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Iodine-catalyzed allylation and propargylation of indoles with allylic and propargylic acetates

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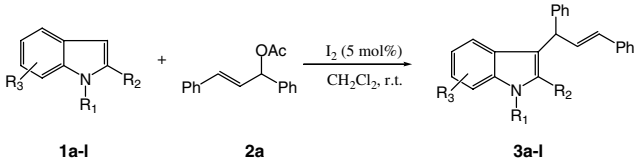
Abstract—A mild and efficient allylation/propargylation of indoles has been developed with high regioselectivity and excellent yields. In the presence of catalytic molecular iodine, various indoles could react with allylic/propargylic acetates smoothly at room temperature to exclusively provide C-3 alkylated products.

Indole moieties wildly occur in natural products, pharmaceuticals, functional materials, agrochemicals, and so on.[1] Recently, the allylation[2] and propargylation[3] of indoles have attracted much attention in the synthesis of indolic alkaloids since facile transformations of the double or triple bonds in the products to other functional groups can provide pharmaceutical intermediates and various important heterocycles. The allylation (Tsuji–Trost reaction)[4] and propargylation of aromatic and hetero-aromatic compounds with allylic and propargylic alcohols or acetates usually employed precious transition metals[5] as catalysts. However, besides C-3 allylation, *N*-allylation or diallylation[2g–i] took place in most cases, which highly decreased regioselectivity of the reactions. On the other hand, this type of reactions can also be promoted by Lewis acids;[6] however, stoichiometric amount of the promoters, harsh conditions (usually heating), as well as tedious operational procedures are often required, which confined to their applications. More recently, $FeCl_3$[7] and $Bi(OTf)_3$[8] were reported to catalyze the mild reaction of propargylic alcohols with some C- and hetero-nucleophiles. However, simple, efficient, and general protocols for both allylation and propargylation of indoles with high regioselectivity still need to be developed.

In recent years, molecular iodine has emerged as a versatile catalyst for various organic transformations such as Michael addition,[9a–c] coupling reaction,[9d] cycloaddition,[9e] silylation,[9f] protection/deprotection,[9g–j] and even multi-component synthesis,[9k–n] in which it can efficiently activate C=C, C=O, C=N, and other functional groups. Iodine is a cheap and commercially available catalyst with high tolerance to air and moisture. To our knowledge, no examples of iodine-catalyzed allylation and propargylation of aromatic compounds with allylic and propargylic acetates have been reported. Herein, we would like to report for the first time an allylation and propargylation of indoles with allylic and propargylic acetates catalyzed by molecule iodine under very mild conditions.

Initially, the reaction of indole **1a** ($R_1 = R_2 = R_3 = H$) with 1,3-diphenyl-allyl acetate **2a** in the presence of iodine (5 mol %) was carried out at room temperature to give allylation product, 3-[(*E*)-1,3-diphenyl-allyl]-1*H*-indole **3a** (Scheme 1). In contrast to other solvents



1a-l **2a** **3a-l**

Scheme 1.

