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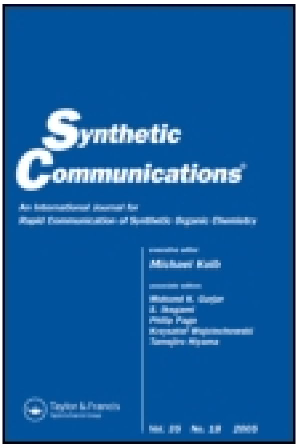

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New Method for the Synthesis of Lactones via Nickel-Catalyzed Isocyanides Insertion

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NEW METHOD FOR THE SYNTHESIS OF LACTONES VIA NICKEL-CATALYZED ISOCYANIDES INSERTION

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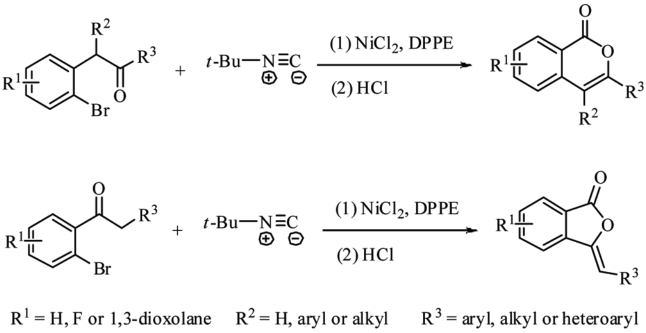
GRAPHICAL ABSTRACT



Abstract *A novel nickel catalyst for the reaction of* tert-*butyl isocyanide insertion was discovered. In this approach, 1,2-bis(diphenylphosphino)ethane (**L3**) serves as an efficient ligand, thereby allowing the preparation of lactones from (*o*-bromophenyl)phenylethanone derivatives. It is noteworthy that this is the first example of nickel acting as a metal catalyst in the reactions of* tert-*butyl isocyanide insertion. The significance of this methodology may draw many chemists' attention in the field of isocyanide-incorporating reactions.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Acid hydrolysis; isocoumarins; isocyanides; nickel catalyst; phthalides

INTRODUCTION

Because of their multifunctional character, (*o*-bromophenyl)ethanone derivatives are useful synthetic intermediates for the preparation of heterocycles.[1–9] Several articles[1–3] reported examples of benzofurans syntheses via intramolecular reactions using 2-(*o*-bromophenyl)-1-ethanone as starting material. Besides, it is not surprising that a number of transition-metal-catalyzed processes have been and are still being

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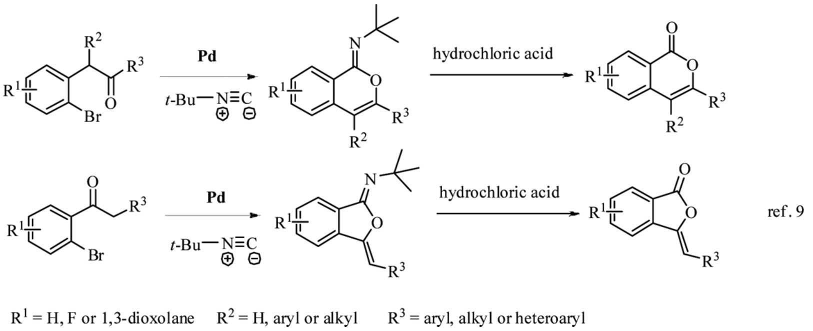


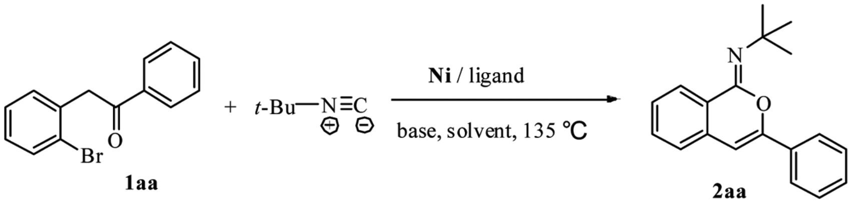
Scheme 1. Transition-metal–catalyzed reactions of *tert*-butyl isocyanide insertion.

