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One-Pot Facile Synthesis of Substituted Isoindolinones via an Ugi Four-Component Condensation/Diels−Alder Cycloaddition/ Deselenization−Aromatization Sequence

Xian Huang*,†,‡ and Jianfeng Xu†

†*Department of Chemistry, Zhejiang University (Xixi Campus), Hangzhou 310028, People's Republic of China, and* ‡*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, People's Republic of China*

huangx@mail.hz.zj.cn

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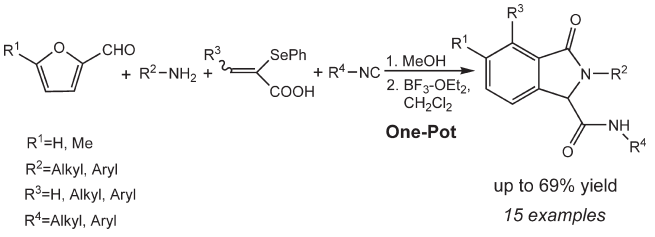

A versatile one-pot synthesis of substituted isoindolinones from 2-furaldehydes, amines, 2-(phenylselanyl)-acrylic acids, and isocyanides is described. The tandem process involves the Ugi four-component condensation, intramolecular Diels−Alder cycloaddition, and subsequent deselenization−aromatization promoted by BF_3−OEt_2. The procedure is general and efficient and the substrates are easily available.

Isoindolinone represents a core skeleton in a large number of natural products and pharmacophores.[1] Experience has shown that compounds with the isoindolinone scaffold often show biological and medical activities.[2] For example (Figure 1), isoindolinone **1** is found to be a potent Cdk4 inhibitor,[2a] isoindolinone **2** displays modest antiproliferative effect against HT-29 and L1210 cell lines,[2b] isoindolinone **3** exhibits strong sedative-hypnotic effects in mice after intravenous administration,[2c] and isoindolinone **4** is a potent inhibitor of DNA gyrase, which shows promising antibacterial activity against Gram-positive bacterial strains.[2d]

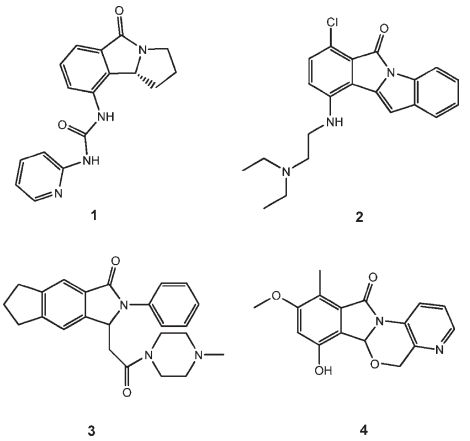

FIGURE 1. Structures of some biological and medical active compounds containing the isoindolinone scaffold.

Traditionally, the preparation of substituted isoindolinones has been carried out by the nucleophilic attack−reduction sequence on phthalimide.[3] More modern achievements in the construction of substituted isoindolinones include rhenium-catalyzed reaction of aromatic aldimines with isocyanates,[4] superacid-catalyzed aza-Nazarov reaction of *N*-acyliminium ion salts,[5] palladium-catalyzed aromatic carbonylation of benzylic amines,[6] and iodoamination of α-substituted secondary 2-vinylbenzamides.[7] However, these methods involve either expensive transition metal catalysts or multistep procedures. Therefore, alternative protocols with mild conditions, low cost, and simple operation are desirable.

Multicomponent reactions (MCRs) have emerged as powerful synthetic strategies for the construction of biologically interesting compounds based on their high efficiency, rich diversity, and easy operation.[8] Among them, the Ugi four-component reaction (Ugi-4CR) has been extensively

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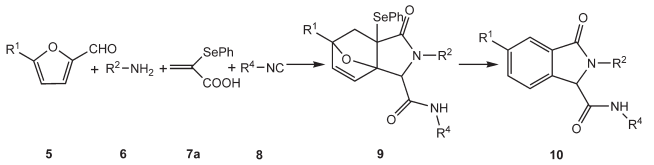
SCHEME 1



