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# A New Route to Indazolone via Amidation Reaction of *o*-Carboxyazobenzene

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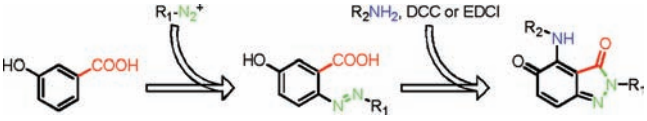
## ABSTRACT

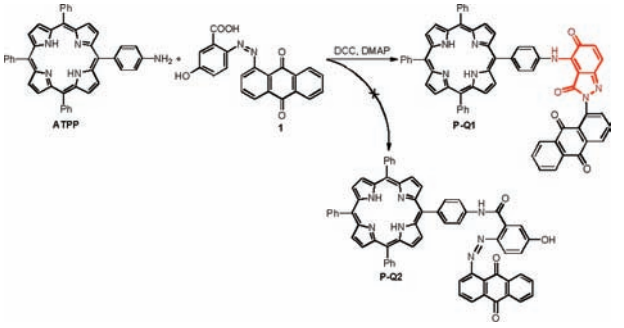



**One new route for the synthesis of amino-substituted indazol-3,5-dione *via* the amidation reaction of *o*-carboxyazobenzenes is reported. Optimization which includes effects of the solvents, molar ratio of starting materials, and dehydrating agents on this reaction has been studied. A possible reaction mechanism has been proposed on the basis of the product's structure, and the steric hindrance could be the main reason for low yield.**

Indazolones, one of the most important derivatives of indazole, have been receiving much attention due to their promising pharmacological activities, mainly as an anti-inflammatory, analgesic, or antipyretic agent.[1−4] Different synthetic routes have been reported to construct the framework of indazolone, including copper-catalyzed intramolecular C−N bond formation of 2-halobenzohydrazides,[5] CuO-catalyzed amination of 2-haloarylcarboxyic acid with methylhydrazine,[6] cobalt-catalyzed carbonylation of azobenzene to form indazole,[7] treating *o*-nitrosobenzaldehyde with amine,[8] cyclization of 2-hydrazinobenzoic acid,[9] cyclization of *N*-(*o*-azidobenzoyl)arylamine,[10] cyclization of nitroaryl substrates through a low-valent titanium reagent,[11] PIFA-mediated intramolecular *N*-acylnitrenium trapping,[12] acid-induced rearrangement of *o*-formylazobenzenes,[13] base-mediated methanolysis of 2,3-dihydrooxazolo-[3,2-*b*]indazole,[14] and many others.[15]

In connection with our findings on the construction of indazolone's framework (Scheme 1) *via* an unexpected rearrangement in the amidation reaction between ATPP and *o*-carboxyazobenzene (**1**) in the presence of DCC,[16] we plan to investigate the possibility of building up indazolone by the same rearrangement in the amidation procedure of different functionalized *o*-carboxyazobenzenes.

**Scheme 1.** Synthetic Route for **P-Q1** Linked by the Indazolone Moiety

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In this paper, we describe the preliminary results in developing a concise and effective one-pot transformation for preparation of the amino-substituted indazol-3,5-dione. This method is based on the dehydrating agent initiated intramolecular C−N formation and the subsequent nucleophilic conjugation addition of amine.

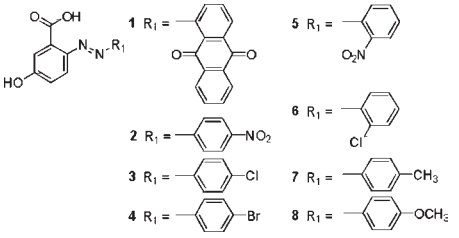
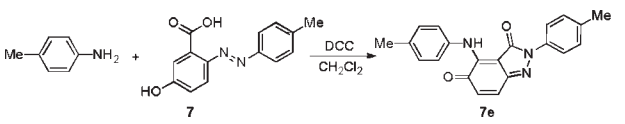



**Figure 1.** Structure of *o*-carboxyazobenzene (**1**−**8**).

In order to investigate the scope of this rearrangement reaction, a series of novel *o*-carboxyazobenzenes have been designed and synthesized to react with different amines (Figure 1). Among them, the *o*-carboxyazobenzene **7** and *p*-toluidine are selected as the model substrates to screen the experimental conditions for the optimization of dehydrating agents, solvents, and molar ratio of **7** and *p*-toluidine (Table 1).

