux. [b] Isolated yield.



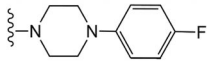
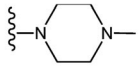

Scheme 4.

### 2.2.2 NH Arylation

Another important feature for the rational design of new isoindolinone-based libraries is related to the possibility of obtaining *N*-arylated and *N*-alkylated products in addition to *N*H-free compounds. This is relevant for the evaluation of the biological activity, as reported in many medicinal chemistry studies,[3a,3b] even if the described synthetic methodologies often focus on limited or particular classes of compounds. Thus, we tested the well-known copper-catalyzed amidation of aryl halides developed by Buchwald and co-workers[13] on the decarboxylated substrates **4a**,**c**,**d** as well as on the dimethyl malonate derivative **3a**, for comparison, and 2-iodopyridine as a model aryl compound (Scheme 5).

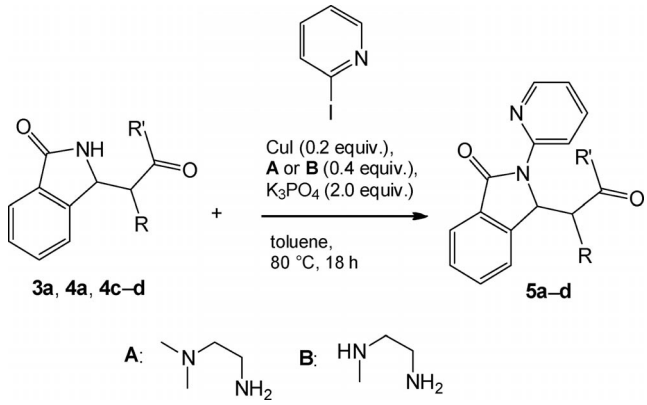
Under the conditions described in Scheme 5 and Table 5, complete conversion of **4a** was not observed in the presence of 5 mol-% $Cu^I$. Thus, an increase in the amount of catalyst to 20 mol-% was necessary to achieve almost complete conversion of the starting material, demonstrating the effective-

Table 5. $Cu^I$-catalyzed *N*H arylation.[a]

| Entry | Substrate | R | R' | CuI [equiv.] | Ligand [equiv.] | *t* [h] | 5 | Yield [%][b] |
|---|---|---|---|---|---|---|---|---|
| 1 | **4a** | H | OMe | 0.05 | **A** (0.10) | 18 | **5a** | 48 |
| 2 | **4a** | H | OMe | 0.20 | **A** (0.40) | 18 | **5a** | 67 |
| 3 | **4a** | H | OMe | 0.20 | **B** (0.40) | 18 | **5a** | 65 |
| 4 | **3a** | $CO_2Me$ | OMe | 0.20 | **B** (0.40) | 18 | **5b** | 67 |
| 5 | **4c** | H |  | 0.20 | **A** (0.40) | 48 | **5c** | 59 |
| 6 | **4d** | H |  | 0.20 | **B** (0.40) | 18 | **5d** | 69 |

[a] Reaction conditions: CuI (0.029 mmol), $K_3PO_4$ (0.292 mmol), **A** or **B** (0.058 mmol), 2-iodopyridine (0.175 mmol), 3-substituted isoindolinone (0.146 mmol), toluene (1 mL), under $N_2$ atmosphere, 80 °C. [b] Isolated yield.

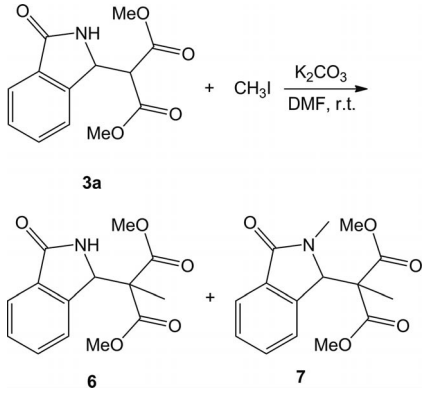



Scheme 5. Cu$^{I}$-catalyzed *N*H arylation.

ness of Buchwald's procedure also with structurally complex substrates. The use of two different ligands **A** and **B** gave similar results, whereas **4c** was found to be less reactive and longer reaction times were necessary to obtain satisfactory conversion. However, in all cases, only moderate to good yields were obtained because of the tendency of the products to decompose during chromatography ($^1$H NMR spectroscopic analysis of the crude reaction mixture did not reveal significant formation of byproducts).

### 2.2.3 CH vs. NH Alkylation

We then analyzed the reactivity of the acidic methine group with model alkylation reactions mainly because obtaining a quaternary carbon in **3a** is not possible directly through the reaction depicted in Scheme 1. The use of nucleophiles such as dimethyl methylmalonate leads to iminophthlane intermediates **b**[5] (Scheme 1) and the lack of the acidic CH proton does not allow subsequent base-catalyzed rearrangement. A possibility to overcome this serious problem is given by the model reaction of Scheme 6, using $K_2CO_3$ and $CH_3I$.




