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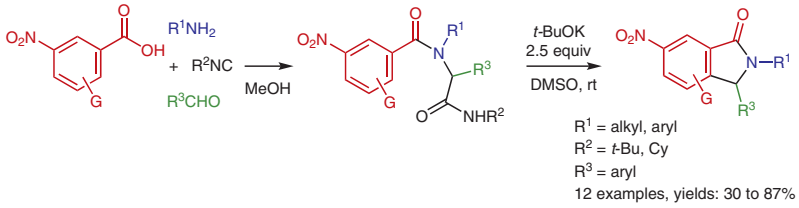
Metal-free Deamidative Ugi Access to Isoindolinones

Samira Baaziz[a,c]
Mansour Dolè Kerim[a]
Marie Cordier[b]
Lamouri Hammal*[c]
Laurent El Kaïm*[a]

[a] Laboratoire de Synthèse Organique, CNRS, Ecole Polytechnique, ENSTA ParisTech - UMR 7652, Université Paris-Saclay, 828 Bd des Maréchaux, 91128 Palaiseau, France
laurent.elkaim@ensta-paristech.fr
[b] Laboratoire de Chimie Moléculaire, CNRS, Ecole Polytechnique - UMR 9168, Université Paris-Saclay, Route de Saclay, 91128 Palaiseau, France
[c] Laboratoire de Chimie Organique Appliquée, Université des Sciences et de la Technologie Houari Boumediene (USTHB), 16111 Alger, Algeria
lhammal@usthb.dz



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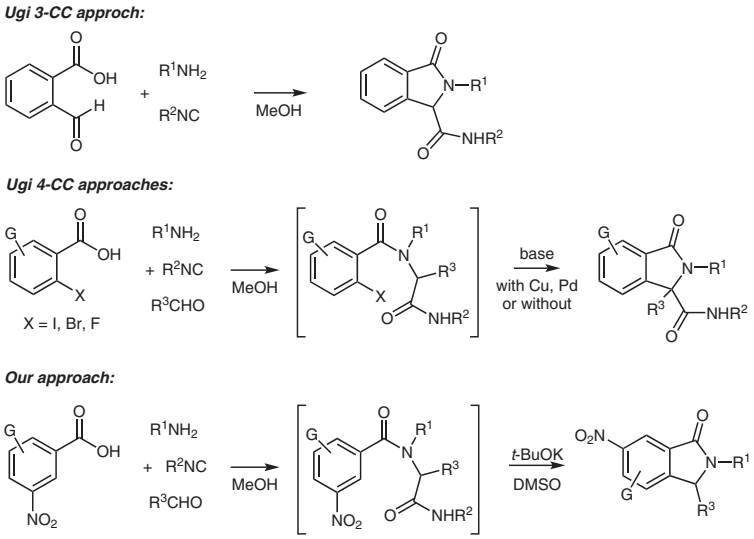
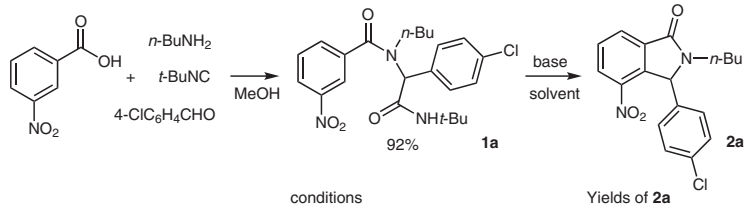
Abstract A two-step isoindolone synthesis has been achieved by using an Ugi/oxidative vicarious nucleophilic substitution sequence starting from 3-nitrobenzoic acid and aromatic aldehydes. Loss of the amido group was observed as well as a further oxidative process towards hydroxyisoindolone derivatives after prolonged stirring open to the atmosphere.