Keywords: Allylation; Propargylation; Indole; Iodine.
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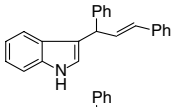
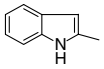
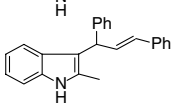
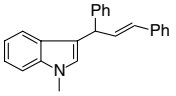
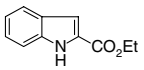
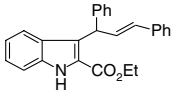
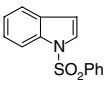
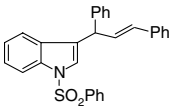
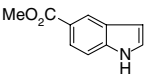
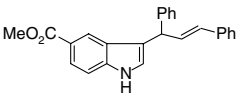
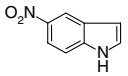
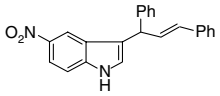
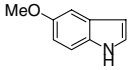
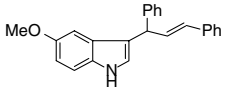
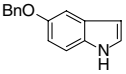
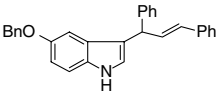
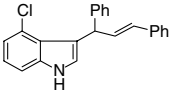
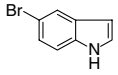
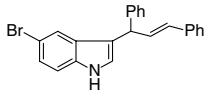
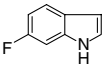
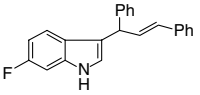
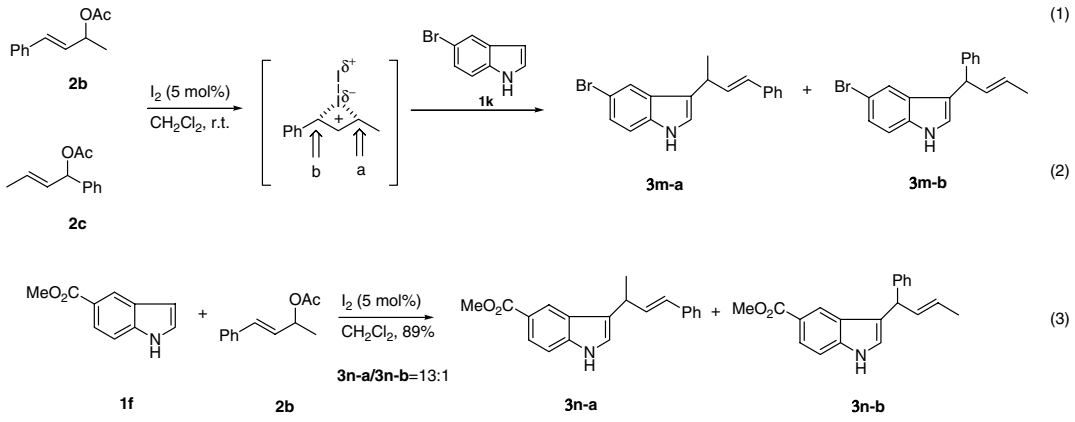
Table 1. Iodine-catalyzed allylation of indoles[a]

Entry	Indole	Time	Product	Yield[b] (%)
1	**1a** 	20 min	**3a** 	95
2	**1b** 	30 min	**3b** 	95
3	**1c** 	30 min	**3c** 	92
4	**1d** 	2 h	**3d** 	92
5	**1e** 	12 h	**3e** 	93
6	**1f** 	30 min	**3f** 	94
7	**1g** 	30 min	**3g** 	99
8	**1h** 	1 h	**3h** 	86
9	**1i** 	1.5 h	**3i** 	92
10	**1j** 	1 h	**3j** 	92
11	**1k** 	30 min	**3k** 	91
12	**1l** 	1 h	**3l** 	93

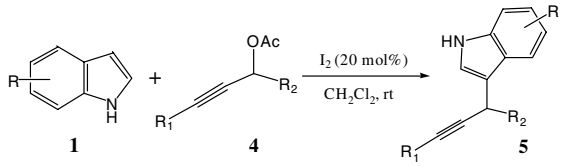
[a] The ratio of reactants is equimolar.
[b] Isolated yield.



Scheme 2.

such as ethanol and THF, the reaction in distilled or even commercial dichloromethane finished within only 20 min to give the product **3a** in excellent yield (95%). Under solvent-free conditions, the yield was also high (94%), however, the substrate scope was limited because of the poor compatibility of some indole substrates in the reaction system. Thus it was found that I_2/CH_2Cl_2 at room temperature was optimum and it was used to explore the reaction generality (Table 1).