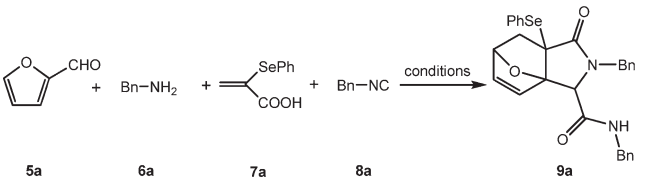
investigated for the generation of small molecule libraries.[9] Recently, efforts have been made to synthesize more complex structures with the tandem Ugi/Diels−Alder reaction.[10] 2-(Phenylselanyl)acrylic acid **7a** is a useful multifunctionalized building block, since it has an acid group with an α,β-unsaturated system, and we believe that it could react smoothly in the Ugi/Diels−Alder reaction. Organoselenium compounds have been widely used in organic synthesis due to its various reactivities.[11] Herein we envisioned that the cycloadduct **9** formed from **7a** via Ugi/Diels−Alder reaction may go further deselenization−aromatization to afford the desired product, isoindolinone **10** (Scheme 1).

Initially, the Ugi/Diels−Alder tandem reaction was performed in CH_2Cl_2 with 2-furaldehyde **5a**, benzylamine **6a**, 2-(phenylselanyl)acrylic acid **7a**, and benzyl isocyanide **8a** as the substrates; the yield was 28% (Table 1, entry 1). A solvent screen found that protic solvent MeOH was the best (Table 1, entries 1−4). Upon adjusting the amount of each component, the highest yield was obtained with 1.2 equiv of **6a** and 1.0 equiv of the other three components (Table 1, entries 5−10). Although heating the reaction could shorten the reaction time, it gave a lower yield (Table 1, entries 6, 11, and 12). Generally, the optimized condition of the Ugi/Diels−Alder reaction used 1.0 equiv of **5a**, 1.2 equiv of **6a**, 1.0 equiv of **7a**, and 1.0 equiv of **8a** in MeOH at 25 °C for 16 h (Table 1, entry 6).

We then tested the deselenization of product **9a** to afford isoindolinone **10a**. Traditional methods applied to deselenization such as oxidation−elimination with H_2O_2, $NaIO_4$ did not give isoindolinone **10a**. We already knew that Lewis acids could be used to open the oxo-bridge to afford a carboncation[12] and the β-phenylselenyl cation could be easily eliminated to form a carbon−carbon double bond.[13] So we proposed that when Lewis acid was added to **9a**, a new β-phenylselenyl cation would form, and elimination of this β-phenylselenyl cation followed by aromatization would produce isoindolinone **10a** (Scheme 2). A variety of Lewis acids were investigated, as shown in Table 2, and the results indicated that $BF_3{-}OEt_2$ was the optimum Lewis acid (Table 2, entry 5).

With the above two optimized conditions in hand, we tried to combine these two steps in one pot, without the isolation

TABLE 1. Effects of Reaction Conditions on the Ugi/Diels−Alder Reaction[a]



entry	**5a**:**6a**:**7a**:**8a** (equiv)	solvent	temp (°C)	time (h)[b]	yield (%)[c]
1	1.0:1.0:1.0:1.0	CH_2Cl_2	25	30	28
2	1.0:1.0:1.0:1.0	toluene	25	36	32
3	1.0:1.0:1.0:1.0	CH_3CN	25	24	54
4	1.0:1.0:1.0:1.0	MeOH	25	16	76
5	1.2:1.0:1.0:1.0	MeOH	25	16	72
6	**1.0:1.2:1.0:1.0**	**MeOH**	**25**	**16**	**83**
7	1.0:1.0:1.2:1.0	MeOH	25	16	80
8	1.0:1.0:1.0:1.2	MeOH	25	16	74
9	1.0:1.2:1.2:1.0	MeOH	25	16	79
10	1.0:1.4:1.0:1.0	MeOH	25	16	82
11	1.0:1.2:1.0:1.0	MeOH	40	12	76
12	1.0:1.2:1.0:1.0	MeOH	reflux	8	60

[a]Unless otherwise specified, the reaction was carried out with **5a** (1.0 mmol), **6a** (1.0 mmol), **7a** (1.0 mmol), and **8a** (1.0 mmol) in 4 mL of solvent under an air atmosphere. [b]The reaction was monitored by TLC. [c]Isolated yields.