Key words Ugi reaction, 3-nitrobenzoic acid, intramolecular vicarious nucleophilic substitution, isolindolones, air oxidation

The development of multicomponent reactions over the last twenty years has been strongly stimulated by the exploitation of the Ugi reaction in cascades towards complex derivatives obtained in very few steps from commercially available compounds.[1] Because of its efficiency and 4-component nature, it is no surprise that many privileged medicinal scaffolds have been targeted with use of this reaction.[2] Isoindole derivatives,[3] for example, which have many uses as axiolytic,[4] antiviral,[5] or anticancer agents,[6] continuously stimulate the efforts to provide new syntheses with even more efficiency. In this context, the Ugi reaction has been used extensively to form isoindolones by combining step economy with high diversity.[7] These approaches toward isoindolones may be divided into two main families. The one using 2-formylbenzoic derivatives in three-component reactions is the most direct but remains limited by the choice of available starting partners (Scheme 1).[7a–f] The second two-step approach involves four-component couplings of benzoic derivatives substituted at the *ortho* position by potential leaving groups (Scheme 1).[7g–m] Among the latter, the synthesis proposed by Chauhan et al.[7j] particularly



Scheme 1 Ugi access to isoindolinones



conditions	Yields of **2a**
NaH (2.5 equiv), DMSO, rt, 1 h	55%
NaH (2.5 equiv), THF, rt, 1 h	0%
NaH (2.5 equiv), DMSO, rt, 1 h	41%
***t*-BuOK (2.5 equiv), DMSO, rt, 1 h**	**60%**
t-BuOK (0.9 equiv), DMSO, rt, 1 h	45%
t-BuOK (2.5 equiv), DMSO, 80 °C, 0.5 h	33%
t-BuOK (2.5 equiv), DMF, rt, 1 h	40%
t-BuOK (2.5 equiv), DMF, 60 °C, 1 h	42%
t-BuOK (2.5 equiv), MeOH, 60 °C, 1 h	30%
Cs_2CO_3 (2.5 equiv), DMSO, rt, 2 h	17%

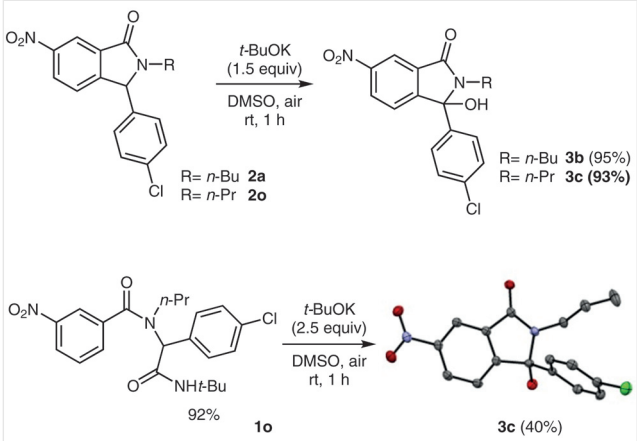
Scheme 2 Optimized conditions for the cyclization of **1a** to isoindolone **2a**

caught our attention. They describe a copper-catalyzed cyclization/deamidation process from the Ugi adduct derived from *o*-iodobenzoic acid.[8] Following our interest in the activation of the peptidyl position of Ugi adducts in the presence of strong bases[9] and puzzled by the mechanism proposed by Chauhan; together with the report by Li et al. on a similar cyclization without copper[7i] (but retaining the amide group, Scheme 1), we decided to launch a study around these cyclizations to gain a better insight into the deamidation and their potential in isoindolinone syntheses. We selected 3-nitrobenzoic acid derivatives as starting materials with the objective of performing an intramolecular vicarious nucleophilic substitution (IVNS)[10] in the cyclization step, which had not been observed before on Ugi adducts.

The Ugi adduct **1a** was thus prepared in a yield of 92% by reaction of chlorobenzaldehyde with 3-nitrobenzoic acid, *tert*-butyl isonitrile, and butylamine. To our delight, in the presence of 2.5 equiv of sodium hydride in anhydrous DMSO (conditions used in our previous studies on the alkylation of dianions from Ugi adducts), after one hour at room temperature, the formation of isoindolone **2a** occurred involving the desired cyclization along with the fragmentation of the amide (Scheme 2).

