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## Straightforward access to complex isoindolinones from the Ugi reaction of *o*-nitrobenzoic acid derivatives

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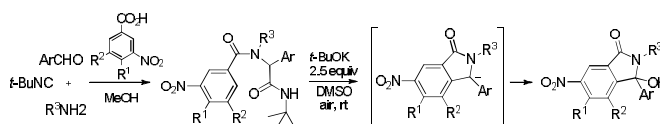
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The Ugi reaction of 2-nitrobenzoic acid derivatives has been used for a Diversity Oriented Synthesis of complex isoindolinones via a  $S_NAr$  reaction involving the peptidyl position. When the cyclization is triggered by strong bases such as potassium *tert*-butylate, the  $S_NAr$  reaction is followed by a deamidification/oxidation sequence leading to 2-hydroxyisoindolinones. The latter may be further transformed into polycyclic fused isoindolinones via Pictet-Spengler type cyclization or *O*-alkylation/metathesis sequences.

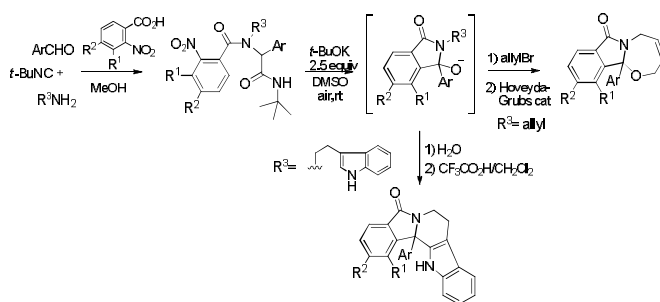
The development of multicomponent reactions over the last twenty years has been strongly stimulated by the use of the Ugi reactions in cascades towards highly diverse polycyclic derivatives with important potential in medicinal chemistry.<sup>1</sup> Together with the ability to afford complex structures within a couple of steps, these syntheses are also valued for the high diversity brought by the 4-component nature of the Ugi coupling. If the number of commercially available isocyanides have grown significantly in the last twenty years, their availability still remains very low and their price quite high with respect to the other components of the coupling. Thus, the amide moiety derived from the isocyanide is often considered as an unwanted travelling companion in many syntheses using the cheapest isocyanides. To gain further diversity, several families of so-called convertible isocyanides<sup>2</sup> have been proposed in order to raise the reactivity of the final amide towards various nucleophiles. Most of these methods allow the conversion of the amide into related carboxylic acid derivatives. We started this project with the idea of modifying the amide function using more complex functional group transformations without loss of diversity. We were particularly attracted by the ability to cleave the amide as an isocyanate

under basic conditions as observed in our previous synthesis of isoindolinones from 3-nitrobenzoic acids (Scheme 1).<sup>3</sup> In this case, following the intramolecular vicarious nucleophilic substitution on the nitrophenyl moiety, the amide is easily cleaved under basic condition thanks to the strong stabilisation of the resulting benzylic anion. Isoindolinones or hydroxyisoindolinones could be formed alternatively according to the presence of oxygen in the basic medium.<sup>3</sup> We envisioned that the potential of such approach could be raised using 2-nitro benzoic acids as starting material while loss of diversity due to removal of isocyanate could be balanced thanks to the new hydroxyl handle brought after oxidation (Scheme 1).

Ugi/Vicarious substitution pathway towards isoindolones:<sup>3</sup>



This work: Ugi/ $S_NAr$  pathway towards fused isoindolones:



**Scheme 1.** Nitrobenzoic acid based Ugi strategies towards polycyclic isoindolinones.

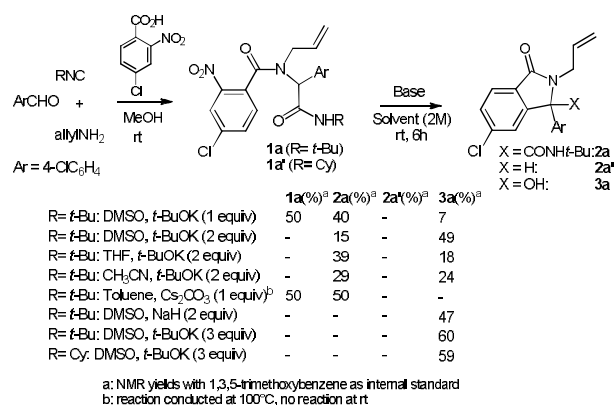
To progress on this project, Ugi starting adduct **1a** was prepared in 77% isolated yield using standard Ugi conditions with *t*-butyl isocyanide, allylamine, 4-chloro-2-nitrobenzoic

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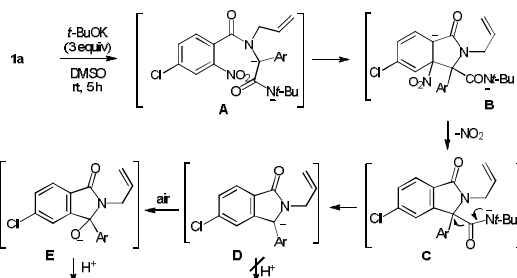
† Footnotes relating to the title and/or authors should appear here. Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

acid and 4-chlorobenzaldehyde. **1a** was then treated under various basic conditions in order to observe the expected  $S_NAr$ /amide elimination sequence (Scheme 2).



