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# Electrophilic Allylations and Benzylations of Indoles in Neutral Aqueous or Alcoholic Solutions[‡]

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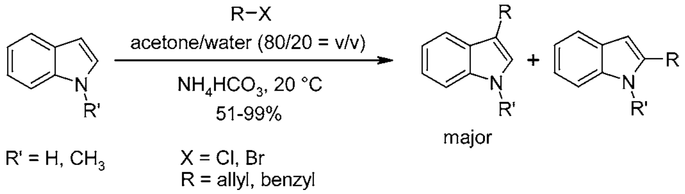
## ABSTRACT



**Indoles are allylated and benzylated in moderate to quantitative yield when stirred with allyl and benzyl halides in 80% aqueous acetone in the presence of $NH_4HCO_3$ at room temperature.**

Facile access to substituted indoles is of general interest because indoles are building blocks of many natural products and have applications as pharmaceuticals, as agrochemicals, and in materials science.[1,2] Among the numerous methods to synthesize substituted indoles, substitution reactions play an important role, among which Friedel−Crafts-type reactions are relatively rare. Although the $BF_3\cdot OEt_2$-induced prenylation of indole with prenyl pyrophosphate gave only 26% of 3-prenylated indoles,[3a] electrophilic allylations of indoles with allyl bromides in the presence of 1.2 equiv of zinc triflate, tetrabutylammonium iodide (1 equiv), and Hünig's base (2.2 equiv) in toluene have been reported to give 30−69% of 3-allylated products.[3b] Transition-metal-catalyzed allylations at the 3-position have been performed with Mo(II),[4a] Ni(II),[4b] and Pd(0) or Pd(II) complexes,[4c,d] and Pd-catalyzed allylations of 3-substituted indoles have also been used for the enantioselective synthesis of 3,3-disubstituted 3*H*-indoles.[4e] An alternative approach employs zinc- or gallium-mediated Barbier reactions,[5] where the initially formed allylmetal compounds deprotonate indoles to yield N-metalated indoles, which act as nucleophiles in the succeeding $S_N2$ reactions to give good yields of the 3-allylated indoles.[6] In contrast, Li and Na salts of indoles are predominantly alkylated and allylated at nitrogen.[7] The

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[‡] Dedicated to Professor Rolf Gleiter on the occasion of his 70th birthday.

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(2) (a) Yamamoto, H. In *Lewis Acids in Organic Synthesis*; Wiley-VCH: Weinheim, 2000. (b) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199−1222.

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(5) (a) Yadav, J. S.; Reddy, B. V. S.; Reddy, P. M.; Srinivas, C. *Tetrahedron Lett.* **2002**, *43*, 5185−5187. (b) Prajapati, D.; Gohain, M.; Gogoi, B. J. *Tetrahedron Lett.* **2006**, *47*, 3535−3539.

(6) For reactions of indolylmagnesium salts with allyl halides, see also: (a) Bodwell, G. J.; Li, J. *Org. Lett.* **2002**, *4*, 127−130. (b) Mirand, C.; Döé de Maindreville, M.; Lévy, J. *Tetrahedron Lett.* **1985**, *26*, 3985−3988.

(7) (a) Bocchi, V.; Casnati, G.; Dossena, A.; Villani, F. *Synthesis* **1976**, 414−416. (b) Guida, W. C.; Mathre, D. J. *J. Org. Chem.* **1980**, *45*, 3172−3176. (c) Bourak, M.; Gallo, R. *Heterocycles* **1990**, *31*, 447−457.

10.1021/ol0618555 CCC: $33.50

3-allylation of N-substituted indoles has also been achieved via 3-halogenation followed by halogen−metal exchange and consecutive treatment with allyl halides.[8] The isolation of up to 30% 3-prenylindole from indole and prenyl bromide in buffered aqueous solutions by Casnati and co-workers[9] is of particular interest for this investigation because this observation indicates that indole can successively compete with the buffer system in the trapping of the intermediate prenyl cation.