Scheme 6. Alkylation reaction of **3a**.

Under the conditions reported in Table 6, it can be clearly seen that at short reaction time it is possible to obtain the monoalkylated compound **6** with good selectively and moderate yield, in a mixture with the starting material **3a**, and only 3% dialkylated **7** (Table 6, entry 1). Conversely, the use of larger amounts of $CH_3I$ and $K_2CO_3$ and a longer reaction time increased the amount of **7** formed (Table 6, entry 2), and allowed a range of products to be obtained that were easily separable by chromatography, simply by changing the reaction conditions.

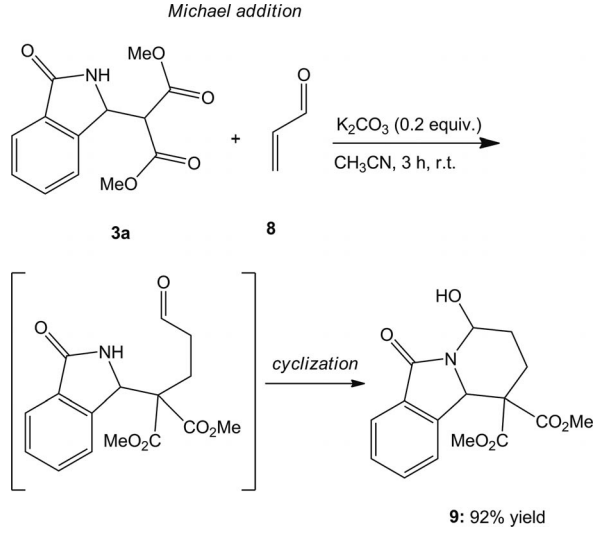
Table 6. Alkylation reaction of **3a**.

| Entry | $K_2CO_3$ [equiv.] | $CH_3I$ [equiv.] | *t* [h] | Yield **6** [%][a] | Yield **7** [%][a] |
|---|---|---|---|---|---|
| 1 | 1.5 | 1.0 | 1 | 61 | 3 |
| 2 | 2.5 | 2.5 | 18 | 41 | 58 |

[a] Isolated yield.

### 2.2.4 Further Evaluation of the Reactivity at the Methine Group: One-Pot Double Tandem Reactions

The reactivity at the acidic methine moiety is an important aspect of these isoindolinone derivatives that can enlarge enormously the molecular diversity of this class of compounds. Thus, we investigated the Michael addition of acroleine **8** on **3a** in the presence of $K_2CO_3$. Interestingly, under the conditions detailed in Scheme 7, we were pleased to observe the formation of the tricyclic compound with hemiaminal functionality **9** in high yields and with high diastereoselectivity. This further reaction is clearly due to a tandem process involving Michael addition followed by a cyclization at the amide group. It is worth noting that a similar tricyclic subunit is present in a non-nucleoside HIV-1 reverse transcriptase inhibitor[3c] and can be considered to be an analogue of indolizidine compounds.[2g]

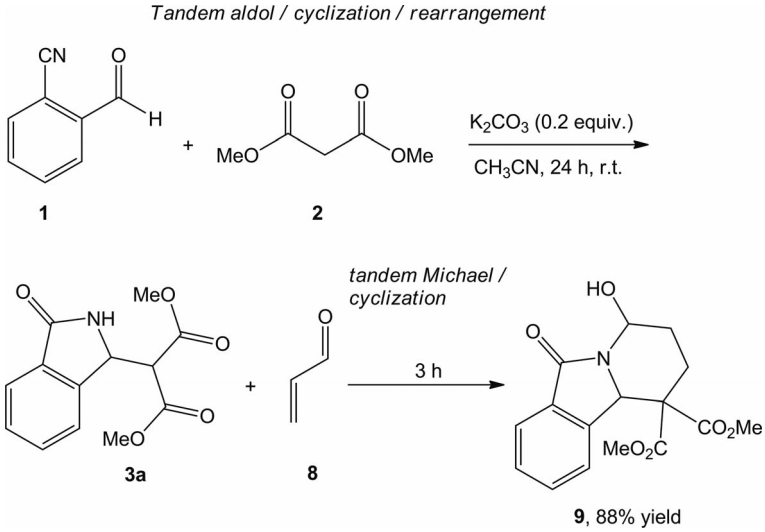



Scheme 7.

Because this further process is also catalyzed by $K_2CO_3$, we thought to combine the isoindolinone synthesis with the Michael/cyclization tandem process, as shown in Scheme 8, simply by adding acrolein after the complete formation of the isoindolinone (detected by TLC analysis).

Remarkably, at the end of the entire one-pot, double tandem process, a high yield of **9** was observed. Furthermore, the procedure was highly diastereoselective, which provides further opportunities to apply this simple chemistry, mainly based on the use of $K_2CO_3$, to the selective synthesis of




Scheme 8. One-pot double tandem reaction.

other members of this interesting class of compounds. The relative configuration of **9** was found to be *R*,*R* (and *S*,*S* for the respective enantiomer), which was established on the basis of X-ray crystallographic analysis of single crystals (Figure 3).

