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A Three-Component Reaction toward the Synthesis of 1-Carboxamido-isoindoles

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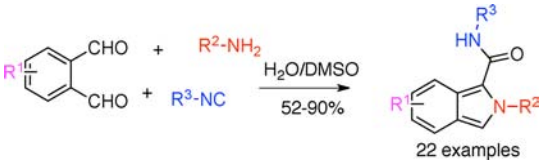
ABSTRACT



An efficient three-component reaction toward the facile synthesis of structurally diverse 1-carboxamido-isoindoles has been developed. The resultant isoindoles can be used in Diels–Alder reactions.

Isoindoles are interesting skeletons because of their fluorescent properties and potential medicinal value.[1] Recently, numerous synthetic strategies have been reported to prepare various isoindole moieties.[2] For instance, Suginome and co-workers used a palladium-catalyzed reaction of isoindolines to prepare 1-borylisoindoles.[3] Sole et al.[4] reported a Pd-catalyzed intramolecular α-arylation of amino acid esters to produce 1-isoindolecarboxylic acid esters. Stevens et al.[5] have synthesized 1-cyanoisoindoles and phosphorylated isoindoles. Multicomponent coupling reactions (MCRs), which enable several reacting partners to join together in a sequential manner under mild and robust conditions, have been shown to be a powerful approach to preparing structurally diverse compounds.[6] Herein, we consider the possibility of exploiting an MCR strategy to synthesize the isoindole derivatives. Identification of suitable partners is the key to achieving such a goal. We are attracted by the rich chemistry of *ortho*-phthalaldehyde (OPA), which has long been known to react with some nucleophiles[7] and widely used to detect the amino group during Edman degradation of peptides.[8] To the best of our knowledge, isonitriles have not been reported to react with OPAs. Herein, we report a three-component reaction toward the synthesis of 1-carboxamido-isoindoles with OPA, amines, and isonitriles.

We envisioned that the monoimine **A**, formed by a reaction between OPA and 1 equiv of amine, can be attacked by the "soft" nucleophile isonitrile as in the Ugi reaction.[9] Then, the thus generated nitrilium cation **B** can be trapped by water to form intermediate **C** via a Ritter-type mechanism.[10]Finally, dehydration-mediated aromatization produces the isoindole product **D** (Figure 1).

According to our proposed mechanism, a model study was initiated with *ortho*-phthalaldehyde **1**, benzylamine **2**, and cyclohexyl isonitrile **3a** or glycine isonitrile **3b** as substrates to explore the working reaction conditions. Disappointingly at the time, initial attempts with a variety of conditions with different solvents (Table 1, entries 1–7) produced no desired product. The major or sole product

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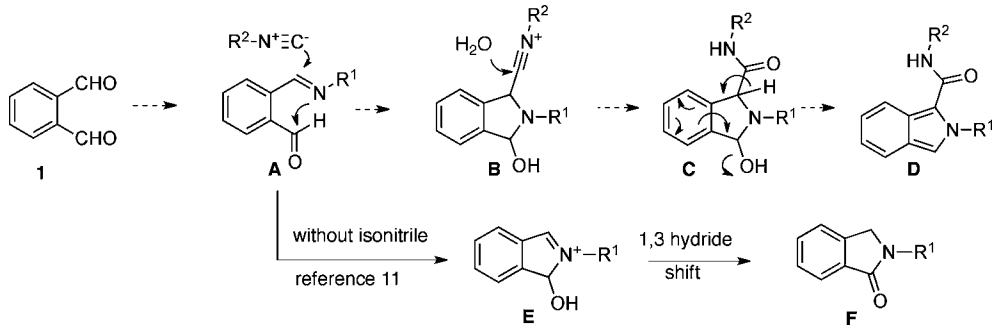

Figure 1. Three-component reaction toward the synthesis of isoindole compounds.

obtained was the *N*-substituted isoindolin-1-ones (cf. **F**), whose formation has been observed and proposed in the literature through a 1,3-hydride shift via the hydroxyiminium species (cf. **E**) (Figure 1).[11] The undesired reaction can be attributed to the low electrophilicity of the imine in **A** and the strong driving force for the lactam formation. In other words, the isonitrile moiety seemed unable to join in the reaction. To increase the electrophilicity of the imine, various Lewis acids/Brønsted acids (entries 8−12) including triflic acid, $Zn(OTf)_2$, and BF_3OEt_2 were tested, but in vain.

