# Copper-Catalyzed Mild and Efficient Entry to 1-Substituted Indazolones

Shinji Tanimori,* Yuka Ozaki, Yasukazu Iesaki, Mitsunori Kirihata

Department of Bioscience and Informatics, Graduate School of Life and Environmental Sciences, Osaka Prefecture University, 1-1 Gakuen-cho, Naka-ku, Sakai, Osaka 599-8531, Japan
Fax +81(72)2549918; E-mail: tanimori@bioinfo.osakafu-u.ac.jp

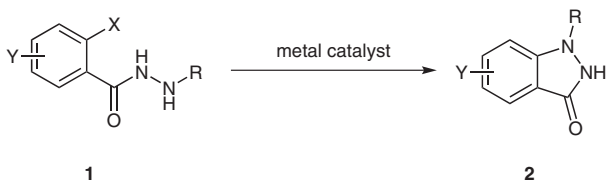
*Received 17 April 2008*

**Abstract:** A variety of 1-alkyl- and aryl-substituted indazolones were synthesized easily starting from commercially available 2-halobenzoic acids and hydrazines via the copper-catalyzed intramolecular C–N bond formation of 2-halobenzohydrazides under mild conditions.

**Key words:** indazolone, copper, proline, coupling, hydrazide

Indazolones and derivatives are an important structural motif for pharmaceutical development.[1] For instance, there are a lot of drugs and candidates possessing such structure including pathway-selective estrogen receptor ligands,[2] inhibitors against sodium nitroprusside-induced apoptosis,[3] antiplatelet agents,[4] selective rhokinase inhibitors.[5] For the reason, there are huge amount of letters dealing with the synthetic methods for indazolones and derivatives, which include palladium-catalyzed intramolecular amination reaction,[6] N–N bond formation through a PIFA-mediated oxidative cyclization,[7] copper-catalyzed cyclization of 2-haloarylcarbonylic compounds,[8] cyclization of *O*-aminobenzoxime by selective activation of the oxime,[9] the [3+2] cycloaddition of diazo compounds with arynes and subsequent acyl migration,[10] and N–N bond-forming heterocyclization.[11] But some examples require harsh reaction conditions, long reaction steps, stoichiometric amount of reagents, and low efficiency, so that the development of mild, flexible, and efficient method for the access to indazolones and derivatives is still highly desirable. In this paper we report a simple and mild method for the preparation of 1-substituted indazolones **2** from 2-halobenzoic acid via copper-mediated intramolecular C–N bond formation[12] of 2-halobenzohydrazide **1** (Scheme 1).

The starting hydrazides **1** were synthesized easily from 2-halobenzoic acid and hydrazine by a standard method.[13] Treatment of **1** (X = I, Y = H, R = Ph) with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, dppf, and $K_2CO_3$ in THF at reflux gave a complex mixture. On the other hand, the reaction of **1** with the use of copper(I) iodide, L-proline,[14] and $K_2CO_3$ in DMSO at 70 °C for three hours produced cyclized product **2**[15] in 91% yield. To delight of the result, we next examined the some reaction conditions using *tert*-butyl hydrazide **1** (X = I, Y = H, R = *t*-Bu), and the results are summarized in Table 1. The coupling reaction proceeded even at room temperature[16] in the presence of 10 mol% of CuI, 20 mol% of L-proline, and two equivalents of potassium carbonate in absolute DMSO (entry 2) for three hours to give indazolone **2** in 82% isolated yield. In the absence of L-proline, the reaction also proceeded to give product **2** in 82% yield, but the purity of product was somewhat low (entry 3). Unpurified DMSO gave a slightly better result than dry DMSO, probably due to the accelerating effect of the reaction rate by small amount of water present (entry 4).[17] When the catalytic amount was reduced to 5 mol% and 1 mol%, the yields were declined to 79% and 63%, respectively (entries 5 and 6), but still good to nice yield.