We now report a novel approach to 3-substituted indoles which compares well with the best yields obtained previously but considerably exceeds previous methods with respect to its simplicity.

Previously, we have shown that the rates of the reactions of carbocations with $n$-, $\pi$-, and $\sigma$-nucleophiles can be described by eq 1.[10]

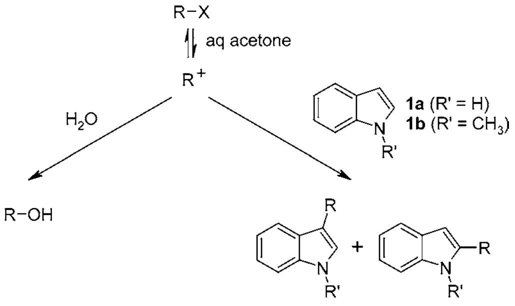
$$\log k = s(N + E) \qquad (1)$$

In eq 1, $k$ is a second-order rate constant at 20 °C ($M^{-1}\,s^{-1}$), $s$ is a nucleophile-specific slope parameter, $N$ a nucleophile-specific parameter, and $E$ is an electrophile-specific parameter.

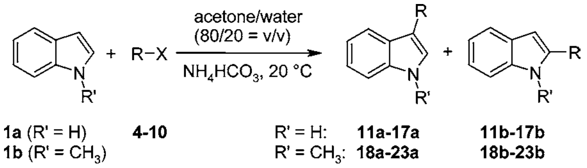
Because eq 1 also holds for the reactions of carbocations with solvents,[11] it can be employed to predict the relative reactivities of $\pi$-nucleophiles and solvents toward carbocations which are generated as intermediates of $S_N1$ processes. Stimulated by our reactivity scales which revealed that many electron-rich $\pi$-systems were more nucleophilic than aqueous acetone or aqueous acetonitrile,[11,12] we have recently introduced a novel protocol for Friedel−Crafts alkylations under neutral or slightly basic conditions by trapping the intermediates of $S_N1$ reactions in aqueous solutions with electron-rich $\pi$-systems.[13]

We now report that this method can be employed for the mild and efficient allylation and benzylation of indoles by dissolving indoles and $S_N1$ active allyl and benzyl halides in aqueous acetone or acetonitrile in the presence of a base (Scheme 1).

**Scheme 1.** Trapping of $S_N1$ Intermediates by Indoles

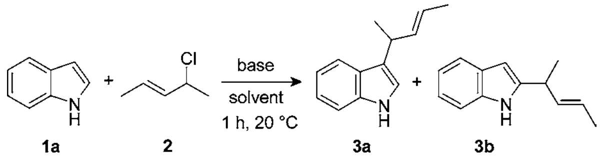


**Scheme 2.** Reactions of Indoles with Allyl and Benzyl Halides **4**−**10**



To optimize the reaction conditions, we examined the reaction of indole (**1a**) with (*E*)-4-chloropent-2-ene (**2**) under various conditions (Scheme 2). Acid catalysis by the liberated HCl was excluded by performing the reactions in the presence of a base. Bisallylation was avoided by employing 5 equiv of **1a**. Table 1 shows that comparable yields of allylation products were obtained when the reactions were performed in 90% aqueous acetonitrile ($N_1$ = 4.56, $s$ = 0.94)[11] or 80% aqueous acetone ($N_1$ = 5.77, $s$ = 0.87)[12] using $Na_2CO_3$, $NaHCO_3$, or $NH_4HCO_3$ as the auxiliary base. The yields were less satisfactory when 2,2,2-trifluoroethanol was

