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Cyclization of Oxa-Bicyclic Alkenes with *β*-Iodo-(Z)-propenoates and *o*-Iodobenzoate Catalyzed by Nickel Complexes: A Simple Efficient Route to Annulated Coumarins

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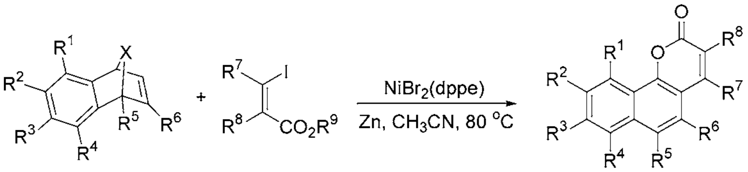
ABSTRACT



In the presence of Ni(dppe)Br$_2$ and Zn powder in acetonitrile at 80 °C, oxa-bicyclic olefins undergo cyclization with *o*-iodobenzoate and with *β*-iodo-(*Z*)-propenoates to give the benzocoumarin derivatives in moderate to good yields. This methodology offers a simple efficient way for the synthesis of structurally complicate coumarins in one pot.

Coumarins are an important class of compounds that show various biological activities[1] and are very useful as organic electroluminescent materials.[2] Despite their utility, the traditional methods for the synthesis of coumarins require harsh reaction conditions and stoichiometric amounts of reagents and often result in low yields.[3] Few transition-metal-catalyzed reactions for coumarin synthesis are known in the literature.[4] Catellani reported a palladium-catalyzed intramolecular cyclization of *o*-iodophenyl 3-butenoate.[4a] Trost revealed the condensation of phenols with propiolates catalyzed by palladium complexes.[4c] Fujiwara disclosed a Pd-catalyzed intramolecular hydroarylation of aryl alkynoates.[4d] Larock reported a palladium-mediated carbonylative annulation of internal alkynes with *o*-iodophenols.[4e] Takahashi described a rhodium-catalyzed cyclic carbonylation of 2-alkynylphenols.[4f] Recently, we have shown that 7-oxabenzonorbornadienes react with propiolates in the presence of nickel complexes and zinc metal powder to give benzocoumarins.[5] In all these reports, the coumarin products were

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(3) (a) George, B.; Nalband, H.; Shantu, A.; Stephen, S, H. *J. Org. Chem.* **1988**, *53*, 1007. (b) Kaufman, K. D.; Kelly, R. C. *J. Heterocycl. Chem.* **1965**, *2*, 91. (c) Johnson, J. R. *Org. React.* **1942**, *1*, 210. (d) Sethna, S.; Phadke, R. *Org. React.* **1953**, *7*, 1. (e) Awasthi, A. K.; Tewari, R. S. *Synthesis* **1986**, 1061. (f) Fischer, E.; Nouri, O. *Chem. Ber.* **1971**, *50*, 693.

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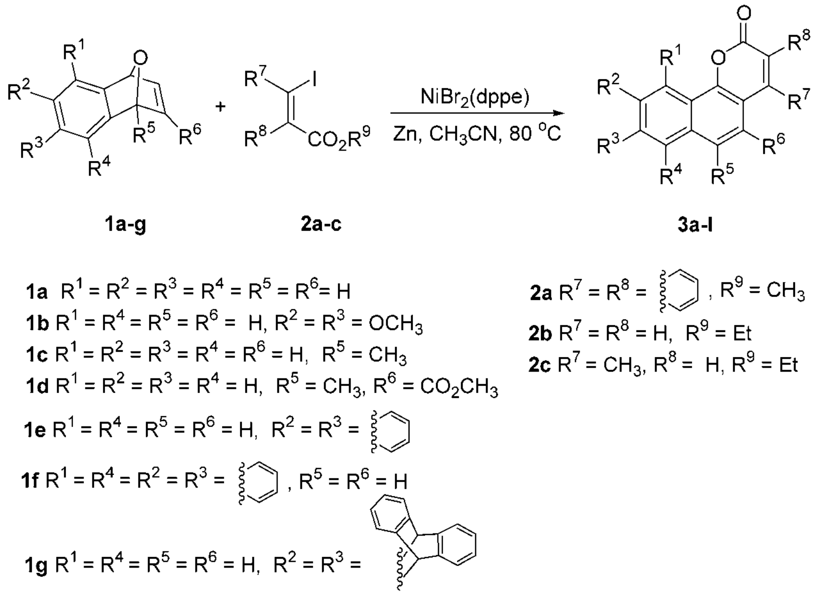
Scheme 1



limited to those with simple substituents. Our continued interest in nickel chemistry[6,7] and coumarin synthesis led us to investigate a new nickel-catalyzed cyclization of oxabicyclic olefins with β-iodo-(*Z*)-propenoates and with *o*-iodobenzoate to give annulated coumarins (Scheme 1). The reaction offers a convenient, one-pot synthesis of a series of structurally complicated coumarins under mild reaction conditions. Herein, we report the results of these studies.