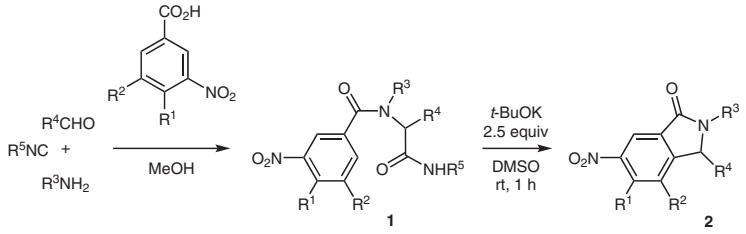
No reaction was observed in THF in accordance with the low reactivity of the hydride in this solvent; DMF gave a substantially lower yield. Potassium *tert*-butylate and cesium carbonate were also tested in different solvents and at different temperatures and in varying amounts (Scheme 2). These tests led us to select 2.5 equiv of potassium *tert*-butylate in anhydrous DMSO as the best conditions for our study. Various Ugi adducts **1** have thus been prepared and the results of the cyclization under these basic conditions are shown in Table 1.

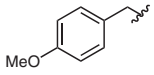
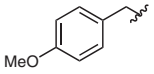
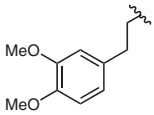
All Ugi adducts prepared led to cyclized products through addition at the *para* position of the nitro group as observed for similar *ortho*/*para* competitions in vicarious nucleophilic substitutions involving tertiary (methinic) carbanions generated from phenyl propionic derivatives.[11a,e] Overall, the cyclization works better for Ugi adducts derived from electron-poor aromatic aldehydes. The low 30 and 40% isolated yields obtained for 4-methoxyaryl derivatives (Table 1, entries 6 and 9) may be best explained by the lower stabilizing effect of the benzylic anions that may be generated during the process (before the cyclization or during the loss of the amide group, see Scheme 4). Our failure to isolate any isoindolone **2g** from the cyclization of **1g** is due to a fast oxidation of **2g** to **3a** under basic conditions. Trying to isolate **2g** by using a shorter reaction time or trying to exclude all traces of oxygen from the reaction were not conclusive, as either the starting material or the hydroxylated product **3g** were observed. This final oxidation is certainly associated with some of the moderate yields obtained in Table 1. Indeed, all reactions were performed under argon but without prior degassing of the solvent because an oxidative step is also required to rearomatize the nitrophenyl ring after cyclization. The sensitivity of isoindolones **2** towards air under basic conditions was further confirmed by a nearly quantitative conversion of **2a** unto **3b** when the isoindolone was left open to the atmosphere at room temperature for one hour in the presence of 1.5 equiv of potassium *tert*-butylate.[12] However, attempts to form hy-

