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Carboxylic Acid Catalyzed Three-Component Aza-Friedel–Crafts Reactions in Water for the Synthesis of 3-Substituted Indoles

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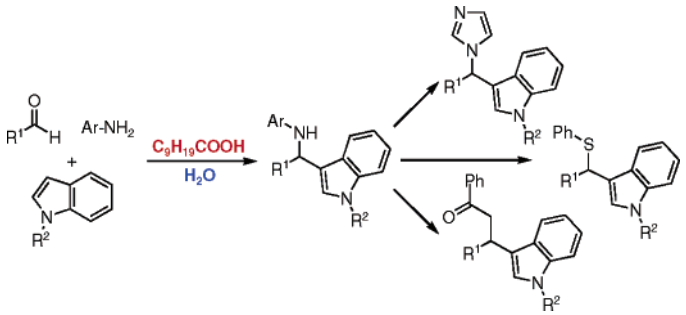
ABSTRACT



The carboxylic acid catalyzed three-component aza-Friedel–Crafts reactions of aldehydes, primary amines, and indoles in water have been developed. The aza-Friedel–Crafts products could be easily transformed to various 3-substituted indoles including biologically active compounds. This system offers a novel efficient method for the synthesis of 3-substituted indoles.

3-Substituted indoles of type **1** have attracted much attention due to the broad scope of their biological activitiy (Figure 1).[1] Recent examples of type **1** indoles in medicinal chemistry include **2**, which was reported to act as a nonsteroidal aromatase inhibitor against breast cancer,[2] and **3**, which worked as a HIV-1 integrase inhibitor.[3] Furthermore, many natural products incorporating this structural key element are known.[4] As a result of their biological and synthetic importance, a variety of methods have been reported for the preparation of 3-substituted indoles.[5] Although these methods constitute a valuable addition to the chemical literature, a

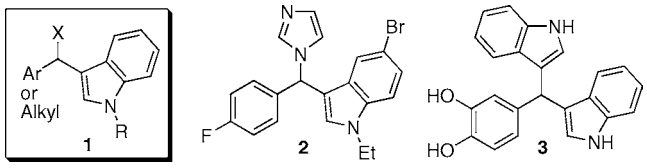


Figure 1. Biologically active 3-substituted indoles.

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(1) (a) Sundberg, R. J. In *Indoles*; Academic Press: San Diego, 1996. (b) Sundberg, R. J. In *The Chemistry of Indoles*; Academic Press: New York, 1970.

(2) (a) Lézé, M.-P.; Le Borgne, M.; Marchand, P.; Loquet, D.; Kogler, M.; Le Baut, G.; Palusczak, A.; Hartmann, R. W. *J. Enzyme Inhib. Med. Chem.* **2004**, *19*, 549. (b) Le Borgne, M.; Marchand, P.; Delevoye-Seiller, B.; Robert, J.-M.; Le Baut, G.; Hartmann, R. W.; Palzer, M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 333.

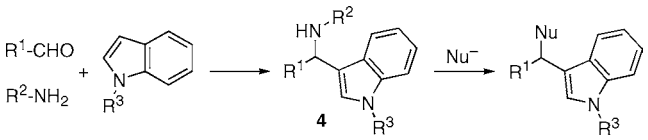
(3) (a) Deng, J.; Sanchez, T.; Neamati, N.; Briggs, J. M. *J. Med. Chem.* **2006**, *49*, 1684. (b) Contractor, R.; Samudio, I. J.; Estrov, Z.; Harris, D.; McCubrey, J. A.; Safe, S. H.; Andreeff, M.; Konopleva, M. *Cancer Res.* **2005**, *65*, 2890.

(4) (a) Gul, W.; Hamann, M. T. *Life Sci.* **2005**, *78*, 442. (b) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73. (c) Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 175.

truly efficient, diverse synthetic scheme[6] for type **1** indoles is still required to construct further indole libraries for medicinal chemistry.