SCHEME 2

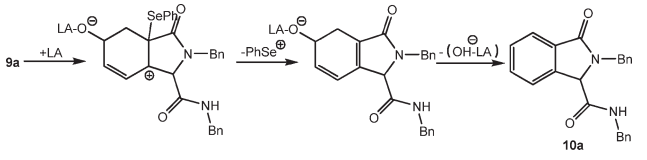
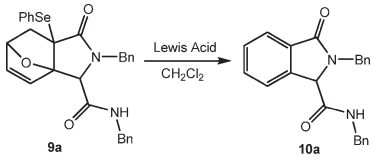


TABLE 2. Effects of Lewis Acids on the Deselenization and Aromatization Reaction[a]



entry	Lewis acid (equiv)	time (h)[b]	yield (%)[c]
1	$ZnCl_2$ (1.0)	10	50
2	$AlCl_3$ (1.0)	6	56
3	$FeCl_3$ (1.0)	1.5	73
4	$TiCl_4$ (1.0)	0.5	77
5	**$BF_3{-}OEt_2$ (1.0)**	**2**	**86**
6	AgOTf (1.0)	40	0
7	$ZrCl_4$ (1.0)	20	38
8	$BF_3{-}OEt_2$ (2.0)	2	84

[a]Unless otherwise specified, the reaction was carried out with **9a** (1.0 mmol) and Lewis acid (1.0 mmol) in 4 mL of CH_2Cl_2 under an air atmosphere at room temperature. [b]The reaction was monitored by TLC. [c]Isolated yields.

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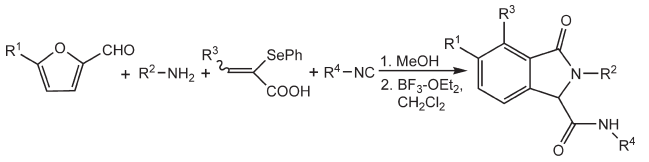
TABLE 3. Synthesis of Various Isoindolinones 10[a]



5 6 7 8 10

entry	5	6	7	8	yield (%)[d]
1	R^1 = H (**5a**)	R^2 = Bn (**6a**)	R^3 = H (**7a**)	R^4 = Bn (**8a**)	**10a**, 65
2[b]	R^1 = Me (**5b**)	**6a**	**7a**	**8a**	**10b**, 47
3	**5a**	R^2 = Pr (**6b**)	**7a**	**8a**	**10c**, 56
4	**5a**	R^2 = Cy (**6c**)	**7a**	**8a**	**10d**, 42
5[c]	**5a**	R^2 = Ph (**6d**)	**7a**	**8a**	**10e**, 58
6[c]	**5a**	R^2 = *p*-$CH_3OC_6H_4$ (**6e**)	**7a**	**8a**	**10f**, 61
7[c]	**5a**	R^2 = *p*-ClC_6H_4 (**6f**)	**7a**	**8a**	**10g**, 69
8[c]	**5a**	**6a**	R^3 = Me (**7b**)	**8a**	**10h**, 49
9[b]	**5a**	**6a**	R^3 = Pr (**7c**)	**8a**	**10i**, 40
10[b]	**5a**	**6a**	R^3 = Ph (**7d**)	**8a**	**10j**, 47
11	**5a**	**6a**	**7a**	R^4 = *p*-$CH_3C_6H_4$ (**8b**)	**10k**, 53
12	**5a**	**6a**	**7a**	R^4 = CH_2COOEt (**8c**)	**10l**, 40
13[b]	**5b**	**6a**	**7b**	**8a**	**10m**, 35
14[c]	**5a**	**6b**	**7b**	**8a**	**10n**, 43
15[c]	**5a**	**6a**	**7b**	**8b**	**10o**, 42

[a]The reaction was carried out with **5** (1.0 mmol), **6** (1.2 mmol), **7** (1.0 mmol), and **8** (1.0 mmol) in 4 mL of MeOH under an air atmosphere at room temperature for 16 h. [b]The reaction was carried out with **5** (1.0 mmol), **6** (1.2 mmol), **7** (1.0 mmol), and **8** (1.0 mmol) in 4 mL of MeOH under an air atmosphere at room temperature for 12 h then reflux for 24 h. [c]The reaction was carried out with **5** (1.0 mmol), **6** (1.2 mmol), **7** (1.0 mmol), and **8** (1.0 mmol) in 4 mL of MeOH under an air atmosphere at room temperature for 12 h then reflux for 8 h. [d]Isolated yields.

