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Metal-free deamidative Ugi access to isoindolinones.

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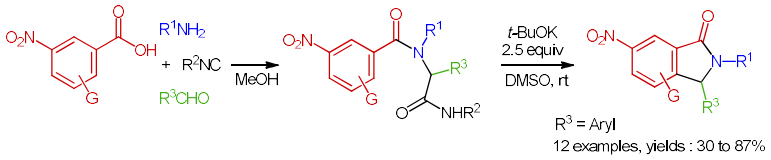

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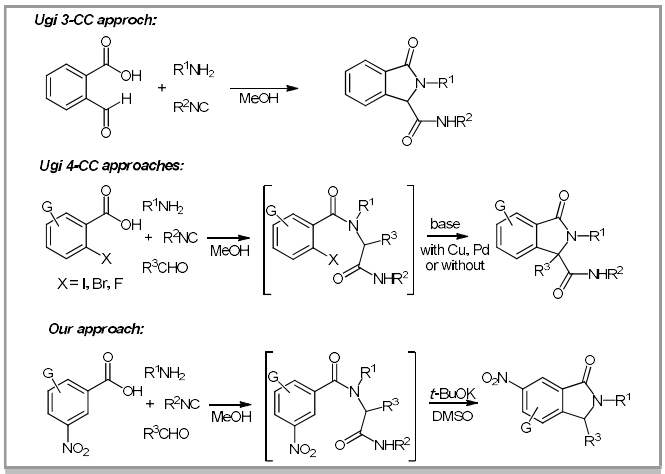
Abstract A two step isoindolone synthesis has been achieved using a Ugi/Oxidative Vicarious Nucleophilic Substitution sequence starting from 3-nitrobenzoic acid and aromatic aldehyde. Loss of the amido group was observed as well as a further oxidative process towards hydroxy-isoindolones derivatives under prolonged stirring under air.

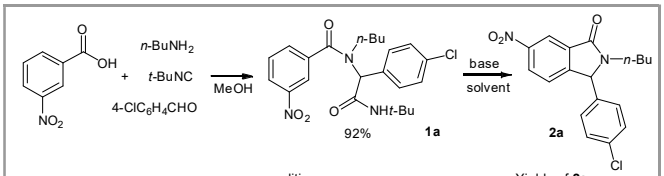
Key words Ugi reaction, 3-nitrobenzoic acid, Vicarious Nucleophilic Substitution, isolindolones, air oxidation.

The development of multicomponent reactions over the last twenty years has been strongly stimulated by the exploitation of the Ugi reactions in cascades towards complex derivatives obtained in very few steps from commercially available compounds.[1] Due to its efficiency and 4-component nature, it is not a surprise that many privileged medicinal scaffolds have been targeted using this reaction.[2] This is the case of isoindole derivatives[3] whose many uses as axiolytic,[4] antiviral,[5] or anticancer agents,[6] continuously stimulate the efforts of chemists to provide new syntheses with even more efficiency. In this context, the Ugi reaction has been used extensively to form isoindolones 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 3-component reactions is the most direct but remains limited by the choice of available starting partners (Scheme 1).[7(a)-7(f)] The second two-step approach involves 4-component couplings of benzoic derivatives substituted at the ortho position by proper leaving groups (Scheme 1).[7(g)-7(m)] Among the latter, the synthesis proposed by Chauhan et al[7(j)] particularly caught our attention. They describe a copper-catalyzed cyclisation / de-amidation process from Ugi adduct derived from o-iodobenzoic acid.[8] Following our interest in 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 similar cyclization without copper[7(i)] (but retaining the amide group, Scheme 1), we decided to launch a study around these cyclisations to have a better insight into the deamidation and their potential in isoindolinone syntheses. To raise the novelty in the cyclization step, we selected 3-nitrobenzoic acid derivatives as starting materials with the objective of performing an intramolecular vicarious nucleophilic substitution (NVS)[10] in the cyclization step which had not been observed before on Ugi adducts.