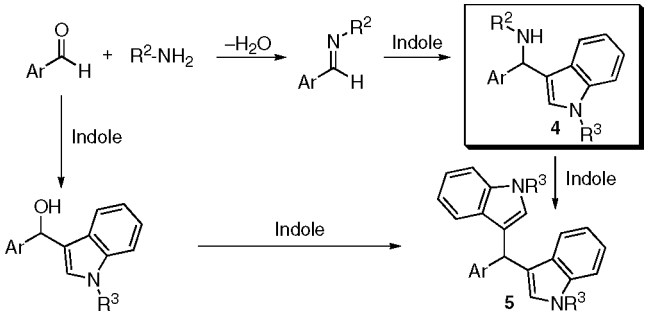
Our strategy for the synthesis of type **1** indoles involves a three-component aza-Friedel−Crafts (AFC) reaction[7] in water[8] (Scheme 1). The AFC product **4** contains a reactive

Scheme 1. Synthetic Scheme of 3-Substituted Indoles Using AFC Reactions



C−N bond, which could be easily transformed to various functional groups. However, three-component AFC reactions of aromatic aldehydes, primary amines, and indoles are to the best of our knowledge unknown, because the initial product **4** is highly reactive and further addition of indoles gives undesired adduct **5** (Scheme 2).[9,10] In addition, aromatic

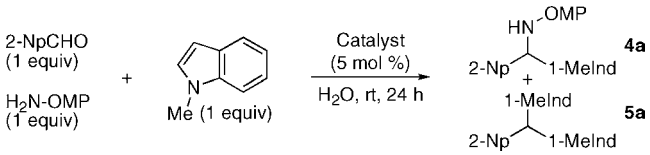
Scheme 2. Side Pathways of AFC Reactions



aldehydes are themselves known to react with indoles directly to afford the undesired bisindolyl products **5**.[11] In an effort to address these shortcomings, we initially undertook development of selective three-component AFC reactions with aromatic aldehydes, primary amines, and indoles.

Recently our group has developed several acid-catalyzed C−C bond-forming reactions in water.[12,13] On the basis of these findings, we first searched for an efficient catalyst in the model three-component AFC reaction of 2-naphthaldehyde (2-NpCHO), *o*-anisidine (H_2N-OMP), and 1-methylindole (1-MeInd) in water (Table 1). Although AcOH and TFA

Table 1. Effect of Catalysts



entry	catalyst	**4a/5a**[a]	yield of **4a** (%)[a]
1	none	>20:1	5
2	AcOH	>20:1	5
3	TFA	>20:1	6
4	$Sc(DS)_3$	3.3:1	46
5	DBSA	5.2:1	65
6	$C_9H_{19}COOH$	>20:1	80 (3^b, 4^c)
7	$C_5H_{11}COOH$	>20:1	6
8	$C_7H_{15}COOH$	>20:1	43
9	$C_8H_{17}COOH$	>20:1	63
10	$C_{10}H_{21}COOH$	>20:1	78
11	$C_{11}H_{23}COOH$	>20:1	45
12	$C_{13}H_{27}COOH$	>20:1	28
13	$C_9H_{19}COOH$[d]	>20:1	91

[a] Determined by ^{1}H NMR analysis. [b] Reaction in CH_2Cl_2. [c] Reaction in THF. [d] 10 mol % of catalyst was used.

did not show any catalytic ability for the system (entries 2 and 3), scandium tris(dodesyl sulfate) ($Sc(DS)_3$) and dodecylbenzenesulfonic acid (DBSA), which are known as effective catalysts for three-component Mannich reactions in water,[13] promoted the reaction effectively; however, a certain amount of undesired adduct **5a** was formed (entries 4 and 5). After screening other catalysts, it was revealed that decanoic acid ($C_9H_{19}COOH$) efficiently promoted the reaction without formation of **5a** (entry 6). Interestingly, this efficient catalysis occurred sluggishly in organic solvents such as CH_2Cl_2 and THF (entry 6, in parentheses). Furthermore, the length of the alkyl chains of the carboxylic acids was found to be crucial for this reaction. Decanoic acid ($C_9H_{19}COOH$) gave the best result, and it was noted that use of carboxylic acids with shorter or longer alkyl chains resulted in lower yields (entries 7−12). Finally, it was discovered that increasing the catalyst loading could further improve the yield of the desired product (entry 13).[14]

(5) (a) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199. (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550. (c) Comins, D. L.; Stroud, E. D. *Tetrahedron Lett.* **1986**, *27*, 1869.

(6) (a) Schreiber, S. L. *Chem. Eng. News* **2003**, *81*, 51. (b) Spring, D. R. *Org. Biomol. Chem.* **2003**, *1*, 3867.

(7) For recent examples of AFC reactions of α-iminoesters, see: (a) Zhao, J.-L.; Liu, L.; Zhang, H.-B.; Wu, Y.-C.; Wang, D.; Chen, Y.-J. *Synlett* **2006**, 96. (b) Jiang, B.; Huang, Z.-G. *Synthesis* **2005**, 2198. (c) Johannsen, M. *Chem. Commun.* **1999**, 2233.