**Table 1.** Product Ratios and Yields of the Reaction of Indole (**1a**) with (*E*)-4-Chloro-pent-2-ene (**2**) Isolated after 1 h at Ambient Temperature



| no. | solvent[a] | base[b] | ratio **3a**:**3b**[c] | yield **3a** + **3b**[d] (%) |
|---|---|---|---|---|
| 1 | 90AN10W | $Na_2CO_3$ (2.0) | 80:20 | >99 |
| 2 | 90AN10W | $NH_4HCO_3$ (2.0) | 83:17 | 96 |
| 3 | 90AN10W | 2,6-lutidine (1.2) | 67:33 | 97 |
| 4 | 80A20W | $Na_2CO_3$ (2.0) | 78:22 | 96 |
| 5 | 80A20W | $NaHCO_3$ (2.0) | 80:20 | 95 |
| 6 | 80A20W | $NH_4HCO_3$ (1.0) | 81:19 | 95 |
| 7 | 80A20W | $NH_4HCO_3$ (2.0) | 80:20 | >99 |
| 8 | TFE | $NH_4HCO_3$ (2.0) | 77:23 | 73 |

[a] Solvent mixtures are given as (v/v). Solvents: A = acetone, AN = acetonitrile, TFE = 2,2,2-trifluoroethanol, W = water. [b] Equivalents of auxiliary base relative to the electrophile are given in parentheses. [c] Peak areas determined by GC-MS of the crude products. [d] Based on the isolated yield of pure **3a** which was obtained after column chromatography.

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[8] (a) Ishikura, M.; Kamada, M.; Oda, I.; Ohta, T.; Terashima, M. *J. Heterocycl. Chem.* **1987**, *24*, 377−386. (b) Amat, M.; Hadida, S.; Sathyanarayana, S.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 10−11.

[9] Bocchi, V.; Casnati, G.; Marchelli, R. *Tetrahedron* **1978**, *34*, 929−932.

[10] Reviews: (a) Mayr, H.; Patz, M. *Angew. Chem.* **1994**, *106*, 990−1010; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938−957. (b) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500−9512. (c) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.

[11] Minegishi, S.; Kobayashi, S.; Mayr, H. *J. Am. Chem. Soc.* **2004**, *126*, 5174−5181.

[12] Denegri, B.; Minegishi, S.; Kronja, O.; Mayr, H. *Angew. Chem.* **2004**, *116*, 2353−2356; *Angew. Chem., Int. Ed.* **2004**, *43*, 2302−2305.

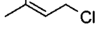
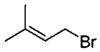
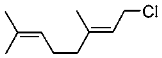
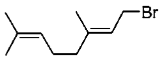
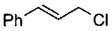
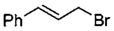
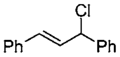
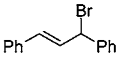
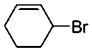
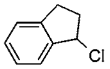
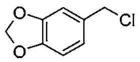
[13] (a) Hofmann, M.; Hampel, N.; Kanzian, T.; Mayr, H. *Angew. Chem.* **2004**, *116*, 5518−5521; *Angew. Chem., Int. Ed.* **2004**, *43*, 5402−5405. (b) Mayr, H.; Hofmann, M.; Minegishi, S.; Hampel, N. PCT Int. Appl. WO 2005077863, 2005; *Chem. Abstr.* **2005**, *143*, 248153.

used as solvent. Possibly, the acidity of this solvent (p$K_a$ = 12.3)[14] is responsible for the formation of some oligomers of indole.[15]

The conditions of experiment no. 7 (Table 1), i.e., dissolving the reactants in 80% aqueous acetone in the presence of $NH_4HCO_3$,[16] were then employed for the reactions of various $S_N1$-reactive allyl and benzyl halides **4**−**10** with the indoles **1a** and **1b** (Scheme 2). The reactions were monitored by GC-MS and interrupted after complete conversion of **4**−**10** or after 3 days.