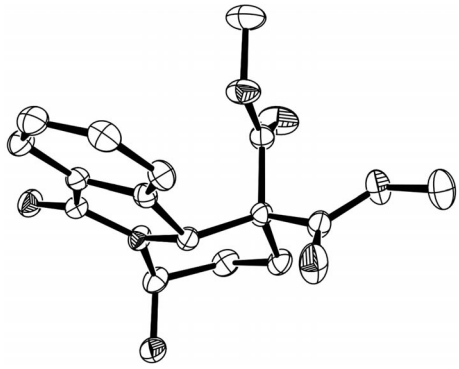


Figure 3. Ortep structure of **9**.

## 3. Conclusions

We have described an improved approach to the synthesis of 3-substituted isoindolinones by employing a $K_2CO_3$-catalyzed tandem aldol/cyclization/rearrangement reaction of 2-cyanobenzaldehyde with malonates and malonoamide methyl esters. Unlike the reaction promoted by $R_3N$,[5] this new method also proved to be effective with hindered nucleophiles and under catalytic conditions, giving the final products in high yields. A systematic study of the second reactivity highlighted the great flexibility of the approach and allowed the synthesis of a wide range of diverse, highly functionalized compounds by employing only a few synthetic steps. This study also provided the opportunity to develop new methods and to test and adapt well-known procedures to generate highly functionalized substrates.

## Experimental Section

**General Remarks:** All reactions were performed using commercially available compounds without further purification. Column chromatographic purification of products was carried out using silica gel 60 (70–230 mesh, Merck). NMR spectra were recorded with Bruker DRX 400, 300, 250 spectrometers (400, 300, and 250 MHz for $^1H$, and 100, 75, and 62.5 MHz for $^{13}C$) and with Varian AV-300 or AV-400 spectrometers. Spectra were referenced to residual $CHCl_3$ ($\delta$ = 7.26 ppm for $^1H$; $\delta$ = 77.23 ppm for $^{13}C$); coupling constants ($J$) are reported in Hz. Yields are given for isolated products showing one spot on a TLC plate and with no detectable impurities in the NMR spectra. Mass spectral analyses were carried out with an electrospray spectrometer (Waters 4 micro quadrupole). Exact masses (HRMS) were recorded with a Bruker Daltonics MicroTof spectrometer (samples in $CH_3OH$ as solvent). Elemental analyses were performed with a FLASHEA 1112 series-Thermo Scientific for CHNS-O apparatus.

**General Procedure for the Synthesis of 3-Substituted Isoindolinones 3a–g:** In a round-bottom flask, aldehyde **1** (0.3 mmol) was added to a solution of malonate ester **2** (1.2 equiv., 0.33 mmol) and $K_2CO_3$ (0.2 equiv., 0.06 mmol) in acetonitrile (0.5 or 1.0 mL). After 18 h (reaction monitored by TLC), the reaction was diluted with $CH_2Cl_2$ (1 mL) and evaporated under reduced pressure to provide, after purification by flash chromatography, the pure compounds **3**.

Compounds **3a**,**b** and **3d**–**f** are known and were characterized by comparison with published data.[5,6]

**Di-(–)-menthyl 2-(3-Oxo-2,3-dihydro-1*H*-isoindol-1-yl)malonate (3c):** Purified by chromatography (hexane/ethyl acetate, 8:2) as an oil; yield 75% (115 mg, 0.22 mmol); mixture of diastereomers. $^1H$ NMR (300 MHz): $\delta$ = 7.88 (m, 1 + 1 H), 7.56–7.51 (m, 4 H), 7.47–7.38 (m, 2 H), 6.80 (br. s, 1 H), 6.75 (br. s, 1 H), 5.21 (m, $J$ = 9.0 Hz, 1 + 1 H), 4.90–4.79 (m, 2 H), 4.74 (dq, $J$ = 3.0, 12.0 Hz, 2 H), 3.64 (d, $J$ = 6.0 Hz, 1 H), 3.53 (d, $J$ = 9.0 Hz, 1 H), 2.13 (m, 2 H), 2.09 (m, 2 H), 1.73–1.69 (m, 10 H), 1.41–1.38 (m, 4 H), 1.28–1.25 (m, 3 H), 0.96–0.94 (m, 4 H), 0.92–080 (m, 7 + 7 + 20 H), 0.69–0.67 (m, 11 H) ppm. $^{13}C$ NMR (100 MHz): $\delta$ = 171.2, 171.1, 168.6, 168.2, 167.9, 167.5, 145.2, 144.9, 135.5, 133.4, 133.1, 133.0, 130.3, 130.2, 125.4, 125.3, 124.8, 124.4, 77.8, 77.6, 61.6, 57.8, 57.4, 56.3, 56.2, 48.1, 48.0, 47.9, 42.0, 41.9, 41.6, 41.5, 35.3, 35.2, 32.7, 32.6, 32.5, 30.9, 27.2, 27.1, 26.9, 26.7, 24.4, 24.3, 24.2, 24.1, 23.3, 23.2,

23.1, 22.2, 22.1 ppm. MS (ESI): *m/z* = 534.68 [M + $Na^+$]. $C_{31}H_{45}NO_5$ (511.70): calcd. C 72.76, H 8.86, N 2.74; found C 72.88, H 8.80, N 2.80.