(8) For Friedel−Crafts-type reactions in water, see: (a) Zhuang, W.; Jørgensen, K. A. *Chem. Commun.* **2002**, 1336. (b) Manabe, K.; Aoyama, N.; Kobayashi, S. *Adv. Synth. Catal.* **2001**, *343*, 174.

(9) (a) Ke, B.; Qin, Y.; He, Q.; Huang, Z.; Wang, F. *Tetrahedron Lett.* **2005**, *46*, 1751. (b) Mi, X.; Luo, S.; He, J.; Cheng, J.-P. *Tetrahedron Lett.* **2004**, *45*, 4567. (c) Xie. W.; Bloomfield, K. M.; Jin, Y.; Dolney, N. Y.; Wang, P. G. *Synlett* **1999**, 498.

(10) A few examples of selective AFC reactions of indoles to aryl imines were reported; see: (a) Jia, Y.-X.; Xie, J.-H.; Duan, H.-F.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 1621. (b) Esquivias, J.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 629. (c) Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156.

(11) For recent examples, see: (a) Deb, M. L.; Bhuyan, P. J. *Tetrahedron Lett.* **2006**, *47*, 1441. (b) Yadav, J. S.; Reddy, B. V. S.; Sunitha, S. *Adv. Synth. Catal.* **2003**, *345*, 349.

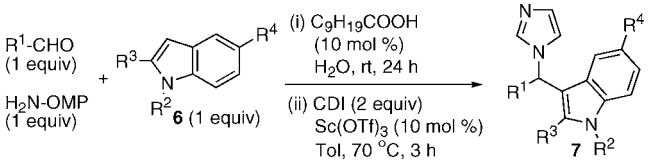
(12) (a) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209. (b) Hamada, T.; Manabe, K.; Kobayashi, S. *Chem. Eur. J.* **2006**, *12*, 1205. (c) Azoulay, S.; Manabe, K.; Kobayashi, S. *Org. Lett.* **2005**, *7*, 4593.

(13) (a) Manabe, K.; Mori, Y.; Kobayashi, S. *Tetrahedron* **2001**, *57*, 2537. (b) Manabe, K.; Mori, Y.; Wakabayashi, T.; Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 7202.

Armed with this information, we then investigated the substrate generality of decanoic acid catalyzed AFC reactions (Table 2). To increase the synthetic utility of the procedure, workup and recrystallization, the desired product **4a** was isolated in 83% yield. It is noteworthy that the present method is very simple and that the pure AFC product can be obtained without tedious column chromatography.

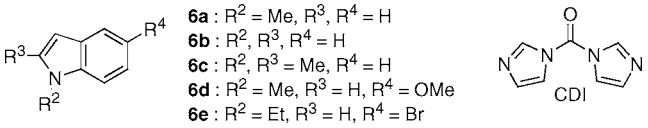
Further examples of the synthetic utility of the present method are demonstrated by the transformation of the AFC product to various 3-substituted indole derivatives (Scheme 4). As a result of the high reactivity of the C−N bond, AFC

Table 2. Synthesis of Aromatase Inhibitor Type Compounds **7** via Three-Component Aza-Friedel−Crafts Reactions in Water



entry	R^1	indole	yield (%)[a]
1	2-naphthyl	**6a**	82 (**7a**)
2	Ph	**6a**	90 (**7b**)
3	4-MeO-C_6H_4	**6a**	89 (**7c**)
4	4-Cl-C_6H_4	**6a**	85 (**7d**)
5	3-thienyl	**6a**	73 (**7e**)
6	$(CH_3)_2CHCH_2$	**6a**	57 (**7f**)
7	*c*-C_6H_{11}	**6a**	53 (**7g**)
8[b]	Ph	**6b**	63 (**7h**)
9	Ph	**6c**	82 (**7i**)
10[c]	Ph	**6d**	64 (**7j**)
11[d]	4-F-C_6H_4	**6e**	70 (**2**)

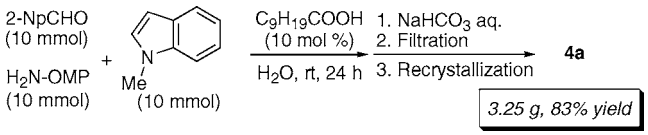
[a] Isolated yield. [b] Reaction conditions in the second step = Tol, rt, 12 h. [c] Reaction conditions in the second step = Tol, 70 °C, 1 h. [d] Reaction conditions in the first step = H_2O, 50 °C, 48 h.



