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Indolynes as Electrophilic Indole Surrogates: Fundamental Reactivity and Synthetic Applications

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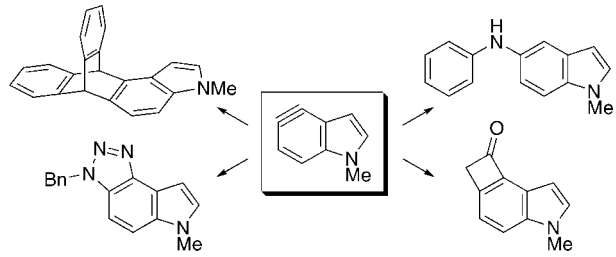
ABSTRACT



A mild method to access a variety of substituted indole derivatives has been developed. The strategy relies on the generation of highly reactive indolyne intermediates, which function as electrophilic indole surrogates.

The indole heterocycle is found in an astonishing number of natural products and medicinal agents.[1,2] More than 10000 biologically active indole derivatives have been discovered to date, with over 200 of these currently being marketed as pharmaceuticals or undergoing clinical trials.[3] In the past century, countless efforts have been devoted to the development of methods that enable the synthesis of functionalized indoles. Although numerous methods for accessing C2- and C3-substituted products from indole building blocks have been discovered, access to C4-, C5-, C6-, or C7-substituted indoles remains a significant challenge.[1]

Our approach to this problem rests opposite the well-known paradigm of indole reactivity. Indoles typically function as excellent nucleophiles that readily participate in electrophilic aromatic substitution reactions (**1** → **2**, Figure 1); in contrast, methods for rendering indoles susceptible to attack by nucleophiles are rare (**1** → **3**).[4] A method for reversing the inherent reactivity of indoles from nucleophilic to electrophilic would be conceptually interesting and could also allow for the preparation of compounds that are difficult to obtain by conventional means. In this paper, we describe an efficient and mild method for accessing electrophilic indole surrogates via the generation of aryne derivatives of indoles, or "indolynes" (i.e., **4**).[5,6]

(1) (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970. (b) Sundberg, R. J. Pyrroles and Their Benzoderivatives: Synthesis and Applications. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, UK, 1984; Vol. 4, pp 313−376. (c) Sundberg, R. J. In *Indoles (Best Synthetic Methods)*; Academic Press: New York, 1996; pp 7−11. (d) Joule, J. A. Indole and its Derivatives. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Thomas, E. J., Ed.; George Thieme Verlag: Stuttgart, Germany, 2000; Category 2, Vol. 10, Chapter 10.13.

(2) Horton, D. A.; Bourne, G. T.; Smyth, M. L. *Chem. Rev.* **2003**, *103*, 893–930.

(3) *MDL Drug Data Report*; MDL Information Systems Inc.: San Leandro, CA.

(4) For the activation of indoles with stoichiometric chromium, see: (a) Semmelhack, M. F.; Rhee, H. *Tetrahedron Lett.* **1993**, *34*, 1399–1402. (b) Semmelhack, M. F.; Knochel, P.; Singleton, T. *Tetrahedron Lett.* **1993**, *34*, 5051–5054. For the Pd-catalyzed enolate arylations of indoles, see: (c) MacKay, J. A.; Bishop, R. L.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 3421–3424. (d) Baudoux, J.; Blake, A. J.; Simpkins, N. S. *Org. Lett.* **2005**, *7*, 4087–4089.

(5) For reviews regarding heteroaromatic arynes, see: (a) Reinecke, M. G. *Tetrahedron* **1982**, *38*, 427–498. (b) Kauffmann, T.; Wirthwein, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 20–33.

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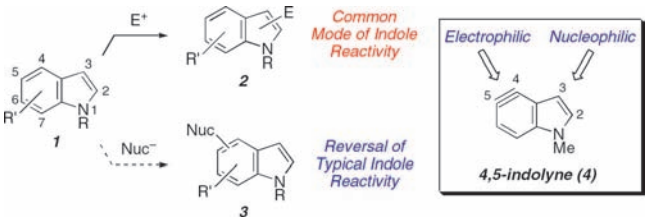


Figure 1. Indolyne **4** as an electrophilic indole surrogate.