Considering the key role of intermediate **E** in the undesired reaction pathway, another possible tactic was to suppress its formation. Sodium bisulfite is known to form a bisulfite adduct with aldehyde groups;[7] thus it probably helped to slow down the formation of the hydroxyiminium species **E**. Gratifyingly, when sodium bisulfite ($NaHSO_3$) was used as the additive, the desired product was obtained in 10−16% yield after 40 h (Table 1, entry 13). Further optimizations revealed that the mixed solvent (DMSO/H_2O) can accelerate the reaction, enabling the completion at room temperature within 8 h to produce a 70% yield (Table 1, entry 15). Furthermore, the reaction temperature was also investigated at 50 and 100 °C; heating the reaction mixture can also help drive the reaction (Table 1, entries 16−17). For a comparison, the reaction at 50 °C without $NaHSO_3$ still failed to produce any desired product, revealing the importance of $NaHSO_3$ (Table 1, entry 18). Thus, the optimal conditions were found, in which *ortho*-phthalaldehyde was mixed with 2 equiv of $NaHSO_3$ sodium bisulfite in DMSO/H_2O (1/1 v/v) for 0.5 h to obtain a homogeneous solution at room temperature, followed by the addition of 1 equiv of amine and 2 equiv of isonitriles. It is noteworthy that, during the process of the reaction, some white solid precipitated out from the reaction mixture, and the simple filtration produced the pure desired compound **4b** in 55% yield. Further chromatography of the mother liquid gave an additional 15% product.

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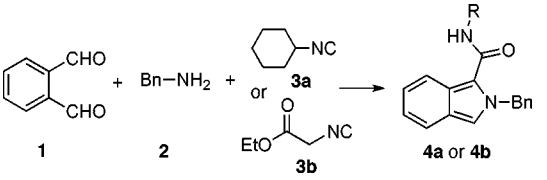
Table 1. Optimization of the Reaction Conditions[a]



entry	3	solvent	temp (°C)	time (h)	additive	yield (%)[b]
1	**3a**	THF	rt	8		0
2	**3a**	H_2O	rt	12		0
3	**3a**	MeOH	rt	9		0
4	**3a**	CH_2Cl_2	rt	9		0
5	**3a**	DMF	rt	9		0
6	**3a**	AcCN	rt	9		0
7	**3a**	TFE	rt	9		0
8	**3a**	CH_2Cl_2	rt	9	TfOH	0
9	**3a**	CH_2Cl_2	rt	9	$Zn(OTf)_2$	0
10	**3a**	CH_2Cl_2	rt	9	BF_3OEt_2	0
11	**3a**	DMF	rt	9	TfOH	0
12	**3a**	DMF	rt	9	$Zn(OTf)_2$	0
13	**3a**	H_2O	rt	40	$NaHSO_3$	10
14	**3b**	H_2O	rt	40	$NaHSO_3$	16
15	**3b**	DMSO/H_2O	rt	8	$NaHSO_3$	70
16	**3b**	DMSO/H_2O	50	2	$NaHSO_3$	41
17	**3b**	DMSO/H_2O	100	2	$NaHSO_3$	65
18	**3b**	DMSO/H_2O	50	2		0

[a] All reactions were carried out with 0.41 mmol of OPA. [b] Isolated yield.

To probe the role of $NaHSO_3$ during the reaction, we mixed OPA and $NaHSO_3$ in *d*-DMSO/*d*-H_2O and recorded the NMR spectrum of the resulting intermediate. The disappearance of the aldehyde proton signal indicated the formation of a bisulfite adduct **G** (Figure 2). It is likely that the adduct **G** could condense with amines, followed by the attack of isonitriles to give **J** (or via **H** and **J**). The Ritter-type reaction converted the nitrilium ion into the carboxamide, and the resultant amine expelled the sodium

sulfite group to yield **C**. Then, aromatization resulted in the desired isoindole compound.

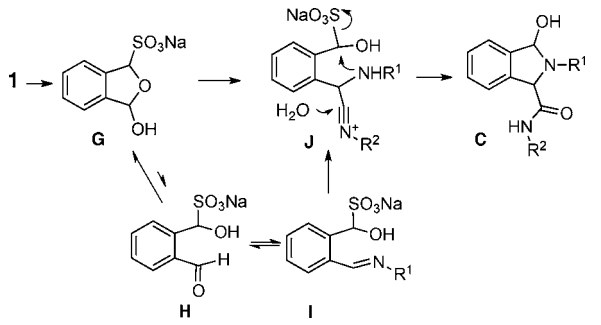


Figure 2. Proposed role of $NaHSO_3$ during the isoindole formation.

Next, we set out to explore the scope and limitations of this reaction, using the optimized conditions. Both *ortho*-phthalaldehyde and 3,4-dimethoxy *ortho*-phthalaldehyde were used, together with benzyl amine derivatives and aniline derivatives. Isonitriles were selected from commercially available *tert*-butylisonitrile, cyclohexyl isonitrile, and glycine isonitrile. As shown in Figure 3, the desired isoindole compounds (**4a**–**4l**) were obtained in modest to good yields (52–85%). Even with the very hindered *tert*-butyl isonitrile, the reaction still worked well. Due to the limited solubility of 3,4-dimethoxy *ortho*-phthalaldehyde in the mixture of DMSO and H_2O, the addition of acetonitrile leading to the reacting solvent as $DMSO/H_2O/CH_3CN$ (4/4/1) was needed for the reaction to proceed effectively to produce isoindoles (**5a**–**5j**) in good yields (55–90%).