Ni(dppe)Br$_2$ effectively catalyzes the reaction of 7-oxabenzonorbornadiene (**1a**) (2.00 mmol) with 2-iodobenzoate (**2a**) (1.00 mmol) in the presence of zinc metal powder (2.75 equiv) in acetonitrile (3.0 mL) at 80 °C to give dibenzocoumarin **3a** in 80% yield. Control experiments revealed that no product **3a** was observed in the absence of either nickel complex or zinc powder. The structure was established by its NMR and mass data and was further confirmed by comparing these values with those reported.[3a,4f] Notably, the skeleton of **3a** is found in arnottin, gilvocarcin, and several other naturally occurring molecules.[8]

To understand the nature of the present catalytic reaction, the effects of catalyst and solvent on the reaction were examined. No desired product was detected by using Ni(cod)$_2$, Ni(acac)$_2$, or Ni(PPh$_3$)$_2$Br$_2$ as the catalyst. Nickel complexes Ni(LL)Br$_2$, where LL is a bidentate ligand such as dppm, dppp, dppb, and dppf, are less effective than Ni(dppe)Br$_2$. The catalytic reaction also depends greatly on the solvent employed. No product was observed in dichloromethane and DMF, whereas THF and toluene afforded 26% and a trace of **3a**, respectively. The best solvent for the catalytic reaction is acetonitrile, affording **3a** in 80% yield.

The cyclization reaction was successfully extended to other substituted oxabicyclic olefins **1b**−**f**. Thus, **2a** reacted with **1b**,**e**,**f** smoothly to afford dibenzocoumarins, **3b**,**e**,**f** in 76, 55, and 61% yield, respectively (Table 1, entries 2, 5, and 6). The reaction of **1c** possessing a bridging methyl group with **2a** is highly regioselective providing **3c** in 63% yield. It is interesting to mention that **1d** with an ester substituent on the double bond also undergoes cyclization with **2a** regioselectively to give **3d** in 68% yield (entry 4).

β-Iodo-(*Z*)-propenoates **2b**,**c** are also successfully employed in this nickel-catalyzed cyclization process. The reaction of **1a** with ethyl (*Z*)-3-iodo-2-propenoate (**2b**) resulted in benzocoumarin **3g** in 56% yield (entry 7). Similarly, bicyclic alkene **1b** reacted with **2b** furnishing benzocoumarin **3h** in good yield. Treatment of **1a** with ethyl (*Z*)-3-iodo-2-butenoate (**2c**) produced 4-methylbenzocoumarin (**3i**) in 81% yield. The present methodology can also be applied to other bicyclic olefins **1b**,**f**,**g** giving benzocoumarins **3j**−**l** in good yields (entries 10−12).

Similar to oxa-bicyclic olefins**1a**−**g**, azabenzonorbornadiene **1h** reacts with **2a** cleanly affording lactam **4** in 80% yield (Scheme 2). This product is fully characterized by its ^{1}H and ^{13}C NMR and mass data. A key evidence for the presence of lactam group in **4** is the resonance at 165 ppm in the ^{13}C NMR. Unlike coumarin products **3a**−**l**, **4** is not

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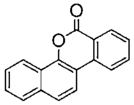
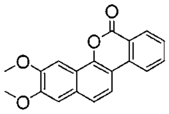
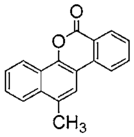
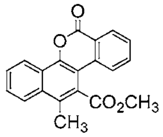
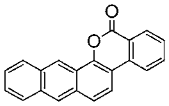
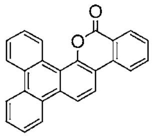
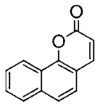
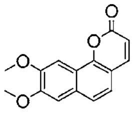
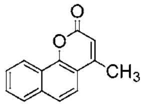
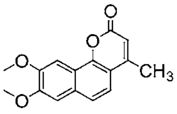
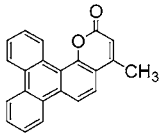
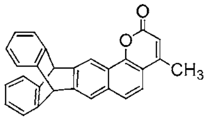
(8) (a) Ishii, H.; Ishikawa, T.; Murota, M.; Aoki, Y.; Harayama, T, *J. Chem. Soc., Perkin Trans. 1* **1993**, 1019. (b) Ishii, H.; Ishikawa, T.; Takeda, S.; Suzuki, M.; Harayama, T. *Chem. Pharm. Bull.* **1992**, *40*, 2002.

