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Catalytic Friedel–Crafts Reaction of Aminocyclopropanes

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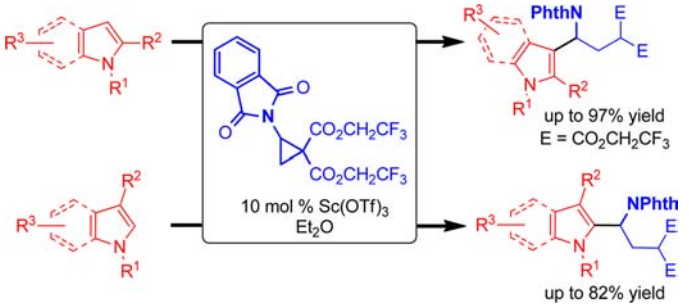
ABSTRACT



A Lewis acid catalyzed Friedel–Crafts reaction between donor–acceptor aminocyclopropanes and indoles and other electron-rich aromatic compounds is reported. Indole alkylation at the C3 position was generally obtained for a broad range of functional groups and substitution patterns. In the case of C3-substituted indoles, C2 alkylation was observed. The reaction gives a rapid access to gamma amino acid derivatives present in numerous bioactive molecules.

Substituted γ-aminobutyric acid (GABA) derivatives are found in numerous natural and synthetic neurotransmitters,[1] in peptidomimetics[2] and in the core of a large number of alkaloid natural products. In particular, electron-rich aromatic substituents are frequently encountered in the γ position of GABA derivatives in important classes of natural products, such as the indole alkaloids vindoline (**1**) and eburnamonine (**2**) or the *Erythrina* alkaloid 3-demethoxyerythratidinone (**3**) (Scheme 1). Consequently, a fast and general approach to these key building blocks would be highly desirable.[3]

In this context, the nucleophilic attack of an electron-rich aromatic or an amine at the γ position of a carbonyl group would give an efficient entry into this important class of GABA derivatives (Scheme 1). In order to achieve this transformation, the *Umpolung* of the normal reactivity at the nucleophilic γ position is required. Activated donor–acceptor (DA) cyclopropanes represent such *Umpolung* synthons and have been used in the past as olefin homologues.[4] In previous studies the nucleophilic attack of an amine onto aromatic DA cyclopropanes has been reported to access GABA analogues (Scheme 1, (1)).[5] If a high diversity in the aromatic substituent is desired, an alternative approach involving attack of a nucleophilic aromatic compound onto a nitrogen-substituted synthon as represented by an aminocyclopropane would be more efficient (Scheme 1, (2)). Nevertheless, such an approach has not yet been exploited.

On the other hand, intermolecular Friedel–Crafts reactions between donor–acceptor cyclopropanes and electron-rich aromatic compounds including indoles have

(1) (a) Johnston, G. A. R. *Pharm. Ther.* **1996**, *69*, 173. (b) Chebib, M.; Johnston, G. A. R. *J. Med. Chem.* **2000**, *43*, 1427.

(2) Sudev, P. G.; Chatterjee, S.; Shamala, N.; Balaram, P. *Chem. Rev.* **2011**, *111*, 657.

(3) Ordóñez, M.; Cativiela, C. *Tetrahedron: Asymmetry* **2007**, *18*, 3.

(4) (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321. (c) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (d) De Simone, F.; Waser, J. *Synthesis* **2009**, *2009*, 3353. (e) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051. Theoretical study: (f) Schneider, T. F.; Werz, D. B. *Org. Lett.* **2011**, *13*, 1848.

(5) (a) Blanchard, L. A.; Schneider, J. A. *J. Org. Chem.* **1986**, *51*, 1372–1374. (b) Lifchits, O.; Charette, A. B. *Org. Lett.* **2008**, *10*, 2809. (c) Lindsay, V. N. G.; Nicolas, C.; Charette, A. B. *J. Am. Chem. Soc.* **2011**, *133*, 8972. (d) So, S. S.; Auvil, T. J.; Garza, V. J.; Mattson, A. E. *Org. Lett.* **2012**, *14*, 444. (e) Zhou, Y. Y.; Wang, L. J.; Li, J.; Sun, X. L.; Tang, Y. *J. Am. Chem. Soc.* **2012**, *134*, 9066. (f) Emmett, M. R.; Grover, H. K.; Kerr, M. A. *J. Org. Chem.* **2012**, *77*, 6634.