1 2

**Scheme 1** Proposed route to 1-substituted indazolone

We next focused on the examination of the scope of this reaction. A variety of 1-substituted indazolones were synthesized from the corresponding 2-halobenzohydrazides including 2-bromo and 2-chloro series using the optimized conditions (Table 1, entry 4), and the results are summarized in Table 2.[18] 2-Bromo- and 2-chlorobenzhydrazides also gave acceptable yield of products, although the latter needed heating (70 °C) and prolonged reaction time (entries 1 and 2). The acceptance of 2-bromo and 2-chloro derivatives in this reaction would be of great advantage for synthesizing a variety of indazolone derivatives, because the commercial source of the substituted 2-iodobenzoic acids is limited. Overall, moderate to excellent yields were observed except for entries 6 and 9.[19] In the case of entry 6, the steric influence of the methoxy group would inhibit the cyclization to afford a low yield of the product. The electron-withdrawing groups would decrease the yield for some reason (entries 9 and 5).

In conclusion, a mild and simple method for synthesizing 1-substituted indazolone derivatives has been developed by the use of copper-catalyzed cyclization reaction. Further studies directed toward the mechanistic investigation of coupling process, derivation of the products,[21] syntheses of other derivatives such as 2-substituted indazolone, and the biological study of the compounds obtained in this study are now under investigation.

*SYNLETT* 2008, No. 13, pp 1973–1976
Advanced online publication: 15.07.2008
DOI: 10.1055/s-2008-1077973; Art ID: U03708ST

**Table 1** Reaction Conditions of Copper-Catalyzed Intramolecular Coupling Reaction

| Entry | X | R | Cu salt (mol%) | Additive (mol%) | Base | Solvent | Conditions | Yield (%)[a] |
|---|---|---|---|---|---|---|---|---|
| 1 | I | Ph | CuI (10) | L-proline (20) | $K_2CO_3$ | dry DMSO | 70 °C, 3 h | 91 |
| 2 | I | *t*-Bu | CuI (10) | L-proline (20) | $K_2CO_3$ | dry DMSO | r.t., 3 h | 82 |
| 3 | I | *t*-Bu | CuI (10) | none | $K_2CO_3$ | dry DMSO | r.t., 3 h | 82 |
| 4 | I | *t*-Bu | CuI (10) | L-proline (20) | $K_2CO_3$ | wet DMSO | r.t., 3 h | 97 |
| 5 | I | *t*-Bu | CuI (5) | L-proline (10) | $K_2CO_3$ | wet DMSO | r.t., 3 h | 79 |
| 6 | I | *t*-Bu | CuI (1) | L-proline (2) | $K_2CO_3$ | wet DMSO | r.t., 3 h | 63 |

[a] Isolated yield.

**Table 2** Synthesis of 1-Substituted Indazolones

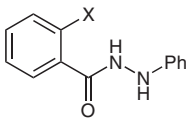
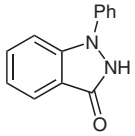
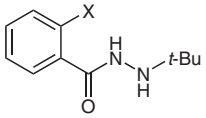
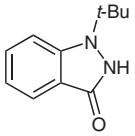
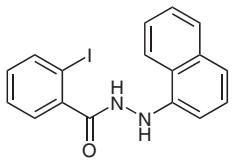
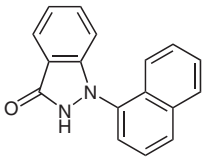
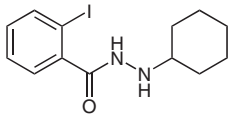
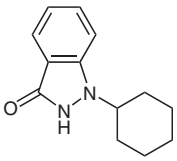
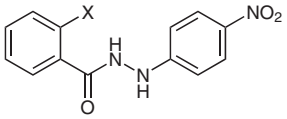
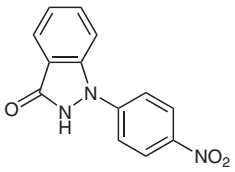
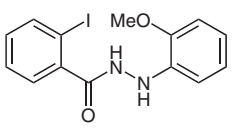
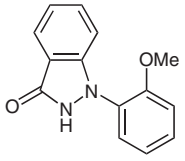
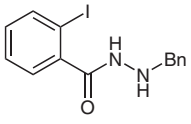
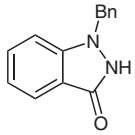
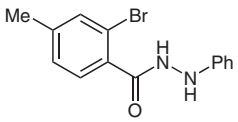
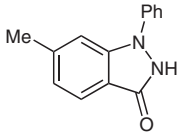
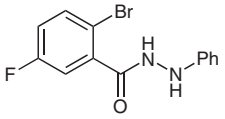
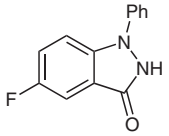
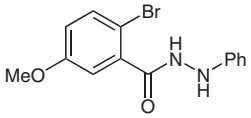
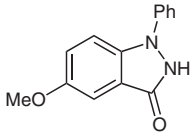
| Entry | Acid hydrazide | Indazole | Yield (%)[a] |
|---|---|---|---|
| 1 |  |  | 91 (X = I)<br>65 (X = Br)<br>66 (X = Cl)[b] |
| 2 |  |  | 97 (X = I)<br>62 (X = Br) |
| 3 |  |  | 96 |
| 4 |  |  | 60 |
| 5 |  |  | 50 (X = I)<br>51 (X = Br) |
| 6 |  |  | 23 |
| 7[20] |  |  | 70 |