**Methyl 2-(Diisopropylcarbamoyl)-2-(3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)acetate (3g):** Purified by chromatography (hexane/ethyl acetate, 8:2) as an oil; yield 76% (75 mg, 0.23 mmol); mixture of diastereomers. $^1$H NMR (300 MHz): $\delta$ = 7.86–7.82 (m, 1 H), 7.54–7.45 (m, 4 H), 6.95 (br. s, 1 H, major diastereomer), 6.58 (br. s, 1 H, minor diastereomer), 5.38–5.34 (m, 1+1 H), 4.11 (hept, *J* = 9.0 Hz, 1 H), 3.87 (s, 3 H, minor diastereomer), 3.86–3.85 (m, 1 H), 3.72 (s, 3 H, major diastereomer), 3.65 (d, *J* = 9.0 Hz, 1 H), 3.51 (d, *J* = 9.0 Hz, 1 H), 3.42 (m, 1 H), 3.42 (m, 1 H), 1.53 (d, *J* = 5.1 Hz, 6 H), 1.44–1.39 (m, 7 H), 1.11 (d, *J* = 5.1 Hz, 7 H), 0.96 (d, *J* = 4.8 Hz, 4 H) ppm. $^{13}$C NMR (100 MHz): $\delta$ = 171.1, 170.9, 169.9, 169.3, 166.3, 165.5, 145.9, 145.7, 133.4, 133.3, 133.2, 132.9, 130.1, 125.4, 125.2, 124.9, 124.2, 57.5, 57.4, 57.2, 56.1, 54.1, 54.1, 50.9, 50.4, 48.1, 47.9, 22.0, 21.9, 21.7, 21.5, 21.4, 21.3, 21.1, 21.0 ppm. MS (ESI): *m/z* = 333.35 [M + $H^+$]. $C_{18}H_{24}N_2O_4$ (332.40): calcd. C 65.04, H 7.28, N 8.43; found C 65.11, H 7.35, N 8.31.

**Methyl 3-[4-(4-Fluorophenyl)piperazin-1-yl]-3-oxo-2-(3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)propanoate (3h):** Purified by chromatography (chloroform/ethyl acetate, 9:1) as an oil; yield 90% (111 mg, 0.27 mmol); mixture of diastereomers. $^1$H NMR (300 MHz): $\delta$ = 7.82 (m, 1+1 H), 7.56–7.51 (m, 2+2 H), 7.49 (d, *J* = 6.0 Hz, 1 H), 7.39 (d, *J* = 6.0 Hz, 1 H), 7.29 (br. s, 1 H), 6.98–6.93 (m, 4 H), 6.85–6.81 (m, 4+1 H), 5.46 (d, *J* = 9.0 Hz, 1 H), 5.40 (d, *J* = 9.0 Hz, 1 H), 3.95–3.92 (m, 2 H), 3.86 (s, 3 H), 3.73 (s, 1 H), 3.65 (s, 3 H), 3.65–3.58 (m, 4 H), 3.52–3.45 (m, 2 H), 3.13 (m, 4 H), 2.99–2.88 (m, 4 H) ppm. $^{13}$C NMR (100 MHz): $\delta$ = 171.1, 171.0, 169.2, 168.8, 166.1, 165.5, 160.2, 157.8, 148.5, 148.4, 145.7, 145.4, 133.4, 133.3, 133.2, 130.3, 125.5, 125.4, 124.7, 124.2, 120.0, 119.9, 119.8, 117.1, 116.9, 57.0, 56.0, 54.4, 51.9, 51.7, 51.5, 47.6, 47.3, 43.8, 43.6 ppm. MS (ESI): *m/z* = 433.89 [M + $Na^+$]. $C_{22}H_{22}FN_3O_4$ (411.43): calcd. C 64.22, H 5.39, N 10.21; found C 64.32, H 5.47, N 10.29.

