# Nickel-catalyzed coupling of isocyanates with 1,3-iodoesters and halobenzenes: a novel method for the synthesis of imide and amide derivatives†

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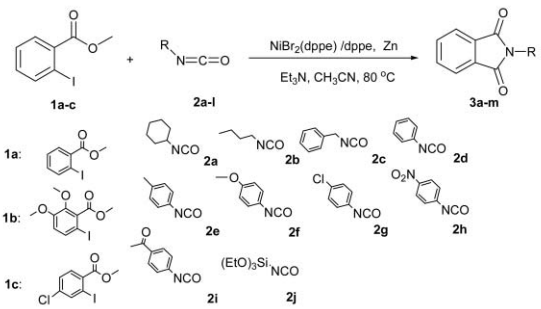
*Received (in Cambridge, UK) 16th May 2005, Accepted 5th July 2005*
*First published as an Advance Article on the web 12th August 2005*
**DOI: 10.1039/b506903c**

**Substituted imide and amide derivatives were conveniently prepared from the reaction of isocyanates with *o*-iodobenzoates and haloarenes catalyzed by the $NiBr_2$(dppe)/dppe/Zn system in moderate to good yields with excellent tolerance of functional groups.**

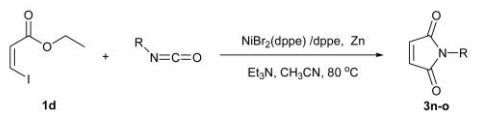
Isocyanate derivatives are very reactive species, but the application of isocyanates is mostly limited to the synthesis of urethane or urea derivatives.[1] Only recently, transition metal-mediated cycloaddition of isocyanates with alkynes to form pyridones has attracted considerable attention.[2] On the other hand, imides are important industrial, biological and medicinal chemicals.[3,4] A common method for the preparation of imides is *via* condensation of amine with anhydride or phthalic acid derivatives.[5,6] Another general method is the palladium-catalyzed reaction of phthalimide with iodocompound.[7] While there are several synthetic procedures for preparing these compounds, limitations as noted below were found. (1) Most of the known procedures for phthalimide formation are compatible only with simple alkyl or aryl substituents on the nitrogen atom. (2) It is difficult to introduce a functional group, especially an electron-donating group, on the phenyl ring of phthalimides. (3) The formation of imide usually requires high reaction temperatures. Thus, a simple and efficient method that can be applied to the synthesis of a wide range of imide derivatives should be attractive. Our interest in nickel-catalyzed cyclization reactions[8] prompted us to explore the possibility of using *o*-iodobenzoates and β-iodoacrylates for cyclization with isocyanates. Herein, we wish to report for the first time a nickel-catalyzed cyclization of 1,3-iodoesters with isocyanates, providing an efficient method for the synthesis of imide derivatives (Schemes 1–2).

Treatment of methyl 2-iodobenzoate (**1a**) with cyclohexylisocyanate (**2a**) in the presence of $Ni(dppe)Br_2$, dppe (bis(diphenylphosphino)ethane), zinc powder and triethylamine in acetonitrile at 80 °C for 36 h afforded 2-cyclohexylisoindoline-1,3-dione (**3a**) in 88% yield. The structure of **3a** was confirmed by its $^1H$ NMR, $^{13}C$ NMR and mass data. In the absence of either the nickel complex or zinc powder, product **3a** was not observed.

To understand the nature of this nickel-catalyzed cyclization, the effect of solvent and nickel complex used on the reaction of **1a** with **2a** was investigated. $Ni(PPh_3)_2Br_2$, and $Ni(dppm)Br_2$ were inactive for the reaction, while $Pd(PPh_3)_4$ and $Ni(dppb)Br_2$ gave **3a** in trace