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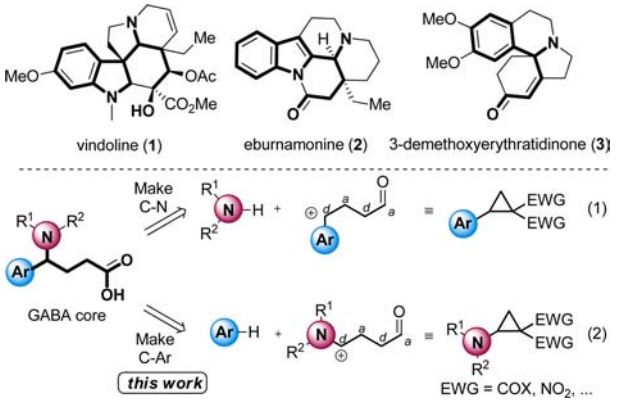
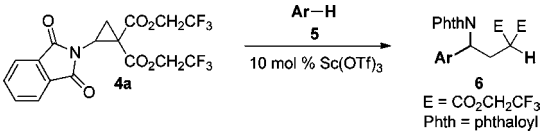
been studied in the past, especially by the groups of Kerr, Pagenkopf and Ivanova.[6] In 2013, Johnson developed an enantioselective Friedel–Crafts reaction between aryl cyclopropane and silyl-protected indoles using a chiral Lewis acid catalyst.[7] However, only alkyl, aryl or alkoxy substituents have been used as the donating group on the cyclopropane.[8]

Scheme 1. Natural Products Containing a GABA-Derived Core and Key Disconnections



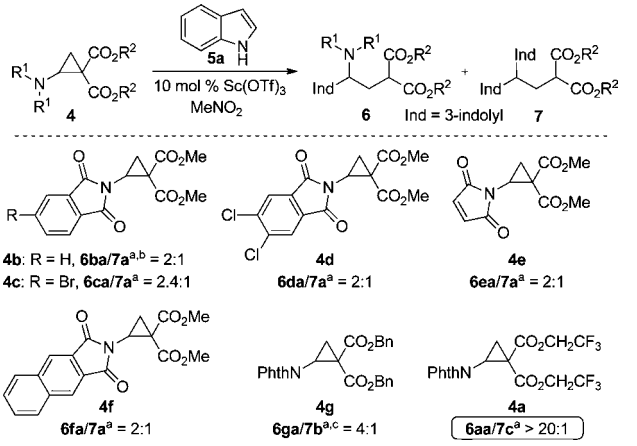
Since 2010, our group has been involved in the study of the reactivity of aminocyclopropanes.[9] The release of ring strain combined with bond polarization allowed the generation of reactive a 1,3 zwitterionic synthon, which could cyclize on indoles or react with enol ethers, aldehydes and ketones to afford cyclopentyl- and tetrahydrofuryl-amines. In this latter work, optimization of the electronic properties of the substituents on the nitrogen resulted in the discovery that phthalimide-substituted cyclopropane diesters afford the right balance between reactivity and stability.[9c–e] Herein, we would like to report the first successful intermolecular Friedel–Crafts reaction of indoles with aminocyclopropanes based on fine-tuning of the electron-withdrawing properties of the diester group and the identification of scandium triflate as the best catalyst (Scheme 2). The reaction worked with unprotected indoles as well as other electron-rich aromatic compounds and tolerated a broad range of functional groups. In the case of C3-substituted indoles, C2-alkylated products could be obtained, probably via a selective 1,2-shift of the amino acid side-chain.

Scheme 2. Friedel–Crafts with Diester Aminocyclopropane **4a**



Preliminary screening of Lewis acids and solvents allowed us to identify scandium triflate in nitromethane as promising conditions for the alkylation of N-protected indoles with the phthaloyl protected aminocyclopropane diester **4b** at room temperature.[10] However, when switching to unprotected indole (**5a**), double addition product **7a** was observed as major side product in the reaction mixture (Scheme 3). Even after extensive optimization of the reaction conditions, it was not possible to achieve full selectivity toward the desired product **6**.