Further derivatization of the resultant isoindole product was also explored. Considering the electron-rich diene

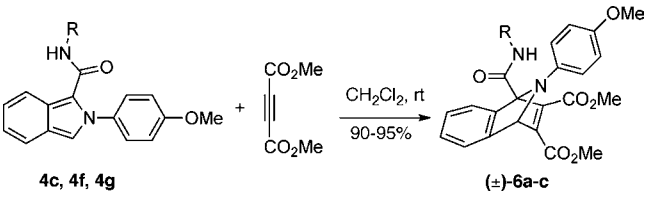


Figure 4. 1-Carboxamido-isoindoles in Diels–Alder reaction.

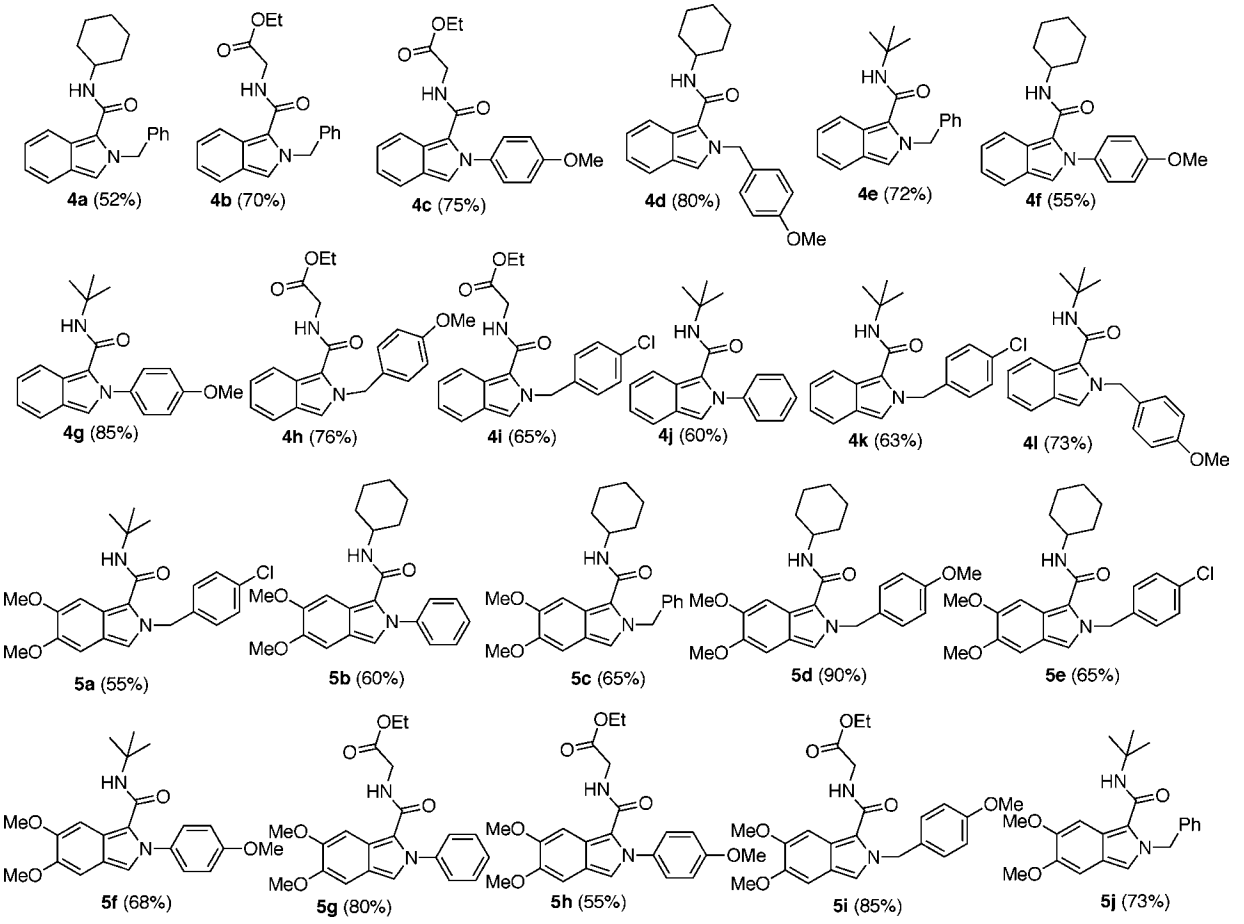


Figure 3. Scope of the multicomponent reaction.

structure in the isoindole molecules, the Diels–Alder reaction with electron-deficient dienophile dimethyl acetylenedicarboxylate (DMAD) and isoindoles (**4c**, **4f**, and **4g**) was conducted in CH_2Cl_2 at room temperature for 1 h. As expected, the cycloadducts **6a**–**c** were smoothly formed in 90–95% yields to generate a fused-ring heterocycle (Figure 4).

In summary, we reported herein a three-component reaction toward the synthesis of 1-carboxamido-isoindoles under mild conditions. The generated isoindoles can be used for the preparation of fused-ring heterocycles via Diels–Alder reactions.

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Supporting Information Available. Experimental procedures, spectroscopic data and copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.