of cycloadduct **9a**. When the Diels–Alder reaction was complete, MeOH was removed and the solvent was replaced with anhydrous CH_2Cl_2. Then 2.0 equiv of BF_3–OEt_2 was added and, after 2 h, the isoindolinone **10a** was obtained in 65% overall yield. By using the established reaction conditions, a variety of 2-furaldehydes **5**, amines **6**, 2-(phenylselanyl)acrylic acids **7**, and isocyanides **8** were investigated. As shown in Table 3, the yields of isoindolinones **10** ranged from 35% to 69%. When substituted 2-furaldehydes, arylamines, and substituted 2-(phenylselanyl)acrylic acids were used, the cycloaddtion step proceeded under reflux conditions. The substituent on 2-furaldehyde made the reaction take place under a more forceful condition, and the yields were lower (Table 3, entries 1, 2 and entries 8, 13). Arylamines gave higher yields than alkylamines (Table 3, entries 1 and 3–7), and the substituents on the aryl group did not influence the reaction much (Table 3, entries 5–7). Both alkyl and aryl subtituents on 2-(phenylselanyl)acrylic acid can be used in this reaction smoothly, and the yields were moderate (Table 3, entries 1, 8–10 and entries 13–15). Substituents on isocyanides also affected this reaction where alkyl isocyanides were generally better than aryl isocyanide and isocyanide with an electron-withdrawing group (Table 3, entries 1, 11, and 12).

In summary, we have developed a one-pot synthesis of substituted isoindolinones from 2-furaldehydes, amines, 2-(phenylselanyl)acrylic acids, and isocyanides. The tandem process involves the Ugi four-component condensation, intramolecular Diels–Alder cycloaddition, and subsequent deselenization–aromatization promoted by BF_3–OEt_2. The procedure is general and efficient and the substrates are easily available. Considering the importance of isoindolinone derivatives, this method may find wide application in the synthesis of more complex polycyclic heterocycles.

Experimental Section

General Procedure for Synthesis of Isoindolinones 10. A 2-furaldehyde **5** (1.0 mmol), a primary amine **6** (1.2 mmol), a 2-(phenylselanyl)acrylic acid **7** (1.0 mmol), and an isocyanide **8** (1.0 mmol) were combined in methanol (4 mL), and the reaction mixture was stirred at 25 °C for 16 h. Then methanol was evaporated and anhydrous CH_2Cl_2 (5 mL) and BF_3–OEt_2 (2.0 mmol) were added, then stirring was continued at 25 °C for an additional 2 h before the reaction was quenched by adding sat. aq $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 2:1 v/v) to give the product **10**.

***N*,2-Dibenzyl-3-oxoisoindoline-1-carboxamide (10a):** pale solid, mp 169–171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (1H, d, J = 7.2 Hz), 7.48–7.51 (1H, m), 7.40 (1H, br, 1H of NH), 7.15–7.34 (12H, m), 5.24 (1H, d, J = 14.8 Hz, 1H of CH_2), 4.88 (1H, s, 1H of CH), 4.44 (1H, dd, J_1 = 14.8 Hz, J_2 = 6.0 Hz, 1H of CH_2), 4.38 (1H, dd, J_1 = 14.8 Hz, J_2 = 6.0 Hz, 1H of CH_2), 4.17 (1H, d, J = 14.8 Hz, 1H of CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 167.5, 141.2, 138.0, 135.9, 132.2, 130.4, 128.9, 128.6, 128.4, 128.0, 127.7, 127.4, 123.7, 112.7, 64.1, 45.6, 43.4; MS (EI) m/z 356 (M^+); IR ν_{max} (cm^{-1}) 1695, 1664, 1541, 1397, 1241, 740, 699; HRMS (EI) m/z calcd for $C_{23}H_{20}N_2O_2$ (M^+) 356.1525, found 356.1522.

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Supporting Information Available: General experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.