**Scheme 2.** Synthesis of Isoindolinones **2a** and **3a** from **1a** under various basic conditions

Compared with our previous study using vicarious nucleophilic addition on 3-nitrobenzoic derivatives, we observed a similar behaviour with the formation of cyclization products without loss of amide using moderately basic conditions (Cs<sub>2</sub>CO<sub>3</sub> in toluene) whereas stronger bases (NaH, *t*-BuOK) lead to cyclization and elimination of the amide moiety at room temperature.<sup>4</sup> In sharp contrast with 3-nitro derivatives for which we could isolate both isoindolinones and hydroxyisoindolinones according to the use of aerobic conditions or not, it was not possible for us to observe non oxidized product working with non degassed solvent under Argon.<sup>5</sup> Trying to exclude oxygen from the mixture (degassed solvent, under Arg) led to longer reaction times and sluggish yields without isolation of the CH isoindolinone **3a**. *tert*-butyl isocyanate was chosen as starting material for this sequence as an higher steric hindrance was expected to afford an easier deamidification. To confirm this point, the cyclohexyl analogue **1a'** was prepared leading to a slightly lower yield of **4a** (Scheme 2). The formation of **4a** may involve the intermediate formation of amide dianion **A** which after cyclization and elimination of nitrite forms anion **C**. Elimination of *t*-butylisocyanate from the latter is assisted by the formation of a stabilized dibenzyl anion which leads after oxidation to alkoxide **E**. The ability to form isoindolinone **2a** under treatment with one equivalent of base suggests that monoanionic intermediates may also account for the observed transformations.



**Scheme 3.** Possible intermediates for the conversion of **1a** into **4a**

The use of excess *t*-BuOK in DMSO at rt was then selected to evaluate the scope of the transformation and a set of Ugi adducts **1a-1j** were prepared from various 2-nitrobenzoic acids under standard Ugi reaction conditions (rt, 2M in methanol) and purified by column chromatography on silica gel. Under our optimized conditions, all Ugi adducts **1a-1e** afforded the expected 2-hydroxy isoindolinones **3a-3e** in good to moderate yields after 4 to 8 hours reaction at room temperature. The cyclization proceeded well for both electron-rich (Table 1, entry 4) and electron-poor (Table 1, entry 3) aromatic aldehydes. For all products, the  $S_NAr$  initial step was fast at rt (completed in less than one hour) whereas the following deamidification and oxidation processes required several hours. Performing the whole sequence under air, led to faster reactions but lower yields probably due to a competing oxidation before intramolecular  $S_NAr$ .

**Table 1.** Ugi/ $S_NAr$  strategy toward isoindolinones analogues

Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	<b>1</b> (%) <sup>a</sup>	<b>3</b> (%) <sup>a</sup>	<b>4</b> (%) <sup>a</sup>
1	Cl	allyl	4-ClC <sub>6</sub> H <sub>4</sub>	<b>1a</b> (77)	<b>3a</b> (60)	<b>4a</b> (79)
2	Cl	(CH <sub>2</sub> ) <sub>2</sub> OMe	4-ClC <sub>6</sub> H <sub>4</sub>	<b>1b</b> (78)	<b>3b</b> (56)	<b>4b</b> (72)
3	Cl	(CH <sub>2</sub> ) <sub>2</sub> OMe	2-pyridyl	<b>1c</b> (90)	<b>3c</b> (70)	
4	Cl	CH <sub>2</sub> CH(OMe) <sub>2</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>	<b>1d</b> (89)	<b>3d</b> (66)	
5	H	CH <sub>2</sub> CH(OMe) <sub>2</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	<b>1e</b> (90)	<b>3e</b> (31)	<b>4e</b> (52)
6	H	allyl	4-ClC <sub>6</sub> H <sub>4</sub>	<b>1f</b> (77)		<b>4f</b> (68)
7	NO <sub>2</sub>	allyl	4-ClC <sub>6</sub> H <sub>4</sub>	<b>1g</b> (74)		<b>4g</b> (67)
8	Cl	(CH <sub>2</sub> ) <sub>2</sub> OMe	4-MeOC <sub>6</sub> H <sub>4</sub>	<b>1h</b> (84)		<b>4h</b> (76)
9	Cl	cyclopropyl	4-ClC <sub>6</sub> H <sub>4</sub>	<b>1i</b> (65)		<b>4i</b> (60)
10	H	allyl	3-pyridyl	<b>1j</b> (83)		<b>4j</b> (60)