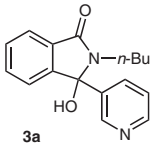


Scheme 3 Aerobic oxidation towards hydroxyisoindolone **3**

Table 1 Synthesis of Isoindolones **2** from Ugi Adducts **1**



Entry	R^1	R^2	R^3	R^4	R^5	Yield of **1** (%)[a]	Yield of **2** (%)[a]
1	H	H	*n*-Bu	4-ClC_6H_4	*t*-Bu	**1a** (92)	**2a** (60)
2	H	H	*n*-Bu	4-ClC_6H_4	Cy	**1a'** (80)	**2a** (60)
3	Me	H	*n*-Bu	4-ClC_6H_4	*t*-Bu	**1b** (58)	**2b** (40)
4	MeO	H	*n*-Bu	4-ClC_6H_4	*t*-Bu	**1c** (78)	**2c** (46)
5	H	NO_2	*n*-Bu	4-ClC_6H_4	*t*-Bu	**1d** (85)	**2d** (58)
6	H	H	*n*-Bu	4-$MeOC_6H_4$	*t*-Bu	**1e** (82)	**2e** (40)
7	H	H	*n*-Bu	4-$NO_2C_6H_4$	*t*-Bu	**1f** (92)	**2f** (55)
8	H	H	*n*-Bu	3-pyridyl	*t*-Bu	**1g** (80)	**2g** (0)
9	MeO	H	*n*-Bu	4-$MeOC_6H_4$	*t*-Bu	**1h** (77)	**2h** (30)
10	MeO	H	*n*-Bu	4-$NO_2C_6H_4$	*t*-Bu	**1i** (58)	**2i** (87)
11	MeO	H	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	*t*-Bu	**1j** (80)	**2j** (57)
12	MeO	H		4-$NO_2C_6H_4$	*t*-Bu	**1k** (78)	**2k** (67)
13	H	H		4-$NO_2C_6H_4$	*t*-Bu	**1l** (53)	**2l** (61)
14	H	H	*n*-Bu	2-furyl	*t*-Bu	**1m** (78)	**2m** (62)
15	MeO	H		4-$NO_2C_6H_4$	*t*-Bu	**1n** (81)	**2n** (50)
16	H	H	*n*-Pr	4-ClC_6H_4	*t*-Bu	**1o** (93)	**2o** (57)

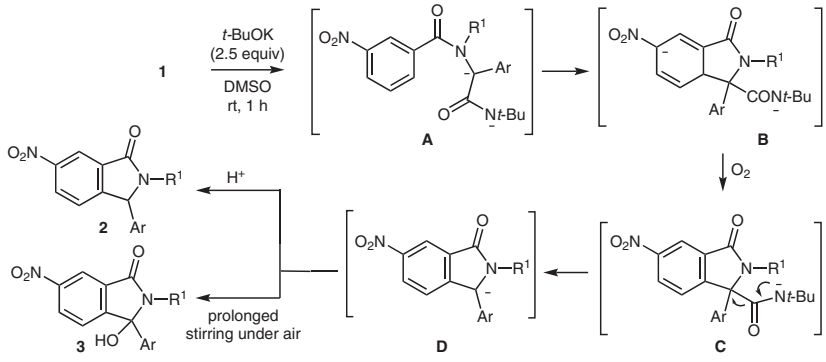


3a

[a] Isolated yields.
[b] Compound **3a** was isolated in 63% yield.

droxyisoindoles **3** directly, through oxidative cyclization of **1** in the presence of air, usually led to lower yields than the stepwise procedure; this is probably due to potential oxidation of the benzylic anions prior to the cyclization. Thus, basic treatment of the propyl adduct **1o** under air at room temperature gave **3c** in a moderate 42% isolated yield.[13] Single-crystal X-ray analysis of **3c**[14] further confirmed the selective substitution at the *para* position of the nitro group (Scheme 3).

A proposed mechanism for these transformations is outlined in Scheme 4. Initial double deprotonation of **1** leads to dianion **A** that cyclizes into **B**. Rearomatization of **B**, thanks to the oxygen present in the non-degassed solvent, affords **C**.[11] Spontaneous loss of isocyanate affords the diaryl anion **D** that, upon protonation, affords **2** or **3** after prolonged stirring open to the atmosphere. Even though the reaction may still be observed with use of one equivalent of base (Scheme 2), the formation of intermediate dianions **A**



Scheme 4 Aerobic oxidation towards hydroxyisoindolone **3**

and **B** is proposed to account for the faster and cleaner conversion of **1** at room temperature when using a larger amount of base (large excess of base may account as well for easier oxidation of intermediate σ^H adducts).[11e]

In conclusion, we have presented an Ugi/oxidative IVNS cascade of 3-nitrobenzoic acid derivatives towards isoindolones.[15] This new application of nitro-substituted Ugi adducts, together with the seminal results of Chauhan on the copper-triggered conversion of Ugi adducts into isoindolones shed some light on the potential mechanism of these cascades. Whereas a copper-based mechanism acting in both the cyclization and amide fragmentation cannot be excluded in the Chauhan study, our study suggests that the fragmentation of the amide residue can be explained by steric strain release, together with the relative stability of the anions involved before and after fragmentation. In our case, the choice of a nitro substituent and a more polar solvent is associated with higher stability of the final anions and hence smoother conversion at room temperature.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610189.