When compound **7** (obtained from 3-hydroxybenzoic acid and 4-methylbenzenediazonium) and *p*-toluidine are dispersed in $CH_2Cl_2$ in the absence of dehydrating agent, no desired product **7e** is observed by the TLC (Table 1, entry 1). After adding DCC or EDCI, **7e** is obtained where DCC appears to be a better activator compared with the other two (Table 1, entries 2, 3, and 6). Subsequently, we investigated the effect of different molar ratios of **7** and *p*-toluidine in order to improve the yield of **7e** (Table 1, entries 4−8). The molar ratio of 5/1 turns out to be effective to obtain an appropriate yield. In addition, the effects of additives have been investigated (Table 1, entries 9−11). It is found that the addition of DMAP and TEA negatively impacts the performance of this reaction. It should be noted that the solvents have a significant influence on the outcome of the reaction. When **7** (5 equiv) is treated with *p*-toluidine (1 equiv) and DCC (7.5 equiv) for 2 h at rt in various solvents, such as $CH_2Cl_2$, $CHCl_3$, THF, $CH_3CN$, $PhCH_3$, DMF, and DMSO (Table 1, entries 7, 12−17), $CH_3CN$ and $PhCH_3$ are found to be poor reaction solvents without formation of **7e** (Table 1, entries 14, 15), while the use of THF or DMSO gives **7e** in yields of only 11% and 7%, respectively (Table 1, entries 13, 17). By contrast, the employment of $CH_2Cl_2$ affords the desired product **7e** with an increased yield of 61%. Thus, we propose that the optimal procedure for the preparation of amino-substituted indazol-3,5-dione is as follows: a mixture of *o*-carboxyazobenzene and amine (5/1, molar ratio) in $CH_2Cl_2$ is stirred in the presence of DCC (1.5 equiv *vs* the case for *o*-carboxyazobenzene) at rt.

**Table 1.** Optimization of Reaction Conditions for Synthesis of **7e**




| entry | solvent | molar ratio (**7**/amine) | dehydrating agent | **7e**[b] (%) |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 2/1 | – | – |
| 2 | $CH_2Cl_2$ | 2/1 | HBTU[a]/ TEA[d] | 40 |
| 3 | $CH_2Cl_2$ | 2/1 | EDCI[a] | 42 |
| 4 | $CH_2Cl_2$ | 0.5/1 | DCC[a] | 43 |
| 5 | $CH_2Cl_2$ | 1/1 | DCC[a] | 39 |
| 6 | $CH_2Cl_2$ | 2/1 | DCC[a] | 57 |
| 7 | $CH_2Cl_2$ | 5/1 | DCC[a] | 61 |
| 8 | $CH_2Cl_2$ | 10/1 | DCC[a] | 38 |
| 9 | $CH_2Cl_2$ | 5/1 | DCC[a]/DMAP[c] | 11 |
| 10 | $CH_2Cl_2$ | 5/1 | DCC[a]/DMAP[c]/ TEA[d] | 8 |
| 11 | $CH_2Cl_2$ | 5/1 | DCC[a]/HOBt[d] | 55 |
| 12 | $CHCl_3$ | 5/1 | DCC[a] | 61 |
| 13 | THF | 5/1 | DCC[a] | 11 |
| 14 | $CH_3CN$ | 5/1 | DCC[a] | – |
| 15 | $PhCH_3$ | 5/1 | DCC[a] | – |
| 16 | DMF | 5/1 | DCC[a] | 41 |
| 17 | DMSO | 5/1 | DCC[a] | 7 |

[a] All reactions were carried out at room temperature for 2 h, and the amount of dehydrating agent is 1.5 equiv *vs* that of **7**. [b] Isolated yield after purification by recrystallization. [c] Catalytic amount. [d] The amount of TEA or HOBt is 1.0 equiv *vs* that of DCC.