**Methyl 3-(4-Methylpiperazin-1-yl)-3-oxo-2-(3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)propanoate (3i):** Purified by chromatography (chloroform/ethyl acetate, 9:1) as an oil; yield 93% (92 mg, 0.28 mmol); mixture of diastereomers. $^1$H NMR (400 MHz): $\delta$ = 7.83 (m, 1+1 H), 7.52–7.46 (m, 2+2 H), 7.34 (d, *J* = 7.1 Hz, 1 H), 7.27 (d, *J* = 1.9 Hz, 1 H), 7.14 (br. s, 1 H), 6.73 (br. s, 1 H), 5.40 (d, *J* = 9.6 Hz, 1 H), 5.34 (d, *J* = 8.2 Hz, 1 H, minor diastereomer), 3.84 (s, 3 H), 3.70 (s, 3 H), 3,62–3.52 (m, 3 H), 3.46–3.44 (m, 3 H), 3.33–3.29 (m, 1 H), 2.41 (m, 4 H), 2.35–2.33 (m, 3 H), 2.25 (s, 9 H), 2.19–2.17 (m, 1 H) ppm. $^{13}$C NMR (100 MHz): $\delta$ = 171.2, 171.0, 169.3, 168.8, 165.9, 165.4, 145.7, 145.4, 133.4, 133.3, 133.2, 130.2, 130.1, 125.4, 125.3, 124.7, 124.2, 57.0, 56.0, 55.9, 55.7, 55.6, 54.3, 47.5, 47.2, 47.1, 47.0, 43.7, 43.5 ppm. MS (ESI): *m/z* = 332.16 [M + $H^+$]. $C_{17}H_{21}N_3O_4$ (331.37): calcd. C 61.62, H 6.39, N 12.68; found C 61.53, H 6.30, N 12.58.

**General Procedure for Decarboxylation of 3-Substituted Isoindolinones:** In a round-bottomed flask equipped with a magnetic bar and water-cooled condenser, 3-substituted isoindolinones **3a** and **3g–i** (0.14 mmol), lithium chloride (0.54 mmol), water (0.4 mL), and DMF (2.0 mL) were placed. The mixture was heated to reflux with an oil bath and stirred for 5 h. After that time, the mixture was cooled, diluted with $CH_2Cl_2$ (1 mL), and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to provide **4**.

Compound **4a** is known and was characterized by comparison with published data.[5]

***N*,*N*-Diisopropyl (3-Oxo-2,3-dihydro-1*H*-isoindol-1-yl)acetamide (4b):** Purified by chromatography (chloroform/ethyl acetate, 7:3) as a very viscous oil; yield 89% (34 mg, 0.12 mmol). $^1$H NMR (400 MHz): $\delta$ = 7.85 (d, *J* = 7.5 Hz, 1 H), 7.55 (t, *J* = 7.6 Hz, 1 H), 7.47 (t, *J* = 7.5 Hz, 1 H), 7.43 (d, *J* = 7.4 Hz, 1 H), 7.01 (br. s, 1 H), 5.01 (dd, *J* = 2.4, 10.6 Hz, 1 H), 3.83 (hept, *J* = 6.9 Hz, 1 H), 3.52–3.45 (m, 1 H), 3.01 (dd, *J* = 2.9, 16.3 Hz, 1 H), 2.32 (dd, *J* = 10.7, 16.3 Hz, 1 H), 1.41 (d, *J* = 6.7 Hz, 6 H), 1.20 (d, *J* = 6.7 Hz, 3 H), 1.13 (d, *J* = 6.6 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz): $\delta$ = 171.0, 169.9, 147.9, 133.5, 132.9, 129.6, 125.3, 123.5, 54.7, 49.7, 47.2, 41.9, 22.0, 21.9, 21.8, 21.7 ppm. MS (ESI): *m/z* = 275.68 [M + $H^+$]. $C_{16}H_{22}N_2O_2$ (274.36): calcd. C 70.04, H 8.08, N 10.21; found C 70.16, H 8.00, N 10.29.

**3-{2-[4-(4-Fluorophenyl)piperazin-1-yl]-2-xoethyl}-2,3-dihydro-1*H*-isoindol-1-one (4c):** Purified by chromatography (ethyl acetate/hexane 7:3) as a beige waxy solid; yield 89% (44 mg, 0.12 mmol). $^1$H NMR (400 MHz): $\delta$ = 7.87 (d, *J* = 8.0 Hz, 1 H), 7.58 (t, *J* = 8.0 Hz, 1 H), 7.55 (t, *J* = 7.5 Hz, 1 H), 7.49 (d, *J* = 7.4 Hz, 1 H), 7.00–6.95 (m, 2 H), 6.89–6.86 (m, 3 H), 5.04 (dd, *J* = 2.4, 10.3 Hz, 1 H), 3.88–3.83 (m, 2 H), 3.56 (t, *J* = 4.0 Hz, 2 H), 3.10–3.04 (m, 5 H), 2.43 (dd, *J* = 10.8, 16.4 Hz, 1 H) ppm. $^{13}$C NMR (100 MHz): $\delta$ = 171.0, 169.8, 148.7, 147.5, 133.3, 133.1, 129.8, 125.4, 123.5, 120.1, 120.0, 117.1, 116.9, 54.5, 51.9, 51.7, 46.6, 43.0, 40.2 ppm. MS (ESI): *m/z* = 375.97 [M + $Na^+$]. $C_{20}H_{20}FN_3O_2$ (353.39): calcd. C 67.97, H 5.70, N 11.89; found C 67.85, H 5.60, N 11.80.