Scheme 3. Fine-Tuning of the Aminocyclopropane Structure for the Friedel–Crafts Alkylation of Indole (**5a**)[d]



[a] Reaction conditions: cyclopropane (0.034 mmol), **5a** (0.051 mmol), $Sc(OTf)_3$ (3.4 μmol), nitromethane (0.2 mL), rt, 1 h. [b] Determined by ^1H NMR of the crude reaction mixture. [c] DCM (0.5 mL) was used. [d] The bis-indole adduct **7b** was not isolated. The NMR ratio was determined by analogy with **7a**.

We then turned our attention to the further adjustment of the structure of the aminocyclopropane. A series of aminocyclopropanes **4c–f** with different nitrogen protecting groups were examined in the alkylation reaction. The use of electron-poor bromo and dichloro derivatives **4c** and **4d** of phthalimide as well as a smaller maleimide **4e** or a

(6) (a) Harrington, P.; Kerr, M. A. *Tetrahedron Lett.* **1997**, *38*, 5949. (b) Kerr, M. A.; Keddy, R. G. *Tetrahedron Lett.* **1999**, *40*, 5671. (c) England, D. B.; Woo, T. K.; Kerr, M. A. *Can. J. Chem.* **2002**, *80*, 992. (d) Grover, H. K.; Lebold, T. P.; Kerr, M. A. *Org. Lett.* **2011**, *13*, 220. (e) Emmett, M. R.; Kerr, M. A. *Org. Lett.* **2011**, *13*, 4180. (f) Bajtos, B.; Yu, M.; Zhao, H. D.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 9631. (g) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Eur. J. Org. Chem.* **2008**, 5329. (h) Chagarovskiy, A. O.; Budynina, E. M.; Ivanova, O. A.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Tetrahedron* **2009**, *65*, 5385.

(7) Wales, S. M.; Walker, M. M.; Johnson, J. S. *Org. Lett.* **2013**, *15*, 2558.

(8) There is a single example of aminocyclopropanes opening by trimethoxybenzene: Gharpure, S. J.; Vijayasree, U.; Reddy, S. R. B. *Org. Biomol. Chem.* **2012**, *10*, 1735. During their recent work on the Friedel–Crafts alkylation of indoles,[7] Johnson and co-workers studied the use of phthalimido-cyclopropanes, but no reactivity was observed under their conditions.

(9) (a) De Simone, F.; Gertsch, J.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5767. (b) De Simone, F.; Saget, T.; Benfatti, F.; Almeida, S.; Waser, J. *Chem.—Eur. J.* **2011**, *17*, 14527. (c) de Nanteuil, F.; Waser, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 12075. (d) Benfatti, F.; de Nanteuil, F.; Waser, J. *Org. Lett.* **2012**, *14*, 386. (e) Benfatti, F.; de Nanteuil, F.; Waser, J. *Chem.—Eur. J.* **2012**, *18*, 4844.

(10) See Supporting Information for a complete list of tested reaction conditions and Lewis acids.

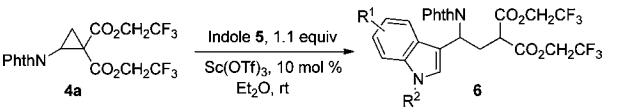
larger naphthylimide **4f** on the cyclopropane did not have a favorable impact on the selectivity. In contrast, modification of the acceptor diester group (cyclopropanes **4g** and **4a**) had a strong influence on the reaction outcome. The best selectivity was obtained using the more electron-withdrawing trifluoro ethanol derivative **4a**, which afforded only the desired product. Finally, replacing the toxic nitromethane by diethyl ether was possible without loss of selectivity.