Although heteroaromatic arynes have been a subject of debate in the past,[5a] the existence of indolynes has been substantiated by experimental data. In the 1960s, it was found that C3-unsubstituted 4,5-indolyne **6** could be generated from 5-bromoindole (**5**) and KNH_2 in ammonia to afford a complex mixture of products, which upon purification furnished 4- and 5-aminoindole products **7** and **8** (Figure 2).[7] In 2007, the Buszek laboratory demonstrated that C3-substituted indolynes could be generated from dihaloindoles in the presence of butyllithium reagents.[8a] The presumed indolyne intermediates were trapped with furan to afford Diels−Alder products (e.g., **9** + **10** → **12**). Further studies have recently been reported[8b,c] that include indolyne Diels−Alder reactions of substituted furans and cyclopentadiene.

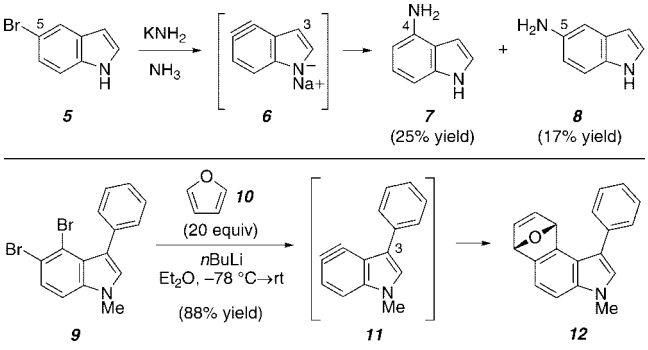


Figure 2. Previous syntheses of indolynes.

Despite these significant advances in the chemistry of indolynes, many areas have remained unexplored, namely (a) the potential to utilize indolynes as building blocks to construct libraries of substituted indoles, (b) the general use of indolynes as electrophilic indole surrogates, and (c) the site preference for nucleophilic attack on indolynes, including its variation as a function of the nucleophile.

To initiate our studies, indolyne **4** was selected as our primary target (Figure 1).[9] Interestingly, indolyne **4** would possess both highly nucleophilic[10] (at C3) and electrophilic[6] (at C4 and C5) sites. As current methods for generating C3-unsubstituted indolynes were relatively harsh for our intended studies (i.e., KNH_2/NH_3 or BuLi),[7,8,11] we sought an alternative method to access the key indolyne species **4**. The approach to arynes by Kobayashi appeared optimal, as it would permit indolyne formation from an indolyl silyltriflate precursor using mild fluoride-mediated conditions.[12]

Although the synthesis of an appropriate indolyl silyltriflate proved challenging,[13] an efficient route was ultimately developed (Scheme 1). Commercially available 5-benzyloxyindole (**13**) was converted to hydroxyindole **14** following a known two-step sequence.[14,15] Next, hydroxyindole **14** was allowed to react with isopropyl isocyanate in the presence of cat. Et_3N to afford carbamate **15**. The net conversion of **13** to carbamate **15** proceeds in 85% yield and requires only one final chromatographic purification event. Following the protocol disclosed by Snieckus and Hoppe,[16] carbamate **15** was lithiated and quenched with TMSCl to provide silyl carbamate **16**.[17] Of note, the relatively acidic C2 proton of the *N*-methylindole is not disturbed in this process, which is testament to the outstanding ortho-directing ability of carbamates.[18] Although initial attempts to elaborate silyl carbamate **16** to silyltriflate **17** in a stepwise fashion were met with difficulty,[19] an efficient one-pot deprotection/triflation sequence proved successful. Our optimized route to silyltriflate **17** can be carried out on multigram scale, and proceeds in 63% overall yield. To confirm that silyltriflate **17** would function as a suitable precursor to the targeted 4,5-indolyne, **17** was reacted with TBAF in the presence of furan (**10**) to afford Diels−Alder product **18** in 85% yield.

(6) For recent reviews regarding aryne chemistry and synthetic applications, see: (a) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701–730. (b) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502–528. (c) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 217–291.

(7) (a) Julia, M.; Huang, Y.; Igolen, J. *C. R. Acad. Sci., Ser. C* **1967**, *265*, 110–112. (b) Igolen, J.; Kolb, A. *C. R. Acad. Sci., Ser. C* **1969**, *269*, 54–56. For related studies, see: (c) Julia, M.; Goffic, F. L.; Igolen, J.; Baillarge, M. *C. R. Acad. Sci., Ser. C* **1967**, *264*, 118–120. (d) Julia, M.; Igolen, J.; Kolb, M. *C. R. Acad. Sci., Ser. C* **1971**, *273*, 1776–1777.