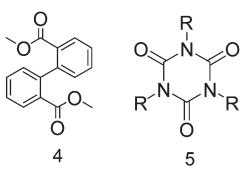



**Scheme 1**




**Scheme 2**

and 43% yields, respectively. The use of $Ni(PPh_3)_2Cl_2$ as the catalyst afforded only the reductive dimerization product **4** (see Scheme 3) of iodobenzoate without any desired cyclization product. $Ni(dppe)Br_2$ was found to be the best catalyst giving product **3a** in 88% yield and a small quantity of reductive dimerization product **4**. The solvent used for the catalytic reaction is also critical. No desired product was found in $Et_2O$ and 1,2-dichloroethane at ambient temperature, whereas THF afforded predominately dimerization product **4** and a trace of the desired product **3a** at 65 °C. Acetonitrile appears to be the best choice of solvent when $Ni(dppe)Br_2$ was used as the catalyst. The presence of extra dppe diminished the reductive dimerization of iodobenzoate. Without additional dppe, the reaction provided **3a** in only 65% yield and the reductive dimer **4** in 24% yield. Triethylamine increased the rate of the catalytic reaction, but the role of this species is not yet understood. No desired product was observed below 60 °C, and the best temperature for this reaction was 80 °C. Most of the extra isocyanate in the catalytic reaction was converted to the corresponding isocyanurate **5**. Similar to **1a**,




**Scheme 3**

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† Electronic supplementary information (ESI) available: Preparation and characterization. See http://dx.doi.org/10.1039/b506903c

methyl *o*-bromobenzoate also reacted with isocyanate **2a** to give product **3a**, but in lower yield (60%); a substantial amount of the bromobenzoate remained unreacted.

This nickel-catalyzed cyclization reaction was successfully extended to various substituted benzoate and β-iodoacrylate and the results are listed in Table 1. Thus, **1a** reacts with *n*-butylisocyanate (**2b**) and benzylisocyanate (**2c**) to give the corresponding cyclization products **3b** and **3c** in 82 and 79% yield. Similarly, aryl isocyanates with various substituents on the aryl rings (**2d–i**) underwent cyclization with **1a** to provide the corresponding imide derivatives **3d–i** in moderate to good yields (entries 4–9). The results show that the yields of product **3** also depends greatly on these functional groups. An isocyanate with an electron-donating group on the aryl ring affords a higher product yield compared to that with an electron-withdrawing substituent. Consistent with this notion, the product yield of imide **3** is generally higher for alkylisocyanates than for arylisocyanates. As shown in entry 10, the catalytic reaction is also compatible with a siloxane group on the isocyanate providing product **3j** in 79% yield.

Under similar reaction conditions, substituted iodobenzoate **1b** bearing two methoxy moieties on the aryl ring also underwent cyclization with isocyanates **2a** and **2e** to give products **3k–3l** in 92 and 75% yields, respectively. The observed higher product yields with substrate **1b** reflects that increasing electron density on the aryl ring of *o*-iodobenzoate also enhances the formation of the corresponding imide product. The reductive dimerization product of dimethoxyiodobenzoate in these three reactions was not clearly observed. However, iodobenzoate **1c** bearing an electron withdrawing chloro group reacted with **2a** (entry 13) to form product **3m** in lower yield (51%).

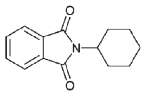
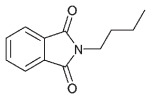
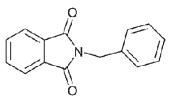
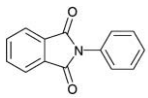
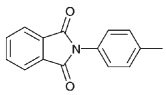
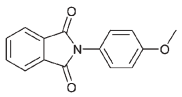
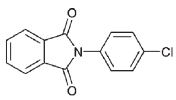
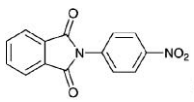
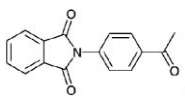
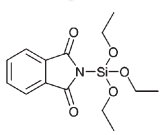
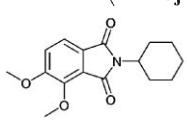
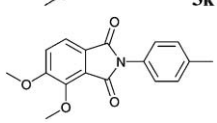
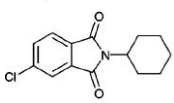
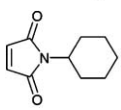
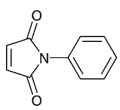
The present method can also be applied to the cyclization of β-iodoacrylate. Treatment of (*Z*)-ethyl-3-iodoacrylate (**1d**) with cyclohexylisocyanate under similar reaction conditions furnished maleimides **3n–o** in yields of 47 and 37%, respectively. The low product yields were accompanied by the formation of a large quantity of the homo reductive dimerization product of iodoacrylate **1d**.