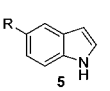
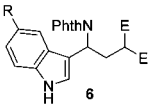
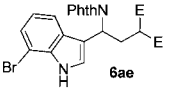
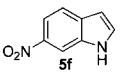
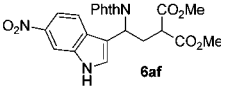
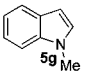
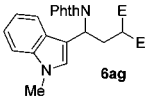
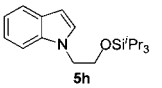
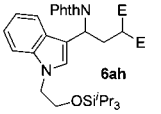
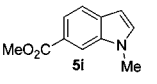
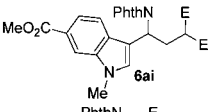
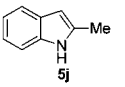
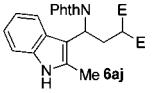
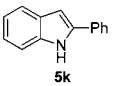
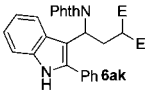
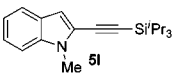
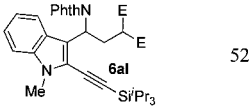
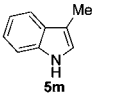
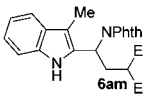
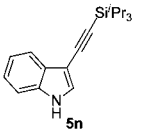
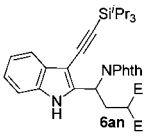
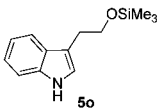
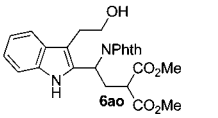
With this simple protocol for the addition of indole to aminocyclopropanes in hand, we investigated the scope of the reaction (Table 1). As showed during optimization, unprotected indole (**5a**) was a suitable partner for the reaction and the product **6aa** could be isolated in 85% yield on a 0.2 mmol scale and in 87% yield on a 2.8 mmol scale, showing that scaling up was straightforward for this transformation (entry 1). Electron-donating (methoxy) and -withdrawing (chloro, bromo and nitro) substituents on the benzene ring were well tolerated (entries 2−6). The compatibility with halogens or a boronic ester is particularly interesting, as the obtained products are easily further functionalized via cross-coupling reactions. Next, the use of *N*-alkyl substituted indoles was investigated (entries 7−9). *N*-Methyl indole (**5g**) afforded the alkylation product **6ag** in 94% yield on a 0.2 mmol scale and in 83% yield on a 2.4 mmol scale (entry 7). A protected alcohol on the *N*-alkyl chain (entry 8) as well as an ester group on the benzene ring (entry 9) were well tolerated. Alkylation of indoles substituted at the position C2 by an alkyl, an aryl or a more sensitive alkynyl[11] functionality was also possible in 52−97% yield (entries 10−12). When C3-substituted indoles were examined as substrates, selective C2-alkylation was observed (entries 13−15). This product is probably formed by C3-alkylation, followed by 1,2-alkyl shift.[6c,12] This result is interesting, as in most reactions of C3-substituted indoles with cyclopropanes, a [3 + 2] annulation occurs preferentially over 1,2-shift.[6b,13] The observed outcome could be due to the ability of the nitrogen substituent to stabilize a partial positive charge during the alkyl shift.

The C2 alkylation was not limited to skatole (entry 13), but the reaction was slower for other substrates, and heating to 60 °C was required to obtain full conversion in the case of 3-alkynyl indole **5n**[14] (entry 14) and protected tryptophol **5o** (entry 15). For the latter, protection of the oxygen was required to prevent side reactions.

Finally, we wondered if this protocol could be extended to other classes of electron-rich aromatic compounds (Figure 1). Although furans and thiophenes were unreactive under these conditions, pyrrole reacted efficiently to

Table 1. Friedel−Crafts Reaction with Aminocyclopropane **4a**[g]



entry	indole	product	yield(%)[a]
			
1	R = H (**5a**)	**6aa**	85 (87)[b]
2	R = Cl (**5b**)	**6ab**	82
3	R = OMe (**5c**)	**6ac**	68
4	R = Bpin (**5d**)	**6ad**	63
5			70
6			58[c]
7			94 (83%)[d]
8			80
9			86
10			97
11			93
12			52
13			82[e]
14			49[f]
15			72[c,f]

[a] E = $CO_2CH_2CF_3$. Reaction conditions: **4a** (0.20 mmol), indole (0.22 mmol), $Sc(OTf)_3$ (0.01 mmol), Et_2O (1.2 mL), rt. [b] Isolated yields. [c] On a 1.5 g scale. [d] Isolated after transesterification (see Supporting Information for more details). [e] On a 1.3 g scale. [f] Reaction in Et_2O at 35 °C. [g] Reaction in toluene at 60 °C.

(11) Obtained in one step by the alkynylation of *N*-methyl indole (**5g**) using a method developed in our group: Tolnai, G. L.; Ganss, S.; Brand, J. P.; Waser, J. *Org. Lett.* **2013**, *15*, 112.

(12) Alternative mechanisms involving direct addition on the C2 position or reversible C3-addition in competition with irreversible C2 addition cannot be completely excluded, but appeared less probable: the former because of the higher electron-density at the C3 position, and the latter as it would require the formation of an highly reactive carbocationic intermediate or a strained cyclopropane.