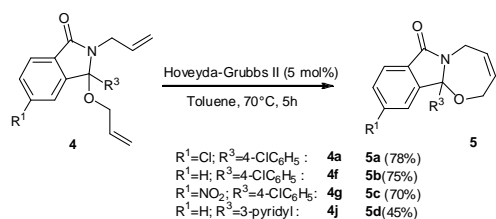
<sup>a</sup> isolated Yield.

When using 2-nitrobenzoic acid instead of 4-chloro-2-nitrobenzoic acid (Table 1, entry 5), we were surprised to observe an important drop in yields difficult to explain at first sight with the electronic nature of the aryl substituents. Figuring that this could be associated with a lower stability of

the hydroxy derivatives **3e** on the silica (via the formation of an intermediate iminium followed by trapping on silica), we decided to allylate the intermediate alkoxide in order to form a more stable hemiaminal ether. After completion of the  $S_NAr$ /oxidation sequence (as determined by tlc), additional *t*-BuOK was introduced together with two equivalents of allyl bromide.<sup>6</sup> Letting the reaction for five hours at rt followed by hydrolysis and purification on silica gel afforded the allyloxy isoindolinone **4e** (Table 1, entry 5) in 52% isolated yield. Gratifyingly, with this new protocol affords an important raise in yields for both 2-nitrobenzoic and 4-chloro-2-nitrobenzoic acid Ugi adducts (Table 1, entries 1, 2 and 5). Thus further O-allyl isoindolinones were prepared using this modified procedure (Table 1, entries 6-10).

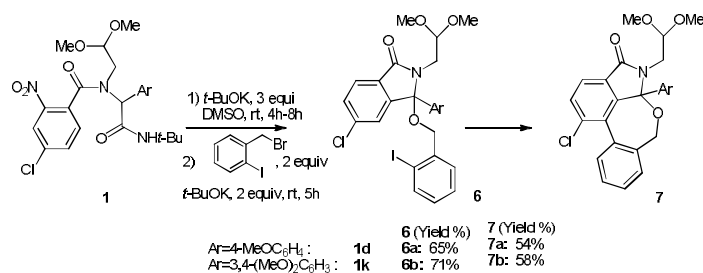
Together with the interest of an increased stability and raises of the diversity, the disclosure of this O-allylation protocol offers further interesting perspectives for the synthesis of complex isoindolinones. Besides some potential ring-closure metathesis (RCM) through the selection of allylamine as starting Ugi amine followed by O-allylation,<sup>7</sup> the protocol should be easily extended to more complex alkylating agents leading to specific cyclizations.

Hoveyda-Grubbs II catalyst for selected for the RCM pathway using **1a**, **1f**, **1g** and **1j** as starting Ugi adducts. The new fused isoindolyl-oxazepines **5a-5d** were all obtained in good yields after heating the O-allyloxy **4a-4j** for few hours in toluene at 70°C (Scheme 4).



**Scheme 4.** RCM of N-allyl-O-allyl isoindolinone **4a-4j**

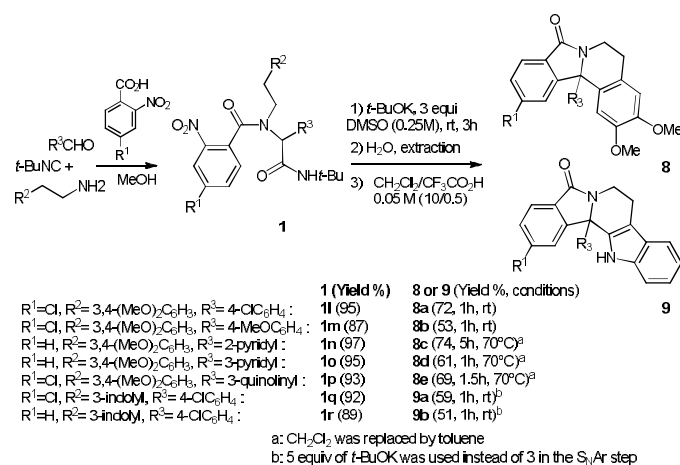
To demonstrate the potential of this approach in further transition metal catalysed formation of complex oxazepines, we performed the  $S_NAr$ /oxidation/O-alkylation sequence using 2-iodobenzyl bromide as alkylating agent instead of allyl bromide (Scheme 5). Starting from Ugi adduct **1d**, a 65% yield of **6a** was obtained after the O-alkylation step. The following palladium triggered CH activation step was performed using a Pd(OAc)<sub>2</sub>/DPPE couple together with Cs<sub>2</sub>CO<sub>3</sub> as a base to afford the new fused oxazepine **7a** in 54% isolated yield. The same sequence was applied to the new Ugi adduct **1k** (obtained in 79% isolated yield from 3,4-dimethoxybenzaldehyde) leading to oxazepine **7b** in a slightly better 58% yield. For both starting Ugi adducts, the CH activation was observed on the electron-poorer aryl ring which is in agreement with the selectivity often observed in CH activations involving a concerted metalation deprotonation mechanism.<sup>8</sup>



