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Nickel-catalyzed [4 + 2] Cycloaddition of Alkynes to Carbonylsalicylamides via Elimination of Isocyanates

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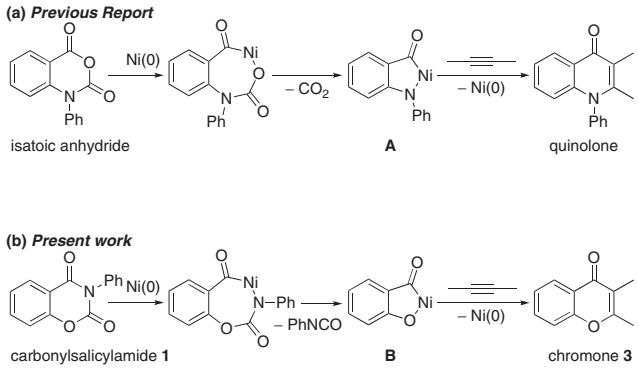
An intermolecular nickel-catalyzed [4 + 2] cycloaddition has been developed where carbonylsalicylamides react with alkynes to afford substituted chromones. The reaction involves an elimination of isocyanates and an addition of alkynes, that is, a formal substitution reaction of an isocyanate by an alkyne.

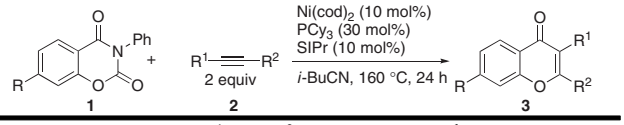
Addition of carbon and heteroatom across unsaturated carbon–carbon bonds to form carbon–carbon and carbon–heteroatom bonds simultaneously would be a potentially useful and straightforward method for introducing a heteroatom function into organic molecules.[1,2] Recently, we demonstrated that an oxidative addition of an isatoic anhydride to a Ni(0) complex and subsequent decarboxylation afford an aza-nickelacycle **A**; the process leads to the carboamination of alkynes to provide quinolon in a single step (Scheme 1a).[3] We postulated that an oxa-nickelacycle **B** might be generated alternatively via an oxidative addition to Ni(0) of carbonylsalicylamide **1**, which is a structural isomer of isatoic anhydrides, and elimination of isocyanate (Scheme 1b). This would allow forming carbon–carbon and carbon–oxygen bonds simultaneously and would open the way for divergent synthesis of chromone **3**.[4,5] Thus, we attempted the [4 + 2] cycloaddition of alkyne **2** to carbonylsalicylamide **1** using Ni(0) catalyst to form chromones **3**.

Our investigation began with an attempted addition of 4-octyne (**2a**) to *N*-phenylcarbonylsalicylamide (**1a**) with 10 mol % of $Ni(cod)_2$ and 30 mol % of PCy_3 in *i*-BuCN for 24 h. However, this resulted in low conversion of **1a** and led to chromone **3aa** in 46% yield (Table 1, Entry 1).[6] A detailed examination of the reaction revealed that nickel-catalyzed [2 + 2 + 2] cycloaddition of **2a** and isocyanate, which is generated during the addition reaction, was a side reaction that prohibited the catalytic reaction (Scheme 2).[7] Thus, we investigated the inactivation of isocyanate, and found that, on addition of 10 mol % of 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene (SIPr), the desired reaction proceeded to furnish **3aa** in 59% yield (Entry 2).[8] The effect of SIPr is likely to result from promoting the cyclotrimerization of isocyanate to afford an isocyanurate,[9] which is inert to oxidative addition to nickel-catalyst. In the case of using SIPr as a single ligand for nickel catalyst, **3aa** was not obtained (Entry 3). This can be rationalized that PCy_3 is an essential ligand for the cycloadditon of **2** to



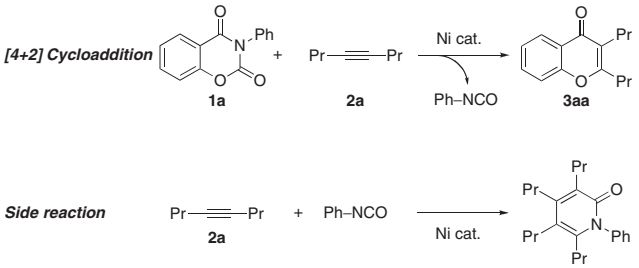
Scheme 1.

Table 1. Nickel-catalyzed [4 + 2] cycloaddition of carbonylsalicylamides to alkynes[a]