**Table 2** Synthesis of 1-Substituted Indazolones (continued)

| Entry | Acid hydrazide | Indazole | Yield (%)[a] |
|---|---|---|---|
| 8 |  |  | 63 |
| 9 |  |  | 25 |
| 10 |  |  | 56 |

[a] Isolated yield.
[b] At 70 °C for 12 h.

## References and Notes


(1) For a review, see: Bräse, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem.* **2002**, *10*, 2415.

(2) Steffan, R. J.; Matelan, E.; Ashwell, M. A.; Moore, W. J.; Solvibile, W. R.; Trybulski, E.; Chadwick, C. C.; Chippari, S.; Kenney, T.; Eckert, A.; Borges-Marcucci, L.; Keith, J. C.; Xu, Z.; Mosyak, L.; Harnish, D. C. *J. Med. Chem.* **2004**, *47*, 6435.

(3) Lien, J.-C.; Lee, F.-Y.; Huang, L.-J.; Pan, S.-L.; Guh, J.-H.; Teng, C.-M.; Kuo, S. C. *J. Med. Chem.* **2002**, *45*, 4947.

(4) Lee, F.-Y.; Lien, J.-C.; Huang, L.-J.; Huang, T.-M.; Tsai, S.-C.; Teng, C.-M.; Wu, C.-C.; Cheng, F.-C.; Kuo, S.-C. *J. Med. Chem.* **2001**, *44*, 3746.

(5) Goodman, K. B.; Cui, H.; Dowdell, S. E.; Gaitanopoulos, D. E.; Ivy, R. L.; Sehon, C. A.; Stavenger, R. A.; Wang, G. Z.; Viet, A. Q.; Xu, W.; Ye, G.; Semus, S. F.; Evans, C.; Fries, H. E.; Jolivette, L. J.; Kirkpatrick, R. B.; Dul, E.; Khandekar, S. S.; Yi, T.; Jung, D. K.; Wright, L. L.; Smith, G. K.; Behm, D. J.; Bentley, R.; Doe, C. P.; Hu, E.; Lee, D. *J. Med. Chem.* **2007**, *50*, 6.

(6) Song, J. J.; Yee, N. K. *Org. Lett.* **2000**, *2*, 519.

(7) Correa, A.; Tellitu, I.; Domínguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 3501.

(8) Viña, D.; Del Olmo, E.; López-Pérez, J. L.; San Feliciano, A. *Org. Lett.* **2007**, *9*, 525.

(9) Counceller, C. M.; Eichman, C. C.; Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2008**, *10*, 1021.

(10) Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219.

(11) (a) Mills, A. D.; Nazer, M. Z.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2006**, *71*, 2687. For some other references for the synthesis of indazolone analogues, see: (b) Baiocchi, L.; Corsi, G.; Palazzo, G. *Synthesis* **1978**, 633. (c) Barton, D. H. R.; Lukacs, G.; Wagle, D. *J. Chem. Soc., Chem. Commun.* **1982**, 450. (d) Wyrick, S. D.; Voorstad, J.; Cocolas, G.; Hall, I. H. *J. Med. Chem.* **1984**, *27*, 768. (e) Bruneau, P.; Delvare, C. *J. Med. Chem.* **1991**, *34*, 1028.