described.[4–8] Recently, we have reported on the use of (*o*-bromophenyl)ethanones as starting materials with *tert*-butyl isocyanide for the synthesis of substituted lactones (Scheme 1),[9] which is a core structure of various natural products[10,11] and designed pharmaceutical molecules.[12–15] Since the pioneering work of Ugi,[16–18] isocyanides have long proved themselves to be irreplaceable building blocks in modern organic chemistry. To date, reactions of isocyanide insertion including two-component reactions[19–22] and multicomponent reactions (MCRs)[23–26] have become increasingly important. Most of the reactions via *tert*-butyl isocyanide insertion were all catalyzed by palladium or were metal free. In a continuation of our interest in lactone syntheses using isocyanides, we are making efforts to explore more novel and efficient synthetic methods. According to Scheme 1,[9] although $Pd(OAc)_2$ has proved to be a good metal catalyst, black Pd^0 could be generated, which made the reaction tube difficult clean. Thus, we considered nickel as a kind of inexpensive transition metal that has characteristics similar to palladium. The idea that nickel might be a good catalyst for this kind of insertion reaction prompted us to investigate the methodology. Thus, we used model substrate **1aa** in our previous work to test different transition-metal catalysts. To our delight, $NiCl_2$/1,2-bis(diphenylphosphino)ethane (DPPE) proved to be an efficient and clean catalyst system. Herein we report a novel approach to the preparation of isocoumarins and phthalides based on the nickel-catalyzed cyclization and hydrochloric acid hydrolysis.

DISCUSSION

Initially, we examined the intermolecular reaction of 2-(*o*-bromophenyl)-1-phenylethanone **1aa** and *tert*-butyl isocyanide as the model substrates to screen the reaction conditions, and the results are depicted in Table 1. Reaction of **1aa** with *tert*-butyl isocyanide was tested in dimethylformamide (DMF) at 135 °C in the presence of $NiCl_2$ (5 mol%) and PPh_3 (10 mol%), which was found to be effective (entry 1, Table 1). Product (*Z*)-(1*H*)-3-phenyl-*N*-*tert*-butylisochromen-1-imine **2aa** was obtained in 68% yield after 12 h. Then, several phosphorus ligands were tested to find an optimal one, which had the best catalytic activity for the reaction (entries 2–6). The expected product **2aa** was formed in 89% yield when **L3** (DPPE) was employed as the ligand (entry 3). A diminished yield was obtained when Cs_2CO_3 was used as

Table 1. Condition optimizations of **1aa** with *tert*-butyl isocyanide[a]



Entry	Catalyst	Ligand	Base	Solvent	Yield[b] (%)
1	$NiCl_2$	**L1**	K_2CO_3	DMF	68
2	$NiCl_2$	**L2**	K_2CO_3	DMF	54
3	$NiCl_2$	**L3**	K_2CO_3	DMF	89
4	$NiCl_2$	**L4**	K_2CO_3	DMF	16
5	$NiCl_2$	**L5**	K_2CO_3	DMF	28
6	$NiCl_2$	**L6**	K_2CO_3	DMF	23
7	$NiCl_2$	**L3**	Cs_2CO_3	DMF	19
8	$NiCl_2$	**L3**	K_2CO_3	DMSO	82
9	$NiCl_2$	**L3**	K_2CO_3	Toluene	0[c]
10	$NiCl_2$	**L3**	K_2CO_3	Dioxane	5[c]
11	$Ni(OAc)_2$	**L3**	K_2CO_3	DMF	46[d]
12	$Ni(acac)_2$	**L3**	K_2CO_3	DMF	80[d]
13	$NiCl_2 \cdot DPPE$	—	K_2CO_3	DMF	53[d]