**Scheme 5.** Synthesis of complex isoindolinones **7d** and **7k** via the  $S_N$  Pd triggered C-H activation.

There have been relatively few reports on the synthesis and properties of such fused oxazepinoisoindolinones. Analogues of **5** have been prepared mostly by an intramolecular cationic trapping of an isoindoline iminium using an oxygen atom as internal nucleophile<sup>9</sup> and have been used as inhibitors of apoptosis protein antagonist in HIV therapy.<sup>10</sup> Analogues of **7** have been only reported in a single patent on the use of fused isoindolinones as modulators of nuclear hormone receptor function.<sup>11</sup>

Considering the ability to reach iminium intermediates from hydroxyisoindolinones **3**, a further synthetic application of this Ugi/ $S_NAr$  oxidative sequence may be easily envisioned using a final Pictet-Spengler cyclization. A simple way to achieve this is the selection of a starting amine possessing a properly positioned nucleophilic aryl moiety. When homoveratryl amine was used in the Ugi step together with 4-chloro-2-nitrobenzoic acid or 2-nitrobenzoic acid, Ugi adducts **1i-1o** were all obtained in good yields (Scheme 6). After completion of the following  $S_NAr$ /deamidification/oxidation sequence (as determined by tlc),<sup>12</sup> extraction of the crude mixture was directly followed by the Pictet-Spengler step (in a 20/1 CH<sub>2</sub>Cl<sub>2</sub>/CF<sub>3</sub>CO<sub>2</sub>H mixture at rt) without purification of the intermediates hydroxy **3**. The good yields observed in the formation of **8a-8e** using both nitrobenzoic acids as starting materials confirm the hypotheses previously made on the stability of **3** over silica gel. For Ugi adducts prepared from pyridine or quinoline aldehydes (Scheme 6, **1n**, **1o**, **1p**), the Pictet-Spengler step required a higher temperature (using a 20/1 mixture of toluene/CF<sub>3</sub>CO<sub>2</sub>H at 70°C) for completion probably due to the protonation of the latter heterocycles making the required iminium intermediate more difficult to reach. Finally replacing homoveratrylamine by tryptamine in the Ugi step led similarly to isoindolinones **9a** and **9b** in slightly lower yields (Scheme 6).



**Scheme 6.** Synthesis of polyheterocycles **8** and **9** via the S<sub>N</sub>Ar/deamidification/oxidation/Pictet-Spengler sequence.

Analogs of **9** have found interesting biological activities against malaria.<sup>13</sup> Analogs of **8** or **9** are classically obtained via the addition of an aryl Grignard onto a phthalimide followed a Pictet-Spengler step.<sup>14</sup> Our straightforward Ugi access to such complex fused isoindolinones **8** and **9** offers the advantage of an easy access from aromatic aldehydes without the need for the preparation of a reactive Grignard intermediate.

## Conclusions

We have developed an IMCR based approach toward the synthesis of complex heterocycles containing the isoindolinone scaffold. The ability to perform these reactions in a one-pot manner further raises the potential of this diversity oriented synthesis.

While supplementing our previous nitroisoindolinone synthesis from 3-nitrobenzoic, the present study demonstrates that the diversity lost during the deamidification process may be recovered via alkylation with valuable molecular fragments. This deamidification/alkylation approach represents a new direction in the use of Ugi adducts for diversity oriented syntheses. In our case, the fast oxidation observed after deamidification may be advantageously exploited in following Pictet-Spengler cyclizations. Further attempts to disclose oxidation-free S<sub>N</sub>Ar/deamidification/alkylation sequence as well as extensions of these deamidifications to other families of Ugi adducts are under study in the group.

## Conflicts of interest

There are no conflicts of interest to declare

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## Conflicts of interest

There are no conflicts to declare.

## Notes and references

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