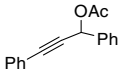
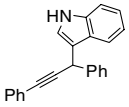
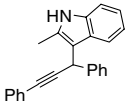
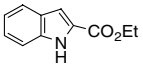
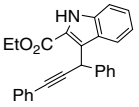
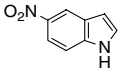
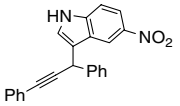
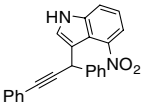
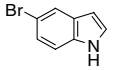
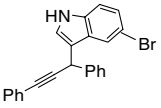
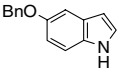
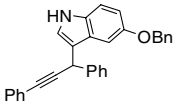
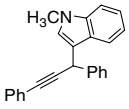
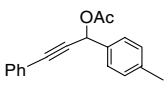
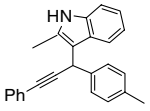
Various indoles bearing electron-withdrawing or electron-donating groups could afford C-3 allylated products exclusively in excellent yields (Table 1). When *N*-SO_2Ph indole (**1e**) was used, the reaction could also afford the corresponding products in good yield, but required longer reaction times (overnight), which indicated that *N*-substituted indole with a strong electron-withdrawing group has a negative effect on its reactivity (entry 5). In contrast to *N*-substituted indoles, substituents on the phenyl ring had little effect. 5-Methoxycarbonyl (**1f**) and 5-nitro (**1g**) indoles gave the corresponding products (**3f–g**) in high yields, 94% and 99%, respectively (entries 6 and 7).



Scheme 3.

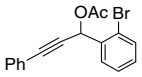
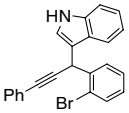
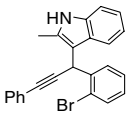
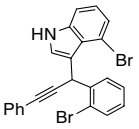
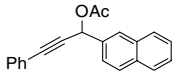
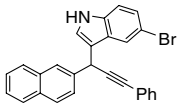
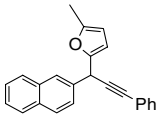
To explore the regioselectivity of this type of allylation, two regio-isomers **2b** and **2c** were employed in the reaction with 5-bromoindole **1k** in the presence of catalyst iodine (5 mol %) to give a mixture of C-3-allylated products, **3m–a** and **3m–b**, in 82% and 80% yields, respectively (Scheme 2, Eqs. 1 and 2). The same regioselectivities were obtained under the same conditions (room temperature for 1 h): for **2b**, the ratio of **3m–a** to **3m–b** was 25:1, and in the case of **2c**, only trace amount of **3m–b** was detected. A comparable regioselectivity (**3n–a/3n–b** = 13:1) was obtained (Scheme 2, Eq. 3) when indole substrate was **1f**. These results were different from those allylation catalyzed by transition metals

Table 2. Iodine-catalyzed propargylation of indoles[a]

Entry	Indole	Propargylic acetate	Time (h)	Product	Yield[b] (%)
1	**1a** 	**4a** 	3	**5a** 	69
2	**1b** 	**4a**	4	**5b** 	76
3	**1d** 	**4a**	20	**5c** 	84
4	**1g** 	**4a**	24	**5d** 	96
5	**1m** 	**4a**	24	**5e** 	79
6	**1k** 	**4a**	20	**5f** 	73
7	**1i** 	**4a**	20	**5g** 	36
8	**1c** 	**4a**	20	**5h** 	71
9	**1b**	**4b** 	3	**5i** 	84

(*continued on next page*)

Table 2 (*continued*)

Entry	Indole	Propargylic acetate	Time (h)	Product	Yield[b] (%)
10	**1a**	**4c** 	14	**5j** 	62
11	**1b**	**4c**	14	**5k** 	47
12	**1n** 	**4c**	16	**5l** 	54
13	**1k**	**4d** 	15	**5m** 	93
14	**1o** 	**4d**	18	**5n** 	81

[a] The ratio of reactants is equimolar.
[b] Isolated yield.

such as Mo complex.[10] On the basis of these experimental data, although we could not put forward an accurate mechanism, it was postulated that a possible and identical allylic cyclic iodonium intermediate was formed during the course of the reaction, leading to the a-attack product (**3m**–**a**) predominately for both regioisomeric allylic acetates **2b** and **2c** (Scheme 2).