[a] Reaction conditions: All reactions were performed with **1aa** (0.5 mmol), *tert*-butyl isocyanide (0.75 mmol), $NiCl_2$ (2.5 mol%), ligand (5 mol%), and base (1.0 mmol) in 3.0 mL of anhydrous solvent at 135 °C for 12 h. **L1**, triphenylphosphine; **L2**, 1,1′-bis(diphenylphosphino)ferrocene; **L3**, 1,2-bis(diphenylphosphino)ethane; **L4**, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; **L5**, bis[(2-diphenylphosphino)phenyl]ether; **L6**, (R)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

[b] Isolated yield.

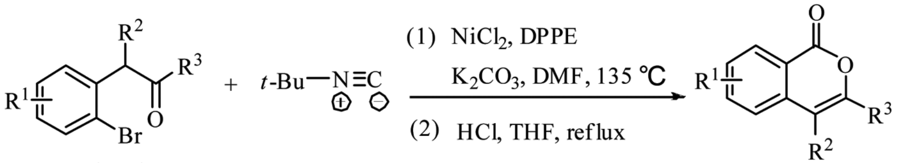
[c] Reaction at 110 °C.

[d] Reaction time for 24 h.

the base (entry 7). When the solvent was switched to dimethylsulfoxide (DMSO), toluene, or dioxane, the yield of **2aa** decreased (entries 8–10). Other Ni catalysts such as $Ni(OAc)_2$, $Ni(acac)_2$, and $NiCl_2 \cdot DPPE$ were also tested, and we obtained lower yields and longer reaction time (entries 11–13). On the basis of these considerations, our catalytic system was set as $NiCl_2$ (5 mol%) and DPPE (10 mol%) in DMF using K_2CO_3 (2 equiv) as a base. Then, acid hydrolysis of **2aa** could form 3-phenylisocoumarin **3aa** in good yield.

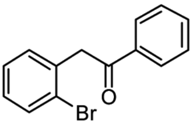
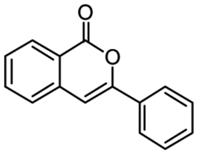
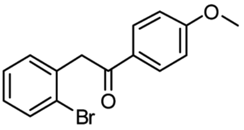
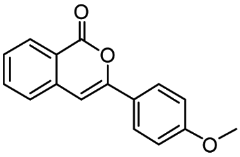
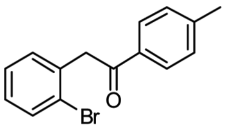
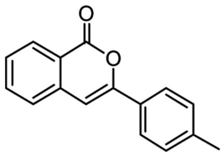
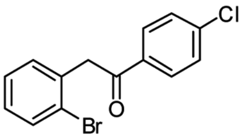
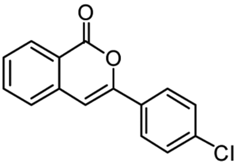
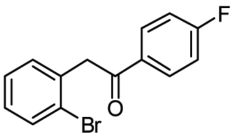
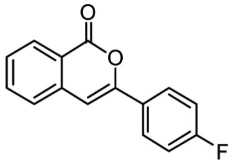
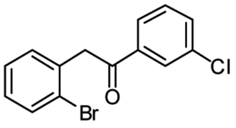
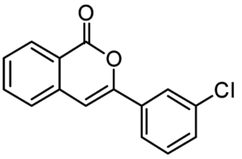
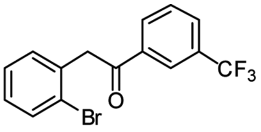
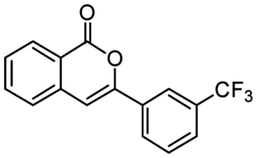
With the optimized reaction conditions established, the scope of the reaction was investigated. Substituents R^3, including aryl (Table 2, entries 1–9), heteroaryl (Table 2, entries 10–12), and alkyl (Table 2, entries 13 and 14), which were present in substrates **1aa–1an**, were well tolerated. 2-(2-Bromophenyl)-1-phenylethanones with methyl, methoxyl, fluoro, and sensitive functional groupss such as chloro and strong electron-withdrawing groups such as trifluoromethyl all gave the corresponding substituted isocoumarins in good to excellent yields (Table 2, entries 2–9). Substrates with electron-deficient aromatics afforded greater yields than electron-rich ones. Note that good yields were obtained when R^3 was a heteroaryl group including pyridyl, furyl, or thiophenyl (Table 2, entries 10–12). Aliphatic groups such as cyclo-