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(15) **Typical Procedure for the Ugi/Oxidative VNS for 1a/2a**

To a solution of 4-chlorobenzaldehyde (281 mg, 2.0 mmol) in MeOH (2 mL) were added successively *n*-butylamine (0.19 mL, 2.0 mmol), 3-nitrobenzoic acid (334 mg, 2.0 mmol), and *tert*-butyl isocyanide (0.22 mL, 2.0 mmol). The resulting mixture was stirred at rt for 1 d. The solvent was removed under reduced pressure and the crude was purified by flash column chromatography on silica gel (EtOAc/*n*-pentane 30:70) to afford the Ugi adduct **1a** as a white solid in 92 % yield (816 mg, 1.8 mmol). Mp 113–114 °C. R_f 0.4 (AcOEt/*n*-pentane 30:70). IR (thin film): 3424, 3315, 309, 2968, 2248, 1654, 1577, 1354, 1301. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32–8.26 (m, 2 H), 7.80 (dt, *J* = 7.6, 1.2 Hz, 1 H), 7.63 (td, *J* = 7.6, 0.9 Hz, 1 H), 7.48–7.37 (m, 4 H), 5.84 (br, 1 H), 5.66 (br, 1H), 3.31–3.19 (m, 2 H), 1.36 (s, 9 H), 1.35–1.22 (m, 2 H), 1.00–0.88 (m, 2 H), 0.58 (br, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.1, 168.0, 147.9, 138.1, 134.7, 133.8, 132.8, 130.7, 129.9, 129.2, 124.4, 121.7, 62.9, 51.8, 48.5, 31.7, 28.6, 19.8, 13.3. HRMS: *m*/*z* [M – CONH*t*-Bu] calcd for $C_{18}H_{18}ClN_2O_3$: 345.1006; found: 345.0999.

To a solution of **1a** (178 mg, 0.4 mmol) in DMSO (1 mL) was added potassium *tert*-butoxide (112 mg, 1 mmol, 2.5 equiv). The resulting mixture was stirred at rt for 1 h under an inert atmosphere. After completion of the reaction, HCl (1 mL, 18% solution in water) was added and the mixture diluted with ethyl acetate and washed with water. The organic layer was dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (Et_2O/*n*-pentane 60:40) to afford isoindolone **2a** as a yellow oil in 60% yield (82 mg, 0.24 mmol). R_f 0.22 (Et_2O/*n*-pentane 60:40). IR (thin film): 2964, 2933, 275, 2249, 1694, 1536, 1349. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (d, *J* = 2.1 Hz, 1 H), 8.34 (dd, *J* = 8.3, 2.1 Hz, 1 H), 7.37 (d, *J* = 8.6 Hz, 2 H), 7.32 (d, *J* = 8.3 Hz, 1 H), 7.08 (d, *J* = 8.6 Hz, 2 H), 5.53 (s, 1 H), 3.95 (dt, *J* = 14.1, 8.0 Hz, 1 H), 2.89–2.82 (m, 1 H), 1.57–1.48 (m, 2 H), 1.34–1.27 (m, 2 H), 0.89 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 166.3, 151.3, 148.8, 135.5, 134.0, 133.5, 129.90, 128.9, 126.9, 124.3, 119.5, 63.8, 40.4, 30.3, 20.2, 13.8. HRMS: *m*/*z* calcd for $C_{18}H_{17}ClN_2O_3$: 344.0928; found: 344.0926.