Furthermore, the propargylation reactions of indoles with propargylic acetates **4a**–**d** were also studied (Scheme 3). It was found in Table 2 that the reaction of indole **1a** with **4a** under the conditions similar to that of iodine-catalyzed allylation could afford the desired product **5a** in an acceptable yield (69%) within 3 h by increasing the catalyst loading from 5 to 20 mol % (Table 2, entry 1). Under the optimized conditions, various indoles with electron-donating or electron-withdrawing groups could afford the corresponding propargylated products in excellent or quantitative yields.[11] Although it was noteworthy that the propargylation could occur smoothly at the benzyl position, no reaction took place when R_2(aryl) was replaced with methyl group, which was in accordance with Zhan's work.[7] When electron-donating or weak electron- withdrawing groups (R_2) were substituted in phenyl ring of indoles, good to excellent yields could be obtained (entries 9–12). In particular, naphthyl propargylic acetate showed better reactivity to give the product in an excellent yield after 15 h (entry 13). 2-Methyl furan **1o** could also tolerate this reaction conditions to give the corresponding product **5n** in 81% yield (entry 14).

In summary, an expedient, mild and effective iodine-promoted allylation and propargylation of indoles has been described for the first time. Operational simplicity, highly efficient catalyst employment, excellent yields, and high chemoselectivity are major advantages of this protocol compared to those reported in the literature. Further studies on the reaction mechanism and applications of this transformation are underway in our laboratories.

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References and notes

1. Sundberg, R. J. *Indoles*; Academic Press: San Diego, 1996.
2. (a) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314; (b) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1424; (c) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narsaiah, A. V.; Prabhakar, A.; Jagadeesh, B. *Tetrahedron Lett.* **2005**, *46*, 639; (d) Ma, S.; Yu, S.; Peng, Z.; Guo, H. *J. Org. Chem.* **2006**, *71*, 9865; (e) Ma, S.; Zhang, J. *Tetrahedron* **2003**, *59*, 6273; (f) Ma, S.; Zhang, J. *Tetrahedron Lett.* **2002**, *43*, 3435; (g) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592; (h) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Org. Lett.* **2004**, *6*, 3199; (i) Trost, B. M.; Krische, M. J.; Berl, V.; Grenzer, E. M. *Org. Lett.* **2002**, *4*, 2005.
3. (a) Smith, J. J. K.; Young, L. A.; Toste, F. D. *Org. Lett.* **2004**, *6*, 1325; (b) Inada, Y.; Yoshikawa, M.; Milton, M. D.; Nishibayashi, Y.; Uemura, S. *Eur. J. Org. Chem.* **2006**, 881.