The foregoing results reveal that the present catalytic reaction can tolerate most of the functional groups on the isocyanates and 1,3-iodoesters tested. Primary and secondary alkyl isocyanates were most reactive and gave high yields of the cyclization products. Aryl isocyanate consisting of electron-donating groups also provided good yields. Aryl isocyanate bearing electron-withdrawing groups also underwent cyclization but with lower yields. For the reaction of dimethoxy iodobenzoate **1b**, both alkyl and aryl isocyanates gave the expected products in high yields. For iodoacrylate **1d**, the cyclization gave only low to moderate yields of the expected imide products.

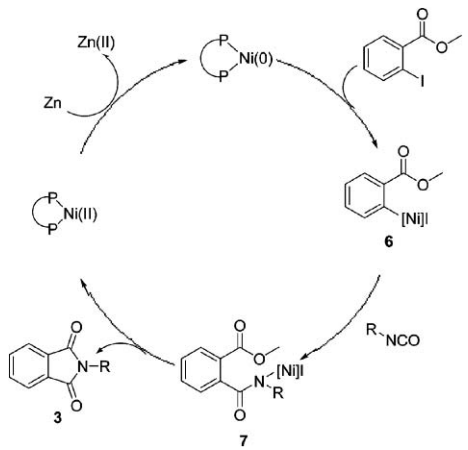
Based on the above results and the known organometallic chemistry, a plausible mechanism is proposed to account for the formation of the imide products (Scheme 4). The catalytic reaction is probably initiated by the reduction of Ni(II) species to Ni(0) species by zinc powder. The iodo compound then undergoes oxidative addition to the Ni(0) complex to form intermediate **6**. Insertion of an isocyanate molecule into **6** provided intermediate **7**. Subsequent imidation leads to product **3** and the regeneration of the Ni(II) species.

This proposed mechanism gains strong support from the formation of homo reductive coupling of the iodoester as a side

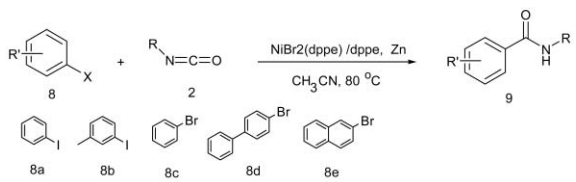
**Table 1** Results of cyclization of 1,3-iodoesters with isocyanates catalyzed by nickel complex Ni(dppe)$Br_2$[a]

| Entry | 1 | 2 | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 | **1a** | **2a** |  **3a** | 88 |
| 2 | **1a** | **2b** |  **3b** | 82 |
| 3 | **1a** | **2c** |  **3c** | 79 |
| 4 | **1a** | **2d** |  **3d** | 61 |
| 5 | **1a** | **2e** |  **3e** | 66 |
| 6 | **1a** | **2f** |  **3f** | 71 |
| 7 | **1a** | **2g** |  **3g** | 53 |
| 8 | **1a** | **2h** |  **3h** | 44 |
| 9 | **1a** | **2i** |  **3i** | 41 |
| 10 | **1a** | **2j** |  **3j** | 79 |
| 11 | **1b** | **2a** |  **3k** | 92 |
| 12 | **1b** | **2e** |  **3l** | 75 |
| 13 | **1c** | **2a** |  **3m** | 51 |
| 14 | **1d** | **2a** |  **3n** | 47 |
| 15 | **1d** | **2d** |  **3o** | 37 |

[a] Unless stated otherwise, all reactions were carried out using iodoester (**1**) (1.0 mmol), isocyanate (**2**) (5.0 mmol), Ni(dppe)$Br_2$ (10 mol%), dppe (10 mol%), triethylamine (10 mol%) and Zn (2.0 mmol) in $CH_3CN$ (2.0 ml) at 80 °C under $N_2$ for 36 h. [b] Isolated yields based on iodoester used.