The reactions with indole (**1a**) gave mixtures of 3- and 2-allylated indoles in moderate to very good yields, when disubstitution was suppressed by employing 5 equiv of **1a**,**b** (Table 2). When indole (**1a**, 10 mmol), prenyl bromide (**4b**, 8.3 mmol), and $NH_4HCO_3$ (10 mmol) were stirred in 80% aqueous acetone (25 mL) for 1 h at room temperature, a significant amount of 2,3-diprenylindole [2,3-bis(2-methylpropenyl)-1*H*-indole, **11c**] was formed, and only 54% of **11a** could be isolated. Under the same conditions, disubstitution was favored when **4b** was used in excess, and compound **11c** was obtained as the major product (83% by GC-MS) from a 1:4 mixture of **1a** and **4b**.

**Table 2.** Reactions of Indole (**1a**) with Allyl and Benzyl Halides **4**−**10** in 80% Aqueous Acetone

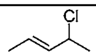
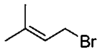
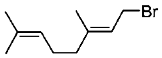
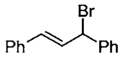
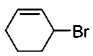
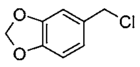
| no. | electrophile | | time / h | product ratio[a] | yield **a** + **b**[b] |
|---|---|---|---|---|---|
| 1 | **4a** |  | 8 | **11a**:**b** (91:9) | 87 (79) |
| 2 | **4b** |  | 2 | **11a**:**b** (91:9) | >99 (91) |
| 3 | **5a** |  | 24 | **12a**:**b** (92:8) | 34 (31) |
| 4 | **5b** |  | 1 | **12a**:**b** (92:8) | 60 (56) |
| 5 | **6a** |  | 72 | **13a**:**c** (62:10)[c] | 22[d] |
| 6 | **6b** |  | 24 | **13a**:**c** (61:13)[e] | 71[d] |
| 7 | **7a** |  | 72 | — | 0 |
| 8 | **7b** |  | 48 | **14a**:**b** (93:7) | 60 (56) |
| 9 | **8** |  | 0.5 | **15a**:**b** (>99:1) | 70 (70)[f] |
| 10 | **9** |  | 24 | **16a**:**b** (94:6) | 51[g] |
| 11 | **10** |  | 24 | **17a**:**b** (92:8) | 86[h](79) |

[a] Peak areas determined by GC-MS of the crude products. [b] Isolated yields of the mixtures of **a** and **b** isomers. The number in parentheses is the isolated yield of the isomers (**11**−**17**)**a**. [c] Besides **13a** and 3-(1-phenylallyl)-1*H*-indole (**13c**), a third isomer was detected by GC/MS (28%, possibly **13b**). [d] 8:1 mixture of **13a** and 3-(1-phenylallyl)-1*H*-indole (**13c**). [e] A third isomer was detected by GC/MS (26%, possibly **13b**). [f] Reaction performed in 90% aqueous acetonitrile. [g] 10:1 mixture of **16a** and **16b**. [h] 15:1 mixture of **17a** and **17b**.

Because of the longer retention times of the 2-substituted isomers (**11**−**13**)**b**, the predominantly formed 3-substitution products (**11**−**13**)**a** could be obtained as pure isomers by chromatography on silica gel. Generally, the allyl bromides reacted faster and gave better yields than the corresponding chlorides. Exclusive 3-attack was observed when indole (**1a**) was treated with 3-bromocyclohexene (**8**) in 90% aqueous acetonitrile (Table 2, entry 9). Surprisingly, the corresponding reaction in 80% aqueous acetone gave only 27% of **15a** along with cyclohex-2-enol as the major product. In the case of **14a**/**b**, **16a**/**b**, and **17a**/**b**, the trace amounts of the 2-isomers were not removed by chromatography, and pure **17a** was obtained by crystallization. Although the 1,1-dialkyl-substituted allyl cations derived from the allyl halides **4** and **5** were selectively attacked at the terminal position of the allyl cation, the 1-phenylallyl cation arising from **6a**/**b** was attacked at both allylic termini, with attack at the nonsubstituted allylic position predominating. As previously reported for Lewis acid-catalyzed allylations of $\pi$-nucleophiles,[17] the regioselectivity of attack is predominantly controlled by steric effects and not by LUMO coefficients or charge distribution in the allyl cations.[18] Entries 10 and 11 of Table 2 show that this novel type of electrophilic substitution of indoles is not restricted to allyl halides but can also be employed for other types of $S_N1$ active substrates such as benzyl halides.