**3-[2-(4-Methylpiperazin-1-yl)-2-oxoethyl]-2,3-dihydro-1*H*-isoindol-1-one (4d):** Purified by chromatography (dichloromethane/methanol, 9.5:0.5) as a beige waxy solid; yield 88% (34 mg, 0.12 mmol). $^1$H NMR (300 MHz): $\delta$ = 7.87 (d, *J* = 7.4 Hz, 1 H), 7.55 (t, *J* = 7.6 Hz, 1 H), 7.49 (t, *J* = 7.4 Hz, 1 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.11 (br. s, 1 H), 5.01 (dd, *J* = 3.0, 9.0 Hz, 1 H), 3.78–3.72 (m, 1 H), 3.63–3.60 (m, 1 H), 3.41 (t, *J* = 6.0 Hz, 2 H), 3.03 (dd, *J* = 3.0, 15.0 Hz, 1 H), 2.42–2.38 (m, 5 H), 2.30 (s, 3 H) ppm. $^{13}$C NMR (75 MHz): $\delta$ = 169.8, 168.4, 146.3, 132.1, 131.7, 128.4, 124.1, 122.2, 54.7, 54.5, 53.2, 45.9, 45.1, 41.6, 38.9 ppm. MS (ESI): *m/z* = 296.73 [M + $Na^+$]. $C_{15}H_{19}N_3O_2$ (273.33): calcd. C 65.91, H 7.01, N 15.37; found C 65.89, H 6.90, N 15.29.

**General Procedure for Arylation of Isoindolinones 3a and 4a, 4c–d:** A Schlenk tube was charged with CuI (0.029 mmol) and $K_3PO_4$ (0.292 mmol), evacuated and backfilled with nitrogen. *N*,*N*-Dimethylethylenediamine **A** or *N*-methylethylenediamine **B** (0.058 mmol), 2-iodopyridine (0.175 mmol), and 3-substituted isoindolinones (0.146 mmol) dissolved in toluene (1 mL) were added under a nitrogen atmosphere. The reaction mixture was heated at 80 °C for 18 or 24 h (reaction monitored by TLC). The resulting pale-brown suspension was cooled to room temperature. After removing the solvent, the residues were separated by chromatography on silica gel to afford the desired compounds **5**.

**Methyl 2-[1-Oxo-2-(pyridin-2-yl)isoindolin-3-yl]acetate (5a):** Purified by chromatography (hexane/ethyl acetate, 5:5) as a waxy solid; yield 65% (27 mg, 0.095 mmol). $^1$H NMR (300 MHz): $\delta$ = 8.58 (d, *J* = 6.0 Hz, 1 H), 8.45 (dd, *J* = 6.0, 3.9 Hz, 1 H), 7.93 (d, *J* = 6.0 Hz, 1 H), 7.76 (dt, *J* = 3.0, 6.0 Hz, 1 H), 7.64–7.49 (m, 3 H), 7.07 (dt, *J* = 3.0, 9.0 Hz, 1 H), 5.99 (dd, *J* = 3. 0, 9.0 Hz, 1 H), 3.67 (s, 3 H), 3.40 (dd, *J* = 3.0, 15 Hz, 1 H), 2.71 (dd, *J* = 9.0, 15.0 Hz, 1 H) ppm. $^{13}$C NMR (100 MHz): $\delta$ = 172.3, 168.7, 152.1, 148.9, 146.2, 139.2, 134.1, 133.0, 129.9, 125.5, 124.0, 120.8, 116.9, 57.7, 53.0, 39.3 ppm. MS (ESI): *m/z* = 283.74 [M + $H^+$]. $C_{16}H_{14}N_2O_3$ (282.30): calcd. C 68.07, H 5.00, N 9.92; found C 68.18, H 5.13, N 9.85.

**Dimethyl 2-[1-Oxo-2-(pyridine-2yl)isoindolin-3-yl]malonate (5b):** Purified by chromatography (hexane/ethyl acetate, 5:5) as a waxy

solid; yield 67% (34 mg, 0.099 mmol). $^1$H NMR (250 MHz): $\delta$ = 8.61 (d, $J$ = 5.2 Hz, 1 H), 8.40 (dd, $J$ = 5.0, 3.2 Hz, 1 H), 7.90 (d, $J$ = 7.7 Hz, 1 H), 7.78 (m, 2 H), 7.62 (m, 1 H), 7.53 (d, $J$ = 7.5 Hz, 1 H), 7.10 (t, $J$ = 5.0 Hz, 1 H), 6.25 (d, $J$ = 3.0 Hz, 1 H), 4.71 (d, $J$ = 3.0 Hz, 1 H), 3.88 (s, 3 H), 3.26 (s, 3 H) ppm. $^{13}$C NMR (100 MHz): $\delta$ = 169.7, 168.8, 168.0, 151.8, 149.0, 143.1, 139.4, 135.5, 134.0, 130.2, 125.6, 125.1, 120.9, 116.9, 59.3, 54.1, 53.9, 53.4 ppm. MS (ESI): $m/z$ = 341.56 [M + H$^+$]. $C_{18}H_{16}N_2O_5$ (340.33): calcd. C 63.52, H 4.74, N 8.23; found C 63.64, H 4.83, N 8.31.

