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Selective Functionalization in Positions 2 and 3 of Indole via an Iodine–Copper Exchange Reaction

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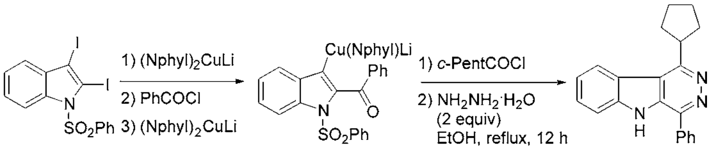
ABSTRACT



Two selectively successive I/Cu exchange reactions performed with (Nphyl)CuLi allow the functionalization of indoles in positions 2 and 3. The 2,3-diketones prepared by this method can readily be converted to tricyclic heterocycles by standard methods.

The indole system occurs in numerous natural products as well as in many therapeutic agents.[1] The preparation of polyfunctional indoles is therefore an important research field, and numerous methods have been developed.[2] The direct lithiation of indoles in positions 2 and 3 has been described;[3] however, the resulting lithiated indoles are compatible with only weakly electrophilic functional groups at the indole ring.[4] Recently, we have shown that mild conditions are required for performing an iodine−copper exchange. The excellent functional group tolerance of organocopper compounds allows the preparation of new polyfunctional arylcopper species bearing even an aldehyde group.[5] Herein, we wish to report an application of the iodine−copper exchange reaction for performing a selective metalation of the 2,3-diiodoindole derivative **1**.[6] Thus, the treatment of **1** with the lithium cuprate $(PhMe_2CCH_2)_2CuLi$ ($(Nphyl)_2CuLi$ (**2**); 25 °C, 0.5 h) in a mixture of THF and diethyl ether ($THF/Et_2O = 3:1$) provides the cuprate **3**. Its treatment with various electrophiles (E^1) furnishes polyfunctional indoles of type **4**. The reactions of the 3-iodoindoles **4** with $(Nphyl)_2CuLi$ in a 3:1 THF/Et_2O mixture at −78 °C for 30 min lead to the highly functionalized copper species of type **5**, which react with electrophiles (E^2) leading to the indole derivatives of type **6** (Scheme 1, Tables 1 and 2).

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(1) Joule, J. A. *Sci. Synth.* **2001**, *10*, 361−652.

(2) For some recent methods, see: (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans* 1. **2000**, 1045−1048. (b) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671−2681. (c) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. Marinelli, F.; Parisi, L. M. *Org. Lett.* **2002**, *4*, 1355−1358. (d) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−704. (e) Beller, M.; Breinde, C.; Riermeier, T. H.; Eichberger, M; Tranlhwein, H *Angew. Chem., Int. Ed.* **1998**, *37*, 3389−3391. (f) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2426−2430. (g) Kondo, Y.; Kojima, S.; Sakamoto, T. *J. Org. Chem.* **1997**, *62*, 6507−6511. (h) Coleman, R. S.; Chen, W. *Org. Lett.* **2001**, *3*, 1141−1144. (i) Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2501−2504. (j) Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662−5663. (k) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251−10263. (l) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571−1578. (m) Köhling, P.; Schmidt, A. M.; Eilbracht, P. *Org. Lett.* **2003**, *5*, 3213−3216. (n) Knepper, K.; Bräse, S. *Org. Lett.* **2003**, *5*, 2829−2832. (o) Barluenga, J. *Pure Appl. Chem.* **2002**, *74*, 1317−1326.

(3) (a) Katritzky, A. R.; Akutagawa, K. *Tetrahedron Lett.* **1985**, *26*, 5935−5938. (b) Matsuzono, M.; Fukuda, T.; Iwao, M. *Tetrahedron Lett.* **2001**, *42*, 7621−7623. (c) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757−761. (d) Liu, Y.; Gribble, G. W. *Tetrahedron Lett.* **2000**, *41*, 8717−8721.