Similar reactions were observed with *N*-methylindole (**1b**, Table 3). Preferential 3-attack is generally accompanied by some 2-attack, but 3-bromocyclohexene (**8**) again attacks the 3-position of **1b** selectively. As before, the reaction with **8** has to be carried out in 90% aqueous acetonitrile because cyclohex-2-enol is the major product in 80% aqueous acetone.

**Table 3.** Reactions of *N*-Methylindole (**1b**) with Allyl and Benzyl Halides **4**−**10** in 80% Aqueous Acetone

| no. | electrophile | | time / h | product ratio[a] | yield **a** + **b**[b] |
|---|---|---|---|---|---|
| 1 | **2** |  | 1 | **18a**:**b** (80:20) | 99[c] |
| 2 | **4b** |  | 1 | **19a**:**b** (92:8) | 85[d] |
| 3 | **5b** |  | 1 | **20a**:**b** (95:5) | 71 (67) |
| 4 | **7b** |  | 48 | **21a**:**b** (98:2) | 50[e] |
| 5 | **8** |  | 24 | **22a**:**b** (>99:1) | 71[f] |
| 6 | **10** |  | 24 | **23a**:**b** (94:6) | 56 (53) |

[a] Peak areas determined by GC-MS of the crude product. [b] Isolated yields of the mixtures of **a** and **b** isomers; isolated yields of the isomers (**18**−**23**)**a** are given in parentheses. [c] 10:1 mixture of **18a** and **18b**. [d] 10:1 mixture of **19a** and **19b**. [e] Product contains traces of **21b**. [f] Reaction performed in 90% aqueous acetonitrile.

Our previously published concept of Friedel−Crafts reactions under acid-free conditions[13] has thus been demonstrated

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[14] Das, U.; Crousse, B.; Kesavan, V.; Bonnet-Delpon, D.; Begué, J. P. *J. Org. Chem.* **2000**, *65*, 6749−6751.

[15] Smith, G. F. *Adv. Heterocycl. Chem.* **1963**, *2*, 287−309.

to be applicable for an important class of compounds. Because indoles are generally more nucleophilic than water in acetone,[11,12] the competing trapping of the intermediate carbocation by water is usually not a problem. The method is rather limited by the rates of ionization of the corresponding allyl and benzyl halides.

Because nucleofugality parameters of $N_f = 2$ and 3 have been reported for chloride and bromide, respectively, in 80% aqueous acetone,[19a] one can expect that ionization half-lives will exceed 1 day as the electrofugality of the carbocation gets smaller than $-7$ in the case of R−Cl and smaller than $-8$ in the case of R−Br. In line with the published electrofugality parameter of the cinnamyl cation ($E_f = -8$),[19b] cinnamyl bromides but not chlorides have successfully been employed in this study. Reactions via less stabilized carbocations will require more harsh conditions.

**Acknowledgment.** This work was financially supported by the Deutsche Forschungsgemeinschaft.

**Supporting Information Available:** Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] General reaction procedure: $NH_4HCO_3$ (10 mmol) was suspended in a solution of indole **1a** or **1b** (25 mmol) in 80% aqueous acetone (25 mL). After the addition of the allyl or benzyl halide (5.0 mmol), the suspension was stirred at ambient temperature for the time specified in Table 2. Water (30 mL) was added, and the organic phase was separated. The aqueous phase was extracted with $Et_2O$ (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), and the solvents were removed in vacuo. Indole (**1a**, bp 103−107 °C/3 × $10^{-3}$ mbar) or 1-methylindole (**1b**, bp 95−98 °C/3 × $10^{-3}$ mbar) was removed from the crude product by Kugelrohr distillation. The residue was purified by flash column chromatography on silica gel with *n*-hexane/ethyl acetate mixtures as eluents.

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