Having established the optimization conditions, we investigated the limitation of this rearrangement reaction. As shown in Table 2, this new reaction could be adapted to a wide range of substrates. The rearrangement proceeds well with *o*-carboxyazobenzene irrelevant of the electronic effects of the substituent on the benzene ring (Table 2, entries 2−8). Therefore, *o*-carboxyazobenzene with nitro, chloro, bromo, methyl, and methoxyl substituents at the 4- or 2-position of the benzene ring reacts to afford the corresponding amino-substituted indazol-3,5-diones with a yield up to 88%. On the contrary, a significant substituent effect of amine is observed and the reaction with 2-nitrophenylamine gives only 33% of the target compound **7g** (Table 2, entry 14). In the case of 2,6-dimethyl or 2,6-diethyl amine, a lower reactivity is observed possibly due to the steric hindrance of the bis *ortho* substituents (Table 2, entries 17, 19−20). The steric hindrance effect has been further determined from the poor yield if the anthraquinone is introduced in the *o*-carboxyazobenzene (Table 2, entry 1).

In addition, the structure of the rearrangement product **1e** is clearly supported by the X-ray diffraction analysis (Figure 2).

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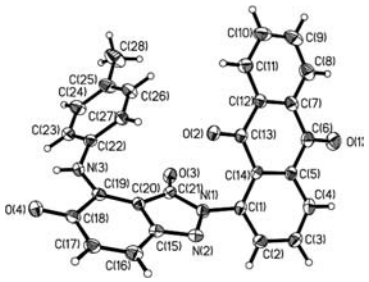
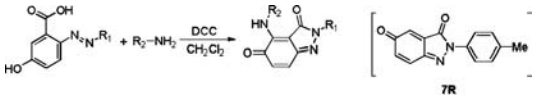


**Figure 2.** X-ray crystallographic structure of **1e**.

**Table 2.** Synthesis of Amino-Substituted Indazol-3,5-dione



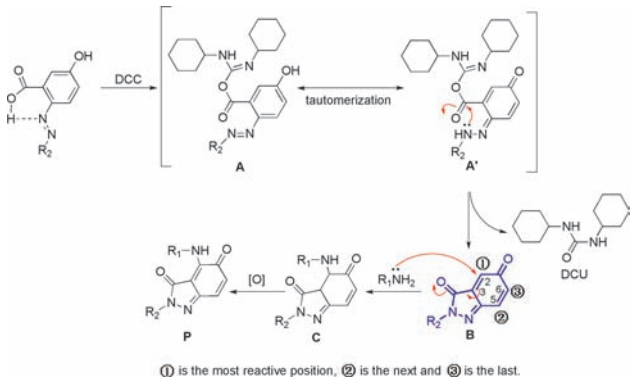
| entry | $R_1$ | $R_2$ | | yield (%)[a] |
|---|---|---|---|---|
| 1 | 9,10-dioxo-9,10-dihydroanthracen-1-yl | 4-$CH_3C_6H_4$ | **1e** | 20 |
| 2 | 4-$NO_2C_6H_4$ | 4-$CH_3C_6H_4$ | **2e** | 88 |
| 3 | 4-$ClC_6H_4$ | 4-$CH_3C_6H_4$ | **3e** | 75 |
| 4 | 4-$BrC_6H_4$ | 4-$CH_3C_6H_4$ | **4e** | 73 |
| 5 | 2-$NO_2C_6H_4$ | 4-$CH_3C_6H_4$ | **5e** | 79 |
| 6 | 2-$ClC_6H_4$ | 4-$CH_3C_6H_4$ | **6e** | 74 |
| 7 | 4-$CH_3C_6H_4$ | 4-$CH_3C_6H_4$ | **7e** | 61 |
| 8 | 4-$CH_3OC_6H_4$ | 4-$CH_3C_6H_4$ | **8e** | 74 |
| 9 | 4-$CH_3C_6H_4$ | 4-$NO_2C_6H_4$ | **7a** | 78 |
| 10 | 4-$CH_3C_6H_4$ | 4-$FC_6H_4$ | **7b** | 40 |
| 11 | 4-$CH_3C_6H_4$ | 4-$ClC_6H_4$ | **7c** | 41 |
| 12 | 4-$CH_3C_6H_4$ | 4-$BrC_6H_4$ | **7d** | 65 |
| 13 | 4-$CH_3C_6H_4$ | 4-$CH_3OC_6H_4$ | **7f** | 42 |
| 14 | 4-$CH_3C_6H_4$ | 2-$NO_2C_6H_4$ | **7g** | 33 |
| 15 | 4-$CH_3C_6H_4$ | 2-$ClC_6H_4$ | **7h** | 65 |
| 16 | 4-$CH_3C_6H_4$ | 2-$BrC_6H_4$ | **7i** | 61 |
| 17 | 4-$CH_3C_6H_4$ | 2-$CH_3OC_6H_4$ | **7j** | 40 |
| 18 | 4-$CH_3C_6H_4$ | Ph | **7k** | 41 |
| 19 | 4-$CH_3C_6H_4$ | 2,6-$(CH_3)_2C_6H_3$ | **7l** | 16 |
| 20 | 4-$CH_3C_6H_4$ | 2,6-$(C_2H_5)_2C_6H_3$ | **7m** | 7 |
| 21 | 4-$CH_3C_6H_4$ | *n*-$C_3H_7$ | **7n** | 54 |
| 22 | 4-$CH_3C_6H_4$ | 4-$HOC_6H_4$ | **7o** | 24 |