Table 2. Synthesis of isocoumarins from substrates with isocyanides



1aa-1aq

3aa-3aq

Entry	Substrate		Product		Yield[a] (%)
1		1aa[27]		3aa	86
2		1ab[27]		3ab	77
3		1ac[27]		3ac	79
4		1ad[27]		3ad	87
5		1ae[27]		3ae	89
6		1af[27]		3af	86
7		1ag[27]		3ag	91

(Continued)

Table 2. Continued

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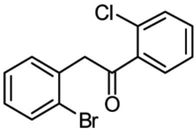
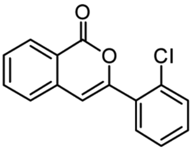
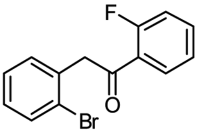
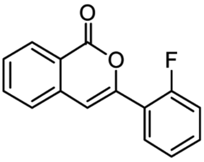
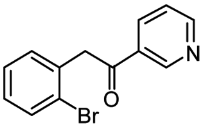
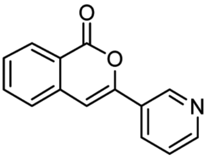
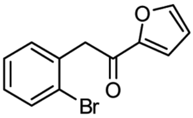
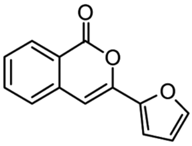
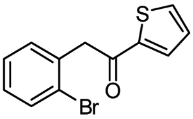
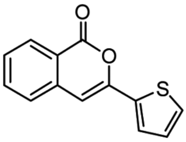
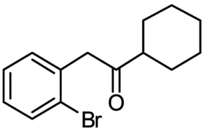
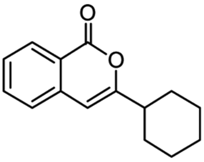
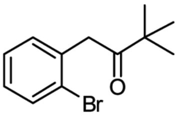
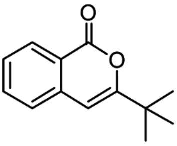
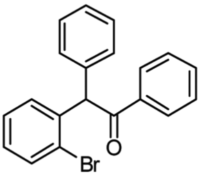
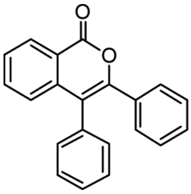
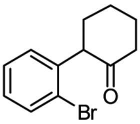
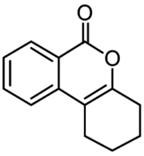
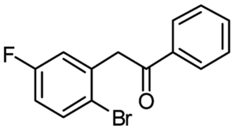
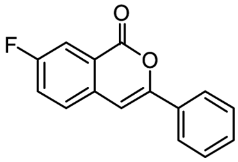
8		**1ah**[27]		**3ah**	61
9		**1ai**[27]		**3ai**	88
10		**1aj**[28]		**3aj**	68[b]
11		**1ak**[29]		**3ak**	55[b]
12		**1al**[29]		**3al**	52[b]
13		**1 am**[27]		**3 am**	68[b]
14		**1an**[27]		**3an**	66[b]
15		**1ao**[30]		**3ao**	86
16		**1ap**[31]		**3ap**	59[b]

(*Continued*)

Table 2. Continued

Entry	Substrate		Product		Yield[a] (%)
17		**1aq**[27]		**3aq**	66

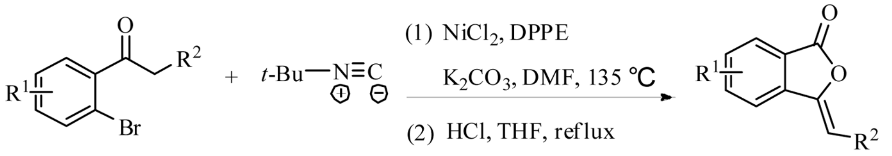
[a]Isolated yield.