(13) Xiong, H.; Xu, H.; Liao, S.; Xie, Z.; Tang, Y. *J. Am. Chem. Soc.* **2013**, *135*, 7851.

(14) Obtained in one step by the alkynylation of indole (**5a**) using a method developed in our group: Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346.

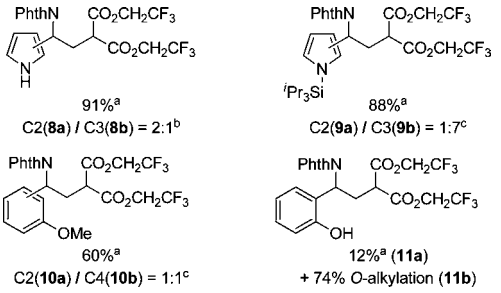


Figure 1. Products of the alkylation of electron-rich aromatic compounds. Reaction conditions: **4a** (0.20 mmol), aromatic compound (0.22 mmol), $Sc(OTf)_3$ (0.01 mmol), Et_2O (1.2 mL), rt. (a) Isolated yield. (b) Ratio of isolated material. (c) Determined by ^1H NMR.

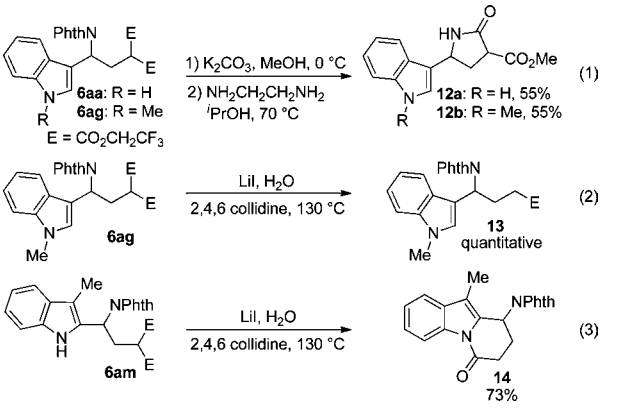
give a 2:1 C2/C3 mixture of regioisomers **8a** and **8b** in 91% yield.[15] Protection of the nitrogen of pyrrole with a triisopropylsilyl group allowed to switch the selectivity and to isolate the C3-alkylated product **9b** with good selectivity. Anisole could also be used, leading to a mixture of *para*/*ortho*-alkylation products **10a** and **10b**. In the case of phenol, product **11b** resulting from *O*-alkylation was the major product. These preliminary results highlight the broad potential of donor–acceptor substituted aminocyclopropanes for the Friedel–Crafts alkylation of electron-rich aromatic compounds.

In order to show that the products are useful synthetic precursors, deprotection of the phthalimide was conducted using diaminoethane in isopropanol after transesterification of the difluoroethanol malonate (Scheme 4, (1)). During this process, the free amine cyclized on the malonic ester giving lactam **12a** and **12b** as a 1:1 ratio of equilibrating diastereoisomers. An efficient access to substituted γ lactams is interesting, as they represent an important class of bioactive natural products and synthetic drugs. Modified Krapcho conditions[16] allowed us to obtain the monoester derivative **13** in quantitative yield (Scheme 4, (2)). When these conditions were applied to C2 adduct **6am**, tricyclic product **14**, which corresponds to the core

(15) These results are in accordance with the lower nucleophilicity of furans and thiophenes as quantified by Mayr's reactivity scale: Mayr, H.; Ofial, A. R. *J. Phys. Org. Chem.* **2008**, *21*, 584.

(16) Kaburagi, Y.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 10246.

Scheme 4. Synthetic Transformations of the Alkylation Products



skeleton of natural products such as eburnamonine (**2**), was isolated in 73% yield (Scheme 4, (3)).

In conclusion, we have shown that phthaloyl protected diester aminocyclopropanes are powerful homo-olefin equivalents in Friedel–Crafts alkylation reactions and readily react with electron-rich aromatic compounds to afford GABA analogues. C2-alkylation was observed for C3-substitued indoles, which is probably the result of C3-alkylation followed by selective shift of the amino-substituted alkyl chain. Finally, the synthetic potential of the products was highlighted by the easy removal of the phthaloyl protecting group, as well as Krapcho decarboxylation. Future works will focus on the development of enantioselective methods, as well as the application of this transformation in the synthesis of bioactive natural products.

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

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