(12) (a) For a recent example for copper-catalyzed intramolecular C–N coupling reaction, see: Lu, H.; Li, C. *Org. Lett.* **2006**, *8*, 5365. (b) During the preparation of this manuscript, Zhu and co-workers disclosed their studies on the synthesis of 2-aryl-2*H*-indazoles via copper(I)-catalyzed intramolecular amination reaction of *N*′-aryl-*N*′-(*o*-bromobenzyl) acetylhydrazines, but the reaction need higher reaction temperature (100–105 °C) and long reaction time (20 h) in a pressure tube. See: Liu, R.; Zhu, Y.; Qin, L.; Ji, S.; Katayama, S. *Heterocycles* **2007**, *71*, 1755.

(13) The acid hydrazides were synthesized from corresponding acid chloride with hydrazine or the condensation of 2-halobenzoic acid with hydrazine using EDC.

(14) (a) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164. (b) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453.

(15) Selwood, D. L.; Brummell, D. G.; Budworth, J.; Burtin, G. E.; Campbell, R. O.; Chana, S. S.; Charles, I. G.; Fernandez, P. A.; Glen, R. C.; Goggin, M. C.; Hobbs, A. J.; Kling, M. R.; Liu, Q.; Madge, D. J.; Meillerais, S.; Powell, K. L.; Reynolds, K.; Spacey, G. D.; Stables, J. N.; Tatlock, M. A.; Wheeler, K. A.; Wishart, G.; Woo, C.-K. *J. Med. Chem.* **2001**, *44*, 78.

(16) For a recent example for copper-catalyzed C–N coupling reactions at room temperature, see: Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742.

(17) Xie, X.; Chen, Y.; Ma, D. *J. Am. Chem. Soc.* **2006**, *128*, 16050.

(18) **Typical Experimental Procedure – Synthesis of 1-*tert*-butyl-1,2-dihydroindazol-3-one**
The mixture of 2-iodobenzoic acid *N*′-*tert*-butylhydrazide (0.32 g, 1.0 mmol), CuI (19 mg, 0.10 mmol, 10 mol%), L-proline (23 mg, 0.20 mmol, 20 mol%), and $K_2CO_3$ (0.28 g, 2.0 mmol) in DMSO (10 mL) was stirred at r.t. for 3 h under nitrogen atmosphere. The mixture was treated with $H_2O$ and the mixture was extracted three times with EtOAc. The combined organic layer was washed with $H_2O$ and brine, and dried over $MgSO_4$. After filtration, solvent was evaporated in vacuo to ca. 1 mL and crystallization afforded 1-*tert*-butyl-1,2-dihydroindazole-3-one (0.19 g, 97%) as white crystals. $R_f$ = 0.36 (hexane–EtOAc, 1:1); mp 115–117 °C. IR (KBr): 2979 (NH), 1648 (C=O), 1538, 1209, 748 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO): δ = 10.47 (br s, 1 H, NH), 7.61 (d, 1 H, *J* = 8.5 Hz, C-4), 7.59 (d, 1 H, *J* = 7.8 Hz, C-7), 7.26 (dd, 1 H, *J* = 6.8, 8.5, Hz, C-5), 6.96 (dd, 1 H, *J* = 6.8, 7.8 Hz, C-6), 1.60 (s, 9 H, *t*-Bu). $^{13}C$ NMR (136 MHz, DMSO): δ = 152.8, 139.5, 126.4, 120.1, 118.2, 113.9, 111.9, 58.3,

29.3 (3 × C). ESI-HRMS: *m/z* calcd for $C_{11}H_{14}N_2O$ 191.1179; found: 191.1182.

(19) Acid hydrazide derived from 2,4,6-trichlorophenylhydrazine, *tert*-butylcarbazide, benzoylhydrazine, and *p*-toluenesulfonylhydrazine did not afford the corresponding indazolone to recover the starting material even at heating conditions (>100 °C).

(20) Gordon, D. W. *Synlett* **1998**, 1065.

(21) A variety of compounds possessing pharmaceutical profile have been prepared from indazolone derivatives, see ref. 15.