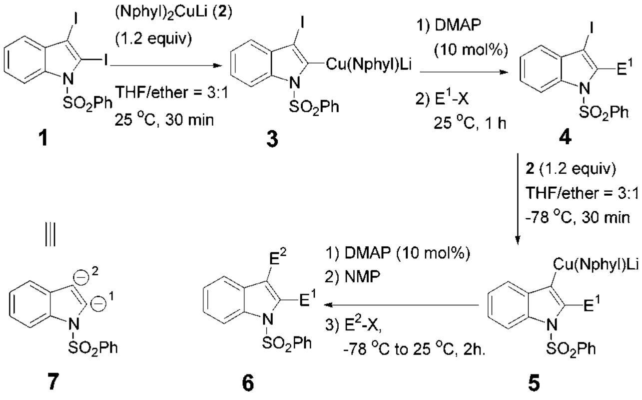
(4) (a) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1968**, *90*, 5615−5616. (b) Knodo, Y.; Matsudaira, T.; Salo, J.; Musata, N.; Sakamolo, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 736−738.

(5) (a) Piazza, C.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3263−3265. (b) Yang, X.; Rotter, T.; Piazza, C.; Knochel, P. *Org. Lett.* **2003**, *5*, 1229−1231. (c) Yang, X.; Knochel, P. *Synlett* **2004**, *1*, 81−84.

(6) Witulski, B.; Buschmann, N.; Bergsträβer, U. *Tetrahedron* **2000**, *56*, 8473−8480. See also ref 3c.

10.1021/ol049498q CCC: $27.50

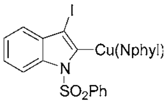
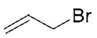
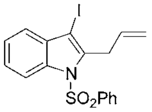
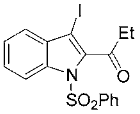
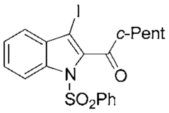
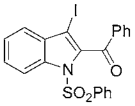
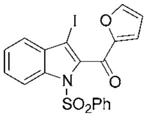
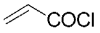
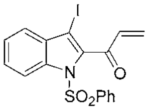
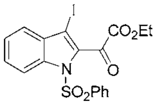
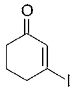
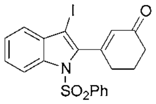
Scheme 1. Selective Functionalization in Positions 2 and 3 of Indole via Iodine−Copper Exchange



According to this sequence, the diiodoindole **1** is a synthetic equivalent of 1,2-bianionic synthon **7**. Thus, the allylation of the cuprate **3** with allyl bromide leads to the 3-iodo-2-allylindole derivative **4a** in 92% yield (entry 1 of Table 1). The acylation of the indolyl cuprate **3** is catalyzed by 4-(dimethylamino)pyridine (DMAP) (10 mol %).[7] Under these conditions, aliphatic acid chlorides (entries 2 and 3) as well as aromatic acid chlorides (entries 4 and 5) provide the iodoketones **4b**−**e** in 78−84% yields. The sensitive acryloyl chloride reacts as expected, furnishing the unsaturated ketone **4f** in 67% yield. The acylation with ethyl oxaloyl chloride leads to the iodoketoester **4g** in 75% yield (entry 7). Finally, the reaction with 3-iodo-2-cyclohexen-1-one provides the addition−elimination product **4h** in 66% yield (entry 8). The selectivity for an I/Cu exchange in position 2 rather than in position 3 is best explained by considering the higher electronegativity of C(2) compared to C(3).[8]

For the second exchange reaction, we have treated the 3-iodoindole **4a**, **4c**, **4d**, and **4h** with (Nphyl)$_2$CuLi (1.2 equiv) in a 3:1 mixture of THF and Et$_2$O at −78 °C followed by the addition of a second electrophile. Thus, the copper reagent **5a** is readily allylated with allyl bromide giving the bis-allylated product **6a** in 88% yield (entry 1 of Table 2). For performing the acylation reactions, we found that the use of *N*-methylpyrrolidinone (NMP) as a cosolvent and DMAP (10 mol %) as a catalyst was advantageous.