[b]Reaction time for 24 h.

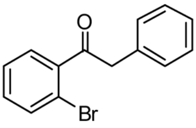
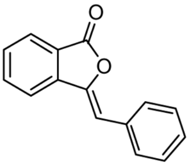
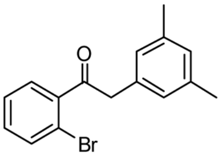
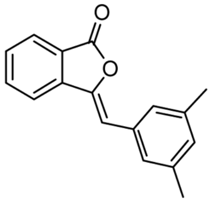
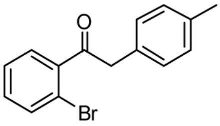
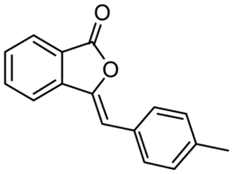
hexyl and *tert*-butyl were also tolerated (Table 2, entries 13 and 14). In addition, substrates including disubstituents R^2 and R^3, such as **1ao** and **1ap**, also afforded **3ao** and **3ap** in moderate yields, respectively (Table 2, entries 15 and 16).

Furthermore, 1-(*o*-bromophenyl)-2-phenylethanones **1ba–1bi** were also investigated, and the results are summarized. This method was successfully applied to

Table 3. Synthesis of phthalides from substrates with isocyanides

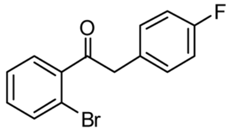
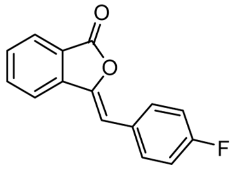
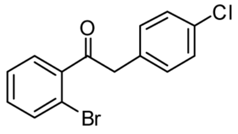
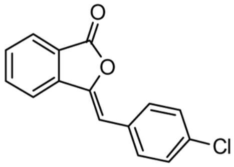
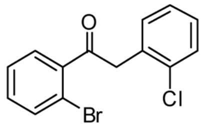
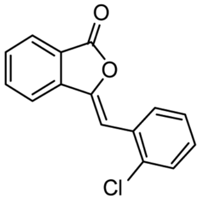
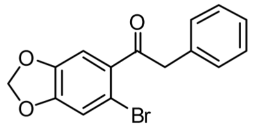
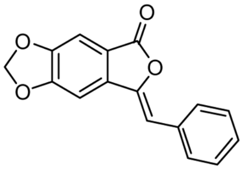
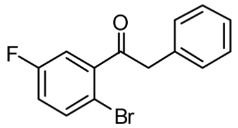
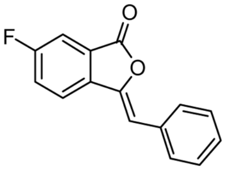
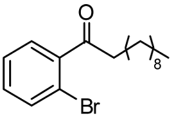
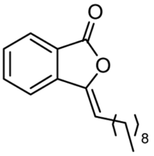


1ba-1bi **3ba-3bi**

Entry	Substrate		Product		Yield[a](%)
1		**1ba**[27]		**3ba**	87
2		**1bb**[27]		**3bb**	78
3		**1bc**[27]		**3bc**	80

(*Continued*)