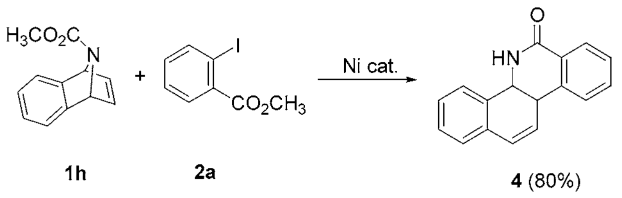
Table 1. Results of Nickel-Catalyzed Cyclization of Oxa-bicyclic Alkenes **1** with β-Iodo-(z)-propenoates **2**[a]

Entry	Alkene	Iodo Ester	Product		Yield[b] (%)
1	**1a**	**2a**		**3a**[4h]	80
2	**1b**	**2a**		**3b**[4h]	76
3	**1c**	**2a**		**3c**	63
4	**1d**	**2a**		**3d**	68
5	**1e**	**2a**		**3e**	55
6[c]	**1f**	**2a**		**3f**	61
7	**1a**	**2b**		**3g**[4c]	56
8	**1b**	**2b**		**3h**	69
9	**1a**	**2c**		**3i**[5]	81
10	**1b**	**2c**		**3j**[5]	72
11	**1f**	**2c**		**3k**[5]	67
12	**1g**	**2c**		**3l**	79

[a] Reaction conditions: iodo ester (1.00 mmol), alkene (2.00 mmol), Ni(dppe)Br$_2$ (0.050 mmol, 5.0 mol %), Zn (2.75 mmol), CH$_3$CN (3.0 mL) at 80 °C for 12 h. [b] Isolated yields. [c] A mixture of THF and CH$_3$CN was used.

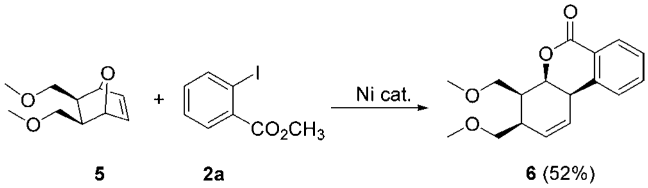
dehydrogenated as indicated by the two characteristic methine proton resonances at 3.8 and 4.8 ppm and the methine two carbon resonances at 38.8 and 52.3 ppm. However, the carbamate group of **1h** was hydrolyzed during the course of reaction and was no longer attached to the lactam group in product. The reason for the lack of dehydrogenation in lactam **4** is not yet clear.

Scheme 2



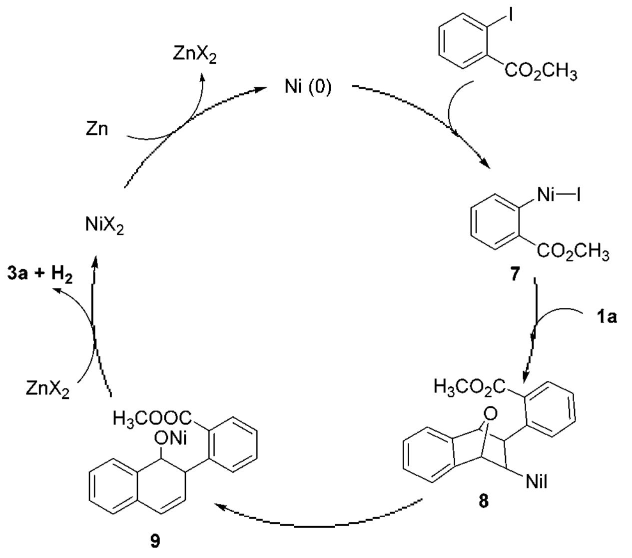
The cyclization of substituted 7-oxanorbornene **5** with **2a** also occurs readily, leading to the formation of tetrahydrocoumarin **6** in a completely stereoselective fashion (Scheme 3). Similar to lactam **4**, no dehydrogenation was observed in the product. The spectroscopic data and HRMS of this product are consistent with the proposed structure in which all of the four substituents on the cyclohexene ring of product **6** are at cis positions. Tetrahydrocoumarins are known to be useful intermediates for the synthesis of natural products.[9]

Scheme 3



While the exact pathway is not very clear, important steps are proposed as shown in Scheme 4 on the basis of the

Scheme 4



preceding results and the established nickel chemistry.[10,11] The reduction of Ni(II) by zinc to Ni(0) likely initiates the catalytic cycle. Oxidative addition of **2** to nickel(0) yields nickel(II) intermediate **7**. Coordination of 7-oxabenzonorbornadine (**1a**) and subsequent insertion leads to the formation of **8**. Then, β-oxyelimination of **8** occurs to give nickel alkoxide **9**, which undergoes transmetalation with ZnX_2, followed by lactonization and dehydrogenation to give the final coumarin product **3a** and Ni(II) species. The latter is reduced by Zn to regenerate the Ni(0) catalyst for the catalytic cycle.

In conclusion, we have demonstrated a new efficient nickel-catalyzed cyclization reaction of oxa-bicyclic alkenes **1** with *o*-iodobenzoate **2a** or β-iodo-(*Z*)-propenoates to give various benzocoumarins in moderate to good yields. The applications of this methodology to the synthesis of useful compounds for light-emitting devices[12] (LED) and natural products are underway.

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Supporting Information Available: Preparation details and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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