Scheme 1 Ugi access to isoindolinones

The Ugi adduct **1a** was thus prepared with a yield of 92% by reacting chlorobenzaldehyde with 3-nitrobenzoic acid, *tert*-butyl isonitrile and butylamine. 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), we had the pleasure to observe after one hour at room temperature the formation of isoindolone **2a** involving the desired cyclization along with the fragmentation of the amide (Scheme 2).

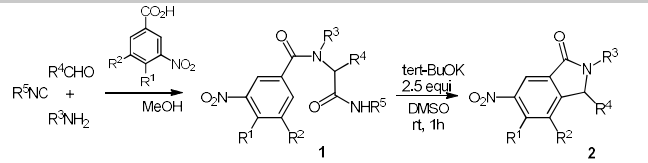


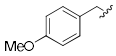
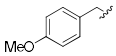
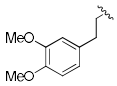
conditions	Yields of **2a**
NaH (2.5 equiv), DMSO, rt, 1 h	55%
NaH (2.5 equiv), THF, rt, 1 h	0%
NaH (2.5 equiv), DMSO, rt, 1 h	41%
***t*-BuOK (2.5 equiv), DMSO, rt, 1 h**	**60%**
t-BuOK (0.9 equiv), DMSO, rt, 1 h	45%
t-BuOK (2.5 equiv), DMSO, 80 °C, 0.5 h	33%
t-BuOK (2.5 equiv), DMF, rt, 1 h	40%
t-BuOK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

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

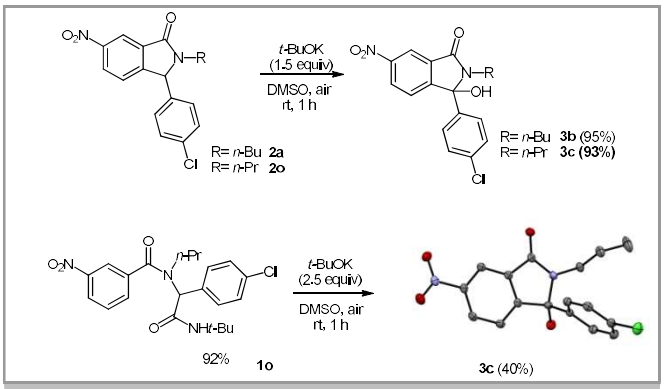
Table 1 Synthesis of isoindolones **2** from Ugi adducts **1**



Entry	R^1	R^2	R^3	R^4	R^5	**1** (%)[a]	**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)

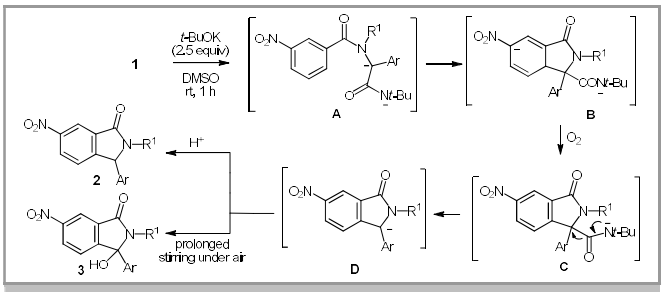
[a] isolated Yield. [b] **3a** was isolated in 63% isolated yield