**3-{2-[4-(4-Fluorophenyl)piperazin-1-yl]-2-oxoethyl}-2-(pyridine-2-yl)isoindolin-1-one (5c):** Purified by chromatography (chloroform/ethyl acetate, 9.5:0.5) as a waxy solid; yield 59% (37 mg, 0.086 mmol). $^1$H NMR (300 MHz): $\delta$ = 8.62 (d, $J$ = 9.0 Hz, 1 H), 8.43 (d, $J$ = 6.0 Hz, 1 H), 7.92 (d, $J$ = 9.0 Hz, 1 H), 7.78–7.76 (m, 1 H),7.73–7.71 (m, 1 H), 7.61 (t, $J$ = 6.0 Hz, 1 H), 7.54 (t, $J$ = 6.0 Hz, 1 H), 7.10–7.06 (m, 1 H), 7.05–7.00 (m, 2 H), 6.97 (t, $J$ = 9.0 Hz, 2 H), 6.13 (dd, $J$ = 3.0, 6.0 Hz, 1 H), 3.89–3.84 (m, 2 H), 3.62–3.56 (m, 3 H), 3.12–3.09 (m, 2 H), 2.98–2.96 (m, 2 H), 2.47 (dd, $J$ = 9.0, 15 Hz, 1 H) ppm. $^{13}$C NMR (100 MHz): $\delta$ = 169.8, 169.0, 152.3, 149.0, 147.0, 139.2, 134.2, 132.8, 129.8, 125.4, 125.1, 120.7, 119.9, 119.8, 117.1, 116.8, 116.7, 58.4, 52.0, 51.8, 46.8, 43.0, 38.8 ppm. MS (ESI): $m/z$ = 431.78 [M + H$^+$]. $C_{25}H_{23}FN_4O_2$ (430.48): calcd. C 69.75, H 5.39, N 13.02; found C 69.67, H 5.45, N 13.18.

**3-[2-(4-Methylpiperazin-1-yl)-2-oxoethyl]-2-(pyridin-2-yl)isoindolin-1-one (5d):** Purified by chromatography (dichloromethane/methanol, 9.9:0.1) as a waxy solid; yield 69% (36 mg, 0.093 mmol). $^1$H NMR (300 MHz): $\delta$ = 8.59 (d, $J$ = 6.0 Hz, 1 H), 8.42 (d, $J$ = 6.0 Hz, 1 H), 7.91 (d, $J$ = 6.0 Hz, 1 H), 7.79–7.69 (m, 2 H), 7.61 (t, $J$ = 6.0 Hz, 1 H), 7.52–7.47 (m, 1 H), 7.09–7.05 (m, 1 H), 6.10 (dd, $J$ = 3.0, 9.0 Hz, 1 H), 3.73 (m, 2 H), 3.53 (dd, $J$ = 3.0, 15.0 Hz, 1 H), 3.46–3.40 (m, 2 H), 2.45–2.40 (m, 4 H), 2.39 (s, 4 H) ppm. $^{13}$C NMR (75 MHz): $\delta$ = 168.4, 167.6, 151.0, 147.7, 145.7, 137.9, 132.8, 131.4, 128.4, 124.0, 123.9, 119.3, 115.4, 57.1, 55.0, 54.6, 45.9, 45.3, 41.6, 37.4 ppm. MS (ESI): $m/z$ = 351.46 [M + H$^+$]. $C_{20}H_{22}N_4O_2$ (350.42): calcd. C 68.55, H 6.33, N 15.99; found C 68.44, H 6.42, N 15.87.

**Procedure for Alkylation Reaction of 3a:** To a solution of **3a** (0.190 mmol, 1.0 equiv.) and $K_2CO_3$ (0.285 mmol, 1.5 equiv. or 2.5 equiv.) in DMF (1.0 mL), iodomethane (0.190 mmol, 1.0 equiv. or 2.5 equiv.) was added dropwise. The reaction was stirred at room temperature for 1 h or 18 h, respectively. After this time, the reaction mixture was diluted in ethyl acetate (2 mL) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 7:3 to 5:5) to give **6** (32 mg, 0.114 mmol, 61%, Table 6, entry 1) or both **6** and **7** (Table 6, entry 2) as waxy white solids.

**Dimethyl 2-Methyl-2-(1-oxoisoindolin-3-yl)malonate (6):** $^1$H NMR (400 MHz): $\delta$ = 7.84 (d, $J$ = 7.6 Hz, 1 H), 7.53–7.46 (m, 2 H), 7.13–7.09 (m, 1 H), 5.35 (s, 1 H), 3.89 (s, 3 H), 3.78 (s, 3 H), 1.06 (s, 3 H) ppm. $^{13}$C NMR (100 MHz): $\delta$ = 172.8, 171.5, 171.2, 143.6, 134.07, 133.3, 130.2, 125.3, 124.1, 59.9, 58.5, 54.57, 54.3, 14.7 ppm. MS (ESI): $m/z$ = 278.10 [M + H$^+$]. $C_{14}H_{15}NO_5$ (277.28): calcd. C 60.64, H 5.45, N 5.05; found C 60.72, H 5.36, N 5.13.