**Scheme 4**




**Scheme 5**

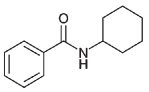
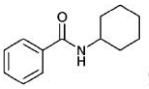
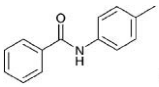
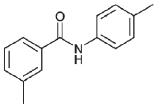
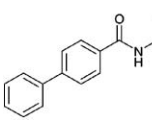
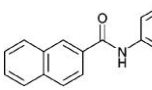
product that can only be formed from intermediate **6**. The observations that electron-donating groups on the aromatic ring of *o*-iodobenzoates and on the isocyanates enhance the yields of phthalimide products indicates that the increase of nucleophilicity of intermediates **6** and **7** to facilitate the insertion of isocyanate and the imidation are critical for the present catalytic reaction.

The catalyst system Ni(dppe)$Br_2$/Zn was further tested for the amidation of aryl iodide and aryl bromide with isocyanates (Scheme 5 and Table 2). A slight modification of reaction conditions was made. The amidation was better carried out in the absence of triethylamine. The reaction of aryliodides with isocyanates gave moderate yields of the expected products. Thus, iodobenzene **8a** reacted with **2a** (Table 2, entry 1) to afford amide derivative **9a** in 34% yield, while 3-methyliodobenzene reacted with *p*-tolyl isocyanate **2e** (entry 4) giving product **9c** in higher yield (61%).

Bromo-substituted arenes generally provided higher yields of the amidation products relative to the corresponding iodoarenes. Thus, bromobenzene (**8c**) reacted with **2a** and **2e** to afford amide derivatives in 71 and 64% yields, respectively (entries 2 and 3). Biphenyl bromide (**8d**) and bromonaphthalene (**8e**) also underwent amidation with *p*-tolyl isocyanate (**2e**) (entries 5–6) to form the corresponding products **9d-e** in 59 and 51% yields. Under the present catalytic reaction conditions, all of these catalytic amidation reactions were accompanied with homo reductive dimerization of the aryl halides. The dimerization product is substantially reduced when aryl iodide is replaced by aryl bromide and this likely accounts for the higher yields of the amidation products when bromoarenes were employed.

In conclusion, we have developed a new methodology for the cyclization of isocyanates with iodoesters and haloarenes catalyzed by nickel complexes to form the imide and amide derivatives. This is the first report that isocyanates can undergo cyclization with 1-3-iodoesters with good tolerance of functional groups. Further studies to extend the scope of the catalytic reactions and determine the mechanistic pathway for these reactions are currently underway.

**Table 2** Results of amide formation from aryl halides with isocyanates catalyzed by Ni(dppe)$Br_2$[a]

| Entry | 1 | 2 | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 | **8a** | **2a** |  **9a** | 34 |
| 2 | **8c** | **2a** |  **9a** | 71 |
| 3 | **8c** | **2e** |  **9b** | 64 |
| 4 | **8b** | **2e** |  **9c** | 61 |
| 5 | **8d** | **2e** |  **9d** | 59 |
| 6 | **8e** | **2e** |  **9e** | 51 |

[a] Unless stated otherwise, all reactions were carried out using aryliodides or arylbromide (8) (1.0 mmol), isocyanate (**2**) (2.0 mmol), Ni(dppe)$Br_2$ (10.0 mol%), dppe (10.0 mol%) and Zn (2.0 mmol) in $CH_3CN$ (2.0 ml) at 80 °C under $N_2$ for 16 h. [b] Isolated yields based on arylhalides used.

We thank the National Science Council of the Republic of China (NSC-93-2113-M-007-033) for the support of this research.

## Notes and references

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