All Ugi adducts prepared led to cyclised 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.[11(a),(e)] Overall, the cyclization works better for Ugi adducts derived from electron poor aromatic aldehydes. The poor 30 and 40%isolated yields obtained for 4-methoxyaryl derivatives (Table 1, entries 6 and 9) may be best explained by a less stabilizing effect of the benzylic anions that may 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** using shorter reaction or trying to exclude any trace of oxygen from the medium were not conclusive as well as either the starting material or the final hydroxyl **3g** were observed. This final oxidation is certainly associated with some of the moderate yields obtained in Table 1. Indeed, reactions were all performed under argon but without prior degassing of solvent as 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 under air at rt for one hour in the presence of 1.5 equiv of potassium *tert*-butylate.[12] However attempts to form directly hydroxyisoindoles **3** through oxidative cyclization of **1** in the presence of air usually led to lower yields than the stepwise procedure probably due to potential oxidation of the benzylic anions prior to the cyclization. Thus basic treatment of the propyl adduct **1o** under air at rt gave **3c** in a moderate 42% isolated yield.[13] A single crystal RX data analysis of **3c**[14] further confirmed the selective substitution at the para position of the nitro group (Scheme 3).



Scheme 3 Aerobic oxidation towards hydroxyisoindolone **3**

A proposed mechanism for these transformations is displayed in Scheme 4. Initial double deprotonation of **1** lead to dianion A that cyclise 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 which upon protonation affords **2** or **3** under prolonged stirring under air. Even though the reaction may still be observed using one equivalent of base (Scheme 2), the formation of intermediate dianions A and B was proposed to account for the faster and cleaner conversion of **1** at rt when using larger amount of bases (large excess of base may account as well for easier oxidation of intermediate σ^H adducts).[11(e)]



Scheme 4 Aerobic oxidation towards hydroxyisoindolone **3**

In conclusion, we have proposed a Ugi/Oxidative VNS cascade of 3-nitrobenzoic 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 into the potential mechanism of these cascades. Whereas a copper based mechanism acting in both cyclization and amide fragmentation can't 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 rt.

Acknowledgment

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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(14) The crystallographic data for compounds **3c** can be obtained free of charge under the reference CCDC 1835817 from the Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request_cif.

(15) A typical procedure for the Ugi/Oxidative VNS is given 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 room temperature for 1 day. The solvent was removed under reduced pressure and the crude was purified by flash column chromatography on silica gel (EtOAc: PE = 30: 70) to afford the Ugi adduct **1a** as a white solid isolated in 92 % yield (816 mg, 1.8 mmol). **M.P. =** 113-114 °C. **R_f:** 0.4 (AcOEt/PE = 30/70). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32-8.26 (m, 2H), 7.80 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.63 (td, *J* = 7.6, 0.9 Hz, 1H), 7.48-7.37 (m, 4H), 5.84 (br, 1H), 5.66 (br, 1H), 3.31-3.19 (m, 2H), 1.36 (s, 9H), 1.35-1.22 (m, 2H), 1.00-0.88 (m, 2H), 0.58 (br, 3H). **^{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:** Calculated for [M-CONHtBu] $C_{18}H_{18}ClN_2O_3$:345.1006, Found: 345.0999. **I.R. (thin film):** 3424, 3315, 309, 2968, 2248, 1654, 1577, 1354, 1301.

To a solution of **1a** (178 mg, 0.4 mmol) in DMSO (1ml) was added potassium *tert*-butoxide (112 mg, 1 mmol, 2.5 equiv). The resulting mixture was stirred at room temperature for 1 hour under inert atmosphere. After completion of the reaction, 1ml of HCl (18% solution in water) was added and the mixture diluted with ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (Et_2O/PE : 60/40) to afford isoindolone **2a** as a yellow oil in 60% isolated yield (82 mg, 0.24 mmol). **R_f:** 0.22 (Et_2O/PE = 60/40). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 2.1 Hz, 1H), 8.34 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 2H), 5.53 (s, 1H), 3.95 (dt, *J* = 14.1, 8.0 Hz, 1H), 2.89-2.82 (m, 1H), 1.57-1.48 (m, 2H), 1.34-1.27 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H). **^{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:** Calculated for $C_{18}H_{17}ClN_2O_3$: 344.0928, Found: 344.0926. **I.R. (thin film):** 2964, 2933, 275, 2249, 1694, 1536, 1349