**Dimethyl 2-Methyl-2-(2-methyl-1-oxoisoindolin-3-yl)malonate (7):** $^1$H NMR (400 MHz): $\delta$ = 7.84–7.82 (m, 1 H), 7.48–7.44 (m, 2 H), 7.22 (d, $J$ = 5.6 Hz, 1 H), 5.49 (s, 1 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 3.00 (s, 3 H), 0.96 (s, 3 H) ppm. $^{13}$C NMR (100 MHz): $\delta$ = 171.4, 171.0, 170.5, 142.9, 134.1, 132.9, 130.2, 124.9, 124.3, 66.1, 58.5, 54.5, 54.3, 30.4, 13.9 ppm. MS (ESI): $m/z$ = 292.18 [M + H$^+$]. $C_{15}H_{17}NO_5$ (291.30): calcd. C 61.85, H 5.88, N 4.81; found C 61.91, H 5.73, N 4.68.

**One-Pot Double Tandem Procedure for the Synthesis of 9:** In a round-bottom flask, aldehyde **1** (0.3 mmol) was added to a solution of malonate ester **2** (1.2 equiv., 0.33 mmol) and $K_2CO_3$ (0.2 equiv., 0.06 mmol) in acetonitrile (0.5 mL). After 18 h (reaction monitored by TLC), acrolein **8** (1.5 equiv., 0.45 mmol) was added to the reaction mixture. At the end of the reaction the solvent was evaporated under reduced pressure to provide, after purification by flash chromatography, pure **9**; yield 88% (25 mg, 0.079 mmol).

**Dimethyl 4-Hydroxy-6-oxo-3,4,6,10b-tetrahydropyrido[2,1-*a*]isoindole-1,1(2*H*)-dicarboxylate (9):** White solid; single diastereoisomer; m.p. 142–143 °C. $^1$H NMR (300 MHz): $\delta$ = 7.70–7.67 (m, 1 H), 7.30–7.40 (m, 3 H), 5.97 (m, 1 H), 5.17 (s, 1 H), 4.68 (m, 1 H), 3.87 (s, 3 H), 3.21 (s, 3 H), 2.45–2.42 (m, 2 H), 2.06–2.02 ppm. $^{13}$C NMR (75 MHz): $\delta$ = 170.9, 167.7, 167.2, 143.4, 131.5, 131.2, 128.2, 124.1, 123.2, 69.8, 57.5, 56.7, 53.1, 52.0, 27.1, 26.6 ppm. MS (ESI): $m/z$ = 320.1 [M + H$^+$]. $C_{16}H_{17}NO_6$ (319.31): calcd. C 60.18, H 5.37, N 4.39; found C 60.26, H 5.25, N 4.55.

**Supporting Information** (see footnote on the first page of this article): Detailed experimental procedures, characterization data, copies of $^1$H and $^{13}$C NMR spectra for all the new compounds and crystallographic data for compound 9.

## Acknowledgments

Financial support from the Ministero dell'Università e della Ricerca (MIUR) (FARB 2011) is gratefully acknowledged.

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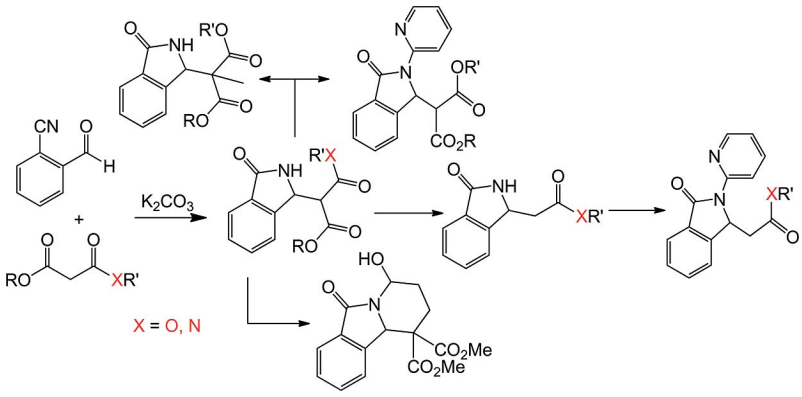
Received: May 19, 2012
Published Online: ■

**Nitrogen Heterocycles**




Potassium carbonate efficiently catalyses the synthesis of 3-substituted isoindolinones through a tandem aldol/cyclization/rearrangement reaction. An exploration of the chemical space of the obtained isoindolinones led to diverse, highly functionalized compounds.

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Synthesis and Reactivity of the 3-Substituted Isoindolinone Framework to Assemble Highly Functionalized Related Structures

**Keywords:** Synthetic methods / Domino reactions / Aldol reactions / Nitrogen heterocycles

  