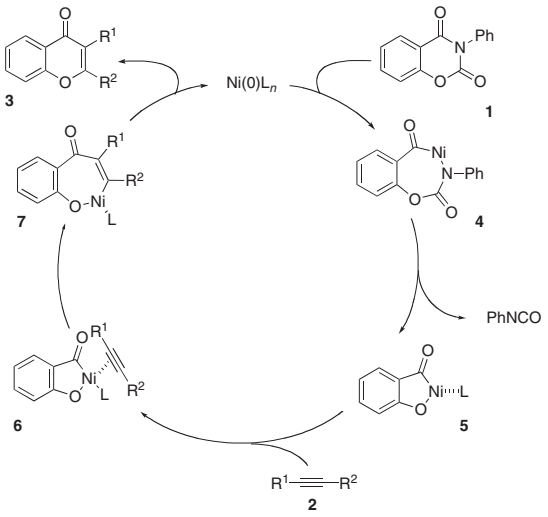


Entry	1	R	2	R^1	R^2	Conversion/%[b]	3	Yield/%[c]
1	**1a**	H	**2a**	Pr	Pr	73	**3aa**	46[d]
2	**1a**	H	**2a**	Pr	Pr	97	**3aa**	59
3	**1a**	H	**2a**	Pr	Pr	19	**3aa**	<1[e]
4	**1a**	H	**2b**	Bu	Et	75	**3ab**	55 (1/1)[f]
5	**1a**	H	**2c**	*i*-Pr	Me	68	**3ac**	50 (1/1)[f]
6	**1a**	H	**2d**	*t*-Bu	Me	54	**3ad**	28
7	**1a**	H	**2e**	Me_3Si	C_6H_{13}	61	**3ae**	55
8	**1b**	CF_3	**2a**	Pr	Pr	98	**3ba**	80
9	**1b**	CF_3	**2b**	Bu	Et	93	**3bb**	52 (1/1)[f]
10	**1b**	CF_3	**2c**	*i*-Pr	Me	82	**3bc**	44 (1/1)[f]
11	**1b**	CF_3	**2d**	*t*-Bu	Me	58	**3bd**	42
12	**1b**	CF_3	**2e**	Me_3Si	C_6H_{13}	94	**3be**	77
13	**1c**	MeO	**2a**	Pr	Pr	33	**3ca**	21
14	**1c**	MeO	**2b**	Bu	Et	46	**3cb**	12 (1/1)[f]
15	**1c**	MeO	**2c**	*i*-Pr	Me	39	**3cc**	11 (1/1)[f]
16	**1c**	MeO	**2d**	*t*-Bu	Me	38	**3cd**	18
17	**1c**	MeO	**2e**	Me_3Si	C_6H_{13}	81	**3ce**	46

[a]Reactions were carried out using $Ni(cod)_2$ (10 mol %), PCy_3 (30 mol %), SIPr (10 mol %), **1** (0.5 mmol), and **2** (1 mmol) in 1 mL of *i*-BuCN at 160 °C for 24 h. [b]Determined by ^1H NMR spectroscopy of crude reaction mixture. [c]Isolated yields. [d]Reaction was carried out without addition of SIPr (10 mol %). [e]Reactions was carried out without addition of PCy_3 (30 mol %). [f]Ratio of regioisomers. Determined by ^1H NMR spectroscopy of crude reaction mixture.



Scheme 2.



Scheme 3.

1, while SIPr promotes cyclotrimerization of eliminated isocyanate to provide isocyanurate.

With the optimized conditions in hand, we investigated the scope of the reaction using various alkynes. The reaction of **1a** with unsymmetrical alkynes such as **2b** and **2c** gave the products consisting of regioisomers in a 1/1 ratio in moderate yields (Entries 4 and 5). The reaction of **1a** with **2d**, containing sterically hindered groups, gave adduct **3ad** as a single product (Entry 6). Bulky trimethylsilyl-substituted alkyne **2e** reacted with **1a** to provide adducts with complete regiocontrol in 55% yield (Entry 7). However, aryl-substituted alkyne and terminal alkynes failed to participate in the reaction. The cycloadditions of alkyne to various carbonylsalicylamides **1** were also examined. The reaction of **2a** with carbonylsalicylamides possessing an electron-withdrawing group **1b** afforded the correspondingly substituted chromone **3ba** in 80% yield (Entry 8). The reaction of **1b** with various alkynes provided chromones in moderate yields (Entries 9–12). The reaction of **2a** with **1c**, which possesses an electron-donating group, afforded **3ca** in 21% yield (Entry 13). The low reactivity of **1c** in the cycloaddition may be ascribed to restrictions on an oxidative addition of **1c** to nickel catalyst.

We propose a plausible mechanism involving oxidative addition of carbonylsalicylamide **1** to Ni(0) having electron-rich phosphine ligands, giving the nickelacycle **4** (Scheme 3). Subsequent elimination of isocyanate through β-oxygen elimination provides oxanickelacycle **5**.[10] Insertion of **2** to C–Ni bond leads to the seven-membered nickelacycle **7**, which undergoes reductive elimination to give **3** and regenerates the starting Ni(0) complex, while eliminated isocyanate was cyclotrimerized by SIPr catalyst during the reaction to form isocyanurate.

In summary, we have developed a new nickel-catalyzed [4 + 2] cycloaddition of alkynes to carbonylsalicylamides to provide chromones. It was demonstrated for the first time that isocyanate is capable of β-elimination, which allows formation of the key oxanickelacycle intermediate.[11] Further studies for explanation of the detailed mechanism are currently under investigation in our laboratories.

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9 The formation of isocyanurate was confirmed by ^{1}H NMR spectroscopy of crude reaction mixture (ca. 30% yield). The side product, *N*-phenyl-3,4,5,6-tetrapropyl-2-pyridone, was observed in ca. 10% yield.

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11 A representive procedure: **1a** (0.5 mmol) and **2a** (1.0 mmol) were added to a solution of bis(1,5-dicyclooctadiene)nickel (14 mg, 0.05 mmol), PCy_3 (42 mg, 0.15 mmol), and SIPr (0.05 mmol) in *i*-BuCN (1 mL) in a dry box. The flask was taken outside the dry box and heated at 160 °C for 24 h under argon atmosphere. The resulting reaction mixture was cooled to ambient temperature and filtered through a silica gel pad, concentrated in vacuo. The residue was purified by flash silica gel column chromatography (20 g, 2 × 15 cm, hexane/ethyl acetate = 5:1) to give chromone **3aa** in 59% yield.