[a] Isolated yield after purification by recrystallization.

To further explore the reaction mechanism, we next mixed DCC and compound **7** together in the absence of amine. We found that the unsubstituted indazole intermediate **7R** (Table 2) was obtained and it was converted to the amino-substituted indazol-3,5-dione **7e** after addition of *p*-toluidine.

Based on the above results and the work of Hecht et al.,[13] we proposed the following mechanisms (Scheme 2). First, the carboxyl group is activated by the dehydrating agent DCC and then attacked by the lone pair electron of the azo-N-atom in **A**′ (a tautomer of **A**) to form **B**. The intramolecular cyclization is then achieved *via* the formation of a C−N bond. Intermediate **B** is then nucleophilically attacked by the amine-N-atom in the form of Michael-type conjugation addition to form **C**. According to the crystal structure of **1e**, the amine should attack the 2-position of semiquinone. This result is consistent with the work of Katrizky et al. where the *ortho*-position to the carbonyl is proposed to be the most reactive site for nucleophilic conjugate addition.[17] Finally, **C** is oxidized to yield the target product **P**. Here, the dehydrating agent could be the key factor to initiate this reaction and the intramolecular nucleophilic attack of the azo-N-atom is preferable to the intermolecular attack of the amine-N-atom.

**Scheme 2.** Proposed Mechanism of the Rearrangement




In summary, the amino-substituted indazol-3,5-dione has been synthesized *via* the intramolecular cyclization in the amidation reaction of *o*-carboxyazobenzenes in the presence of a dehydrating agent, e.g. DCC or EDCI, in which a Michael-type conjugate addition may have taken place. A range of electron-rich and -deficient *o*-carboxyazobenzenes and amines can be used. This new rearrangement offers a potential way to build up the amino substituted indazole-3,5-dione with conveniently obtainable starting materials in mild conditions giving rise to an appropriate yield. It should be pointed out that the steric hindrance effect could be the main reason for poor performance. In addition, the proposed rearrangement mechanism has been derived according to the structure of the product. Further work on the *o*-carboxyazobenzene without the OH group at the *meta*-position to the carboxyl group in the benzene ring is in progress.

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**Supporting Information Available.** Full experimental section and the related analytical data for **1**−**8**, **1e**−**8e**, **7a**−**d**, and **7f**−**2o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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