4. (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, 395; (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, 2921.
5. (a) Nishibayashi, Y.; Inada, Y.; Yoshikawa, M.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1495; (b) Nishibayashi, Y.; Wakiji, I.; Hidai, M. *J. Am. Chem. Soc.* **2000**, *122*, 11019; (c) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 11846; (d) Kondo, T.; Kanda, Y.; Baba, A.; Fukuda, K.; Nakamura, A.; Wada, K.; Morisaki, Y.; Mitsudo, T. *J. Am. Chem. Soc.* **2002**, *124*, 12960; (e) Nishibayashi, Y.; Milton, M. D.; Inada, Y.; Yoshikawa, M.; Wakiji, I.; Hidai, M.; Uemura, S. *Chem. Eur. J.* **2005**, *11*, 1433; (f) Nishibayashi, Y.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 7900; (g) Fischmeister, C.; Toupet, L.; Dixneuf, P. H. *New. J. Chem.* **2005**, *29*, 765; (h) Bustelo, E.; Dixneuf, P. H. *Adv. Synth. Catal.* **2005**, *347*, 393; (i) Georgy, M.; Boucard, V.; Campagne, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 14180.
6. (a) Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 793; (b) Shiina, I.; Suzuki, M. *Tetrahedron Lett.* **2002**, *43*, 6391; (c) Li, J.-H.; Liu, W.-J.; Yin, D.-L. *Synth. Commun.* **2004**, *34*, 3161; (d) Mahrwald, R.; Quint, S.; Scholtis, S. *Tetrahedron* **2002**, *58*, 9847; (e) Mahrwald, R.; Quint, S. *Tetrahedron* **2000**, *56*, 7463; (f) Mahrwald, R.; Quint, S. *Tetrahedron Lett.* **2001**, *42*, 1655; (g) Ishikawa, T.; Aikawa, T.; Mori, Y.; Saito, S. *Org. Lett.* **2003**, *5*, 51; (h) Liu, J.; Muth, E.; Florke, U.; Henkel, G.; Merz, K.; Sauvageau, J.; Schwake, E.; Dyker, G. *Adv. Synth. Catal.* **2006**, *348*, 456; (i) Ishikawa, T.; Manabe, S.; Aikawa, T.; Kudo, T.; Saito, S. *Org. Lett.* **2004**, *6*, 2361; (j) Schwier, T.; Rubin, M.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1999.
7. Zhan, Z.; Yu, J.; Liu, H.; Cui, Y.; Yang, R.; Yang, W.; Li, J. *J. Org. Chem.* **2006**, *71*, 8298.
8. Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409.
9. (a) Chu, C.; Gao, S.; Sastry, M. N. V.; Yao, C. *Tetrahedron Lett.* **2005**, *46*, 4971; (b) Gao, S.; Tzeng, T.; Sastry, M. N. V.; Chu, C.; Liu, J.; Lin, C.; Yao, C. *Tetrahedron Lett.* **2006**, *47*, 1889; (c) Lin, C.; Hsu, J.; Sastry, M. N. V.; Fang, H.; Tu, Z.; Liu, J.; Yao, C. *Tetrahedron* **2005**, *61*, 11751; (d) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S. *Synlett* **2003**, 1722; (e) Yadav, J. S.; Reddy, B. V. S.; Rao, C. V.; Rao, K. V. *J. Chem. Soc., Perkin. Trans. I* **2002**, 1401; (f) Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Tetrahedron Lett.* **2002**, *43*, 3653; (g) Sun, J.; Dong, Y.; Cao, L.; Wang, X.; Wang, S.; Hu, Y. *J. Org. Chem.* **2004**, *69*, 8932; (h) Varala, R.; Nuvula, S.; Adapa, S. R. *J. Org. Chem.* **2006**, *71*, 8283; (i) Das, B.; Banerjee, J.; Ramu, R.; Pal, R.; Ravindranath, N.; Ramesh, C. *Tetrahedron Lett.* **2003**, *44*, 5465; (j) Lokhande, P. D.; Sakate, S. S.; Taksande, K. N.; Navghare, B. *Tetrahedron Lett.* **2005**, *46*, 1573; (k) Bhosale, R. S.; Bhosale, S. V.; Bhosale, S. V.; Wang, T.; Zubaidha, P. K. *Tetrahedron Lett.* **2004**, *45*, 9111; (l) Phukan, P. *J. Org. Chem.* **2004**, *69*, 4005; (m) Lee, B. S.; Mahajan, S.; Janda, K. D. *Synlett* **2005**, 1325; (n) Lin, C.; Fang, H.; Tu, Z.; Liu, J.; Yao, C. *J. Org. Chem.* **2006**, *71*, 6588.
10. Malkov, A. V.; Davis, S. L.; Baxendale, I. R.; Mitchell, W. L.; Kocovsky, P. *J. Org. Chem.* **1999**, *64*, 2751.
11. *Typical experimental procedure for allylation/propargylation of indoles*: 1, 3-Diphenyl propargyl acetate **4a** (58 mg, 0.23 mmol) and indole **1a** (27 mg, 0.23 mmol) were added into a flask. Dichloromethane (5 ml) was then poured and the mixture was vigorously stirred. Molecular iodine (12 mg, 0.047 mmol) was added and the resulting system was stirred at room temperature for 3 h, monitored by TLC. After the completion of reactions, saturated solution of $Na_2S_2O_3$ (2×5 ml) was added and extracted with Et_2O (3×5 ml). The combined organic phases were dried by anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash chromatograph (silica gel, petroleum ether–ethyl acetate 30:1) to afford the pure product **5a** as brown oil (49 mg, 69%).