Table 3. Continued

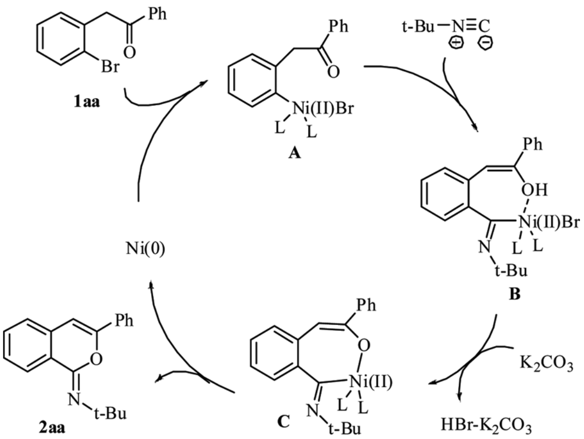
Entry	Substrate		Product		Yield[a](%)
4		**1bd**[27]		**3bd**	86
5		**1be**[27]		**3be**	84
6		**1bf**[27]		**3bf**	59
7		**1bg**[27]		**3bg**	58
8		**1bh**[27]		**3bh**	67
9		**1bi**[27]		**3bi**	48[b]

[a] Isolated yield.

[b] Reaction time for 24 h.

synthesize various phthalides. As illustrated in Table 3, substrates containing electron-donating and electron-withdrawing groups could be used and provided the corresponding products in moderate to good yields (Table 3, entries 1–8). Note that substrate with aliphatic group such as 1-(*o*-bromophenyl)undecan-1-one also gave product **3bi** in moderate yield (Table 3, entry 9).

A plausible mechanism of this reaction is outlined in Scheme 2. Oxidative addition[32–34] of **1aa** to Ni^0 leads to form complex **A**, followed by *tert*-butyl isocyanide insertion to form **B**. Nickel^{II} in complex **B**, which coordinates to the oxygen



Scheme 2. Plausible mechanism of nickel-catalyzed cyclization reaction.

atom of hydroxyl group,[35] promotes the form of **C**. Reductive elimination[32–34] of **C** leads to the intermediate **2aa** with the regeneration of Ni^0 species.

In summary, we have developed novel and efficient $NiCl_2$-catalyzed reactions for the synthesis of isocoumarins and phthalides from easily accessible substrates and *tert*-butyl isocyanide. The mechanism was investigated, and a key intermediate was isolated and characterized. The advantage that electron-deficient substrates showed greater reactivity than electron-rich ones was found to be contrary to the Pd catalyst system. This approach provides one of the easiest pathways for accessing this class of valuable compounds.

EXPERIMENTAL

General Procedure for the Synthesis of Lactones 3

A sealed tube was charged with a magnetic stir bar, and **1** (0.5 mmol), *tert*-butyl isocyanide (0.75 mmol), $NiCl_2$ (2.5 mol%), DPPE (5 mmol%), K_2CO_3 (1.0 mmol, 138 mg), and anhydrous dimethylformamide (DMF, 3 mL) were added at the same time. The tube was purged with nitrogen gas and stirred at 135 °C for 12 h. After reaction completion, the mixture was filtered through a short plug of celite, and DMF was removed by vacuum. The combined filtrates were refluxed in tetrahydrofuran (THF, 15 mL) and HCl (1 M, 3 mL) for 2 h. Then, the mixture was extracted with EtOAc, dried (Na_2SO_4), and evaporated. The residue was purified on a silica-gel column using petroleum ether / EtOAc as the eluent to give the pure target products **3**.

3-Phenyl-*1H*-isochromen-1-one (3aa)[9]

White solid, 80–82 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, $J = 8.1$ Hz, 1H), 7.87 (d, $J = 7.8$ Hz, 2H), 7.71 (t, $J = 7.6$ Hz, 1H), 7.52–7.41 (m, 5H), 6.94 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 153.6, 137.5, 134.9, 131.9, 129.9, 129.6, 128.8, 128.1, 125.9, 125.2, 120.5, 101.8.

SUPPORTING INFORMATION

Full experimental details and ^{1}H and ^{13}C NMR spectra can be found via the Supplementary Content section of this article's Web page.

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