Table 1. 3-Iodoindole of Type **4** Obtained by the Reaction of the Cuprate **3** with Electrophiles

entry	copper reagent	electrophile	product of type **4**	yield (%)[a]
1	 **3**		 **4a**	92
2	**3**	EtCOCl	 **4b**	84[b]
3	**3**	*c*-PentCOCl	 **4c**	86[b]
4	**3**	PhCOCl	 **4d**	84[b]
5	**3**	2-FurCOCl	 **4e**	78[b]
6	**3**		 **4f**	67[b]
7	**3**	ClCOCO$_2$Et	 **4g**	75[b]
8	**3**		 **4h**	66[b]

[a] Isolated yield of analytically pure product. [b] Reaction was performed in the presence of DMAP (10 mol %).

Thus, the reaction of **5a** with pivaloyl chloride furnished the desired indolyl ketone **6b** in 68% yield (entry 2). The keto-substituted indolylcuprates **5b** and **5c** can be readily prepared by the I/Cu exchange reaction. Good yields of the corresponding 1,2-diketones **6c**−**h** can therefore be obtained (entries 3−8). Remarkably, even the α,*β*-unsaturated keto-substituted indolylcuprate **5d** can be readily prepared in this way. After acylation with propionyl chloride and ethyl oxalyl chloride, the desired products **6i** and **6j** were obtained in 80 and 72% yields (entries 9 and 10).

This method provides functionalized organocopper intermediates and gives a simple access to diketones otherwise difficult to prepare. These diketones can be converted to more complex heterocycles. Thus, treating the diketone **6h** with

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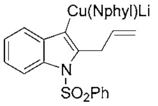
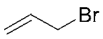
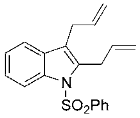
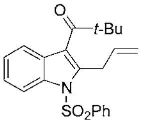
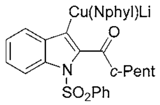
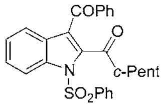
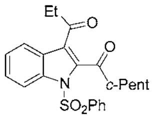
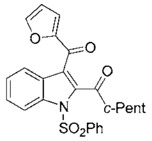
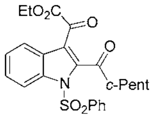
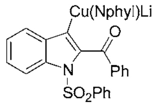
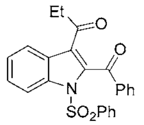
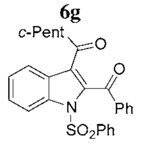
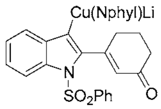
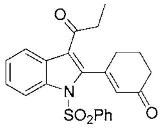
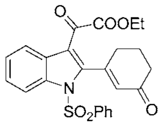
(7) (a) Heinrich, M. R.; Klisa, H. S.; Mayr, H.; Steglich, W.; Zipse, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4826−4828. (b) Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981−983. (c) Höfle, G.; Steglich, W.; Vorbrüggen, A. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569−583.

(8) **Typical Procedure for Synthesis of the 3-Iodoindole (4c).** A dry and argon-flushed 25 mL flask, equipped with a magnetic stirrer and a septum, was charged with CuCN (216 mg, 2.4 mmol) and dry THF (8 mL). A solution of neophyllithium in Et$_2$O (1.1 M, 4.4 mL, 4.8 mmol) was added at −78 °C. The resulting solution was warmed to room temperature for 10 min and then cannulated into a solution of 1-benzenesulfonyl-2,3-diiodo-1*H*-indole (**1**) (1.02 g, 2.0 mmol) in dry THF (4 mL) at −78 °C. The reaction was stirred at room temperature for 30 min. DMAP (24 mg, 0.2 mmol) and cyclopentane carbonyl chloride (840 mg, 6.0 mmol) were added successively at room temperature. The resulting solution was stirred at room temperature for 1 h, quenched with saturated aqueous NH$_4$Cl solution, and poured into water (40 mL). The aqueous phase was extracted with diethyl ether (3 × 30 mL). The combined organic fractions were washed with brine (30 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. Purification by flash chromatography yielded 824 mg (86%) of **4c** as a white solid, mp 153 °C.