AFC products were directly transformed to imidazole-substituted compounds **7**. Thus, after the AFC reactions the crude products were treated with CDI in the presence of $Sc(OTf)_3$ as a catalyst. As shown in Table 2, the reactions of aldehydes bearing aromatic, heteroaromatic, and alkyl groups gave the corresponding products in moderate to high yields in two steps. Moreover, a range of indole derivatives could be employed in the reaction system. It should be noted that nonsteroidal aromatase inhibitor **2** itself (entry 11) and its derivatives were prepared efficiently using these reactions.

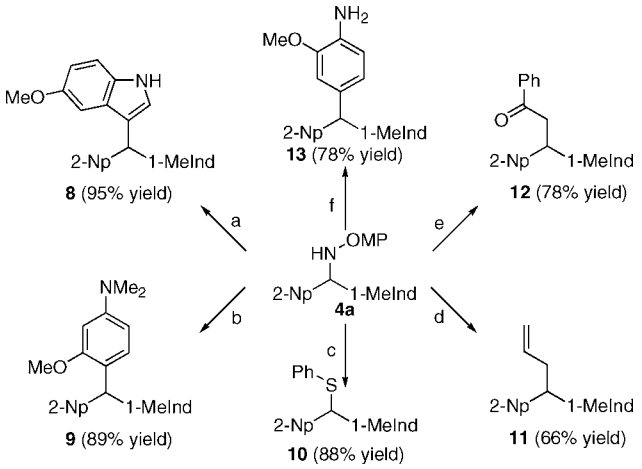
The present AFC reaction was conducted on a 10 mmol scale (Scheme 3). Accordingly, 2-naphthaldehyde was treated

Scheme 3. Larger Scale Synthesis



with *o*-anisidine and 1-methylindole successively in water in the presence of 10 mol % of decanoic acid. After simple

Scheme 4. Transformations of Aza-Friedel−Crafts Product **4a**[a]



[a] Reagents and Conditions: (a) 5-MeO-indole (1.2 equiv), DBSA (10 mol %), H_2O, rt, 24 h; (b) *N*,*N*-dimethyl-*m*-anisidine (1.2 equiv), $Sc(OTf)_3$ (10 mol %), toluene, 70 °C, 24 h; (c) PhSH (3 equiv), $Sc(OTf)_3$ (10 mol %), toluene, 70 °C, 24 h; (d) $Sn(CH_2CH{=}CH_2)_4$ (1.2 equiv), $Sc(OTf)_3$ (10 mol %), toluene, 70 °C, 24 h; (e) $Me_3SiO(Ph)C{=}CH_2$ (2 equiv), $Sc(OTf)_3$ (10 mol %), toluene, 70 °C, 24 h; (f) $Sc(OTf)_3$ (10 mol %), toluene, 70 °C, 24 h.

product **4a** was readily converted to various nucleophiles in the presence of DBSA or $Sc(OTf)_3$ as a catalyst. Friedel−Crafts type substitution reactions occurred cleanly by treatment with electron-rich heteroaromatic or aromatic compounds to afford the unsymmetrical triaryl methanes **8** and **9**, respectively.[15] Substitution using thiol, allyltin, and silyl enol ether nucleophiles also proceeded smoothly and gave the valuable compounds **10**, **11**, and **12** in good yields. Furthermore, when **4a** was treated with $Sc(OTf)_3$ without addition of any nucleophile in toluene, triaryl methane **13** was obtained via cleavage of the C−N bond of **4a** followed by Friedel−Crafts-type addition of the cleaved *o*-anisidine.

In summary, we have developed a novel protocol for three-component AFC reactions of aldehydes, primary amines, and indoles in water catalyzed by carboxylic acids. The AFC reactions have been known to be difficult to control, but the present reaction system enabled the desired products to be obtained in high yields. It is noted that the reaction proceeded

(14) The reaction under neat conditions caused a slight decrease of the selectivity of **4a**/**5a**.

(15) Friedel−Crafts-type substitution reactions via cleavage of a C−N bond were also reported in ref 10b.

under nonmetallic conditions in water and that various 3-substituted indoles including biologically active compounds were prepared by utilizing the reactive C−N bond. This simple system offers a novel efficient method for the synthesis of various 3-substituted indoles.

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

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