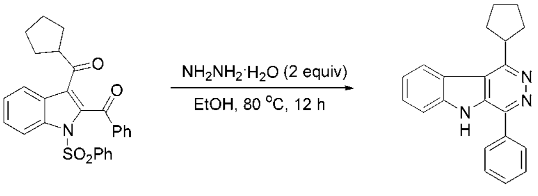
Table 2. 2,3-Disubstituted Indoles Obtained by the Reaction of the Copper Reagents **5a**−**d** with Electrophiles

entry	copper reagent	electrophile	product of type **4**	yield (%)^a
1	 **5a**		 **6a**	88
2	**5a**	*t*-BuCOCl	 **6b**	68^b
3	 **5b**	PhCOCl	 **6c**	73^b
4	**5b**	EtCOCl	 **6d**	68^b
5	**5b**	2-FurCOCl	 **6e**	63^b
6	**5b**	EtO_2COCl	 **6f**	71^b
7	 **5c**	EtCOCl	 **6g**	70^b
8	**5c**	*c*-PentCOCl	 **6h**	65^b
9	 **5d**	EtCOCl	 **6i**	80
10	**5d**	EtO_2COCl	 **6j**	72

^{a} Isolated yield of analytically pure product. ^{b} Reaction was performed using NMP as a cosolvent and DMAP (10 mol %) as a catalyst.

$NH_2NH_2{\cdot}H_2O$ (2 equiv) in refluxing ethanol for 12 h affords the tricyclic heterocycle **8**. The phenylsulfonyl group is also removed during the heterocycle synthesis (Scheme 2).[9]

Scheme 2. Synthesis of Triazafluorene of Type **8**

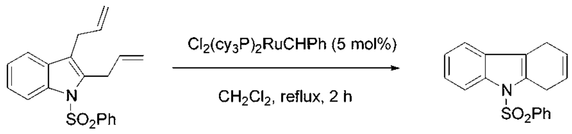


6h

8: 88%

By performing a metathesis reaction of the diallylated product **6a** with Grubbs catalyst (5 mol %) in refluxing CH_2Cl_2, we have obtained the carbazole **9** in nearly quantitative yield (Scheme 3).[10]

Scheme 3. Formation of Carbazole **9** via RCM Reaction



6a

9: 95%

In conclusion, we have shown that the 2,3-diiodoindole derivative **1** can selectively undergo two successive iodine−copper exchange reactions and react with two different electrophiles. This method gives an easy access to 2,3-diketoindoles, which can be readily converted to new heterocycles. Further extension of this method is currently underway in our laboratory.[11]

Acknowledgment. We thank the Fonds der Chemischen Industrie for financial support. We thank Chemetall GmbH, Degussa AG, BASF AG, and Wacker-Chemie for gifts of chemicals.

Supporting Information Available: Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Haddadin, M. J.; Agha, B. J.; Tabri, R. F. *J. Org. Chem.* **1979**, *44*, 494−497.

(10) (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (b) Clark, J. S.; Hamelin, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 372−374. (c) Grobelny, Z.; Stolarzewicz, A.; Adamus, G.; Buika, G.; Grazulevicius, J. V. *J. Organomet. Chem.* **2000**, *595*, 66−69.

(11) **Typical Procedure for Synthesis of the 2,3-Diketone (6c).** A dry and argon-flushed 25 mL flask, equipped with a magnetic stirrer and a septum, was charged with CuCN (54 mg, 0.6 mmol) and dry THF (2 mL). A solution of neophyllithium in Et_2O (1.1 M, 1.1 mL, 1.2 mmol) was added at −78 °C. The resulting solution was warmed to room temperature for 10 min and then cannulated into a solution of **4c** (239 mg, 0.5 mmol) in dry THF (2 mL) at −78 °C. The reaction mixture was stirred at room temperature for 30 min. Then, DMAP (6 mg, 0.05 mmol) and NMP (0.2 mL) were added successively at −78 °C and the resulting mixture was kept stirring for 15 min at this temperature. Benzoyl chloride (420 mg, 1.5 mmol) was added, and the resulting solution was stirred at room temperature for 2 h. It was quenched with saturated aqueous NH_4Cl solution and poured into water (15 mL). The aqueous phase was extracted with diethyl ether (3 × 15 mL). The organic fractions were washed with brine (15 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography yielded 167 mg (73%) of **6c** as a white solid, mp 122 °C.