(8) (a) Buszek, K. R.; Luo, D.; Kondrashov, M.; Brown, N.; VanderVelde, D. *Org. Lett.* **2007**, *9*, 4135–4137. (b) Brown, N.; Luo, D.; VanderVelde, D.; Yang, S.; Brassfield, A.; Buszek, K. R. *Tetrahedron Lett.* **2009**, *50*, 63–65. (c) Buszek, K. R.; Brown, N.; Luo, D. *Org. Lett.* **2009**, *11*, 201–204.

(9) Attempts to synthesize 2,3-indolynes have been met without success; see: (a) Muller, H. Dissertation, University of Heidelberg, 1964. (b) Hoffman, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. (c) Conway, S. C.; Gribble, G. W. *Heterocycles* **1992**, *34*, 2095–2108. See also ref 5a.

(10) For the nucleophilicity of *N*-methylindole, see: Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66–77.

(11) During preparation of this manuscript, Buszek and co-workers reported the synthesis of C3-substituted indolyl silyltriflates using a Fischer indolization strategy; see ref 8b.

(12) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, *12*, 1211–1214.

(13) Challenges are primarily associated with the acidity of the C2 hydrogen and the electron-rich nature of the indole ring (e.g., undesired reactivity at C3 and propensity to undergo protodesilylation at C4).

(14) (a) Stadlwieser, J. F.; Dambaur, M. E. *Helv. Chim. Acta* **2006**, *89*, 936–946. (b) Gwaltney, S. L.; et al. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 871–874.

(15) 5-Hydroxyindoles can also be readily prepared by the classic Nenitzescu indole synthesis; for a review, see: Allen, G. R. *Org. React.* **1973**, *20*, 337–454.

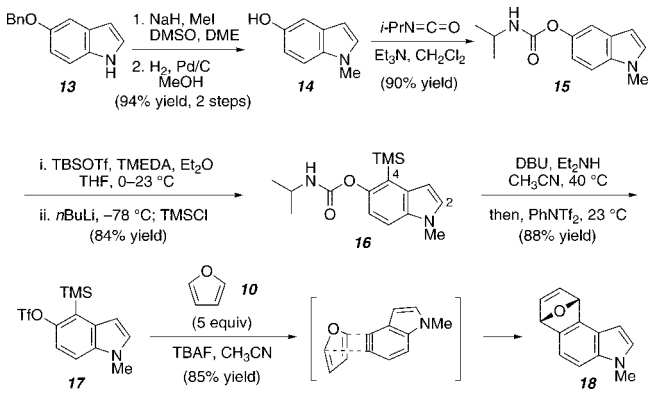
(16) (a) Kauch, M.; Snieckus, V.; Hoppe, D. *J. Org. Chem.* **2005**, *70*, 7149–7158. (b) Kauch, M.; Hoppe, D. *Synthesis* **2006**, 1578–1589.

(17) For the selective C4 lithiation of a related *N*-silylated substrate, see: Griffen, E. J.; Roe, D. G.; Snieckus, V. *J. Org. Chem.* **1995**, *60*, 1484–1485.

(18) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933.

(19) Cleavage of the carbamate of **16** was routinely accompanied by loss of the C4 silyl substituent under a variety of reaction conditions.

Scheme 1. Synthesis of Silyltriflate **17** and Diels−Alder Product **18**



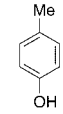
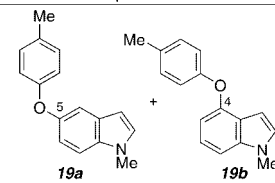
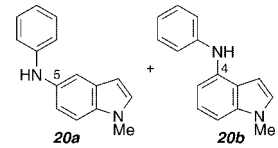
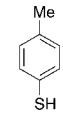
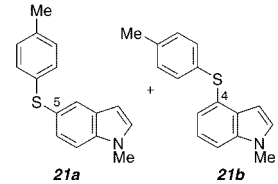
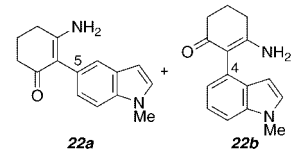
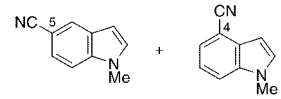
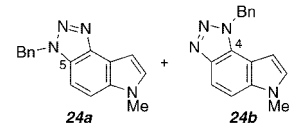
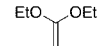
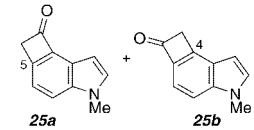
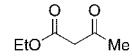
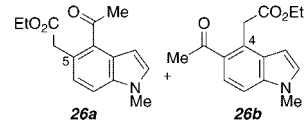
As shown in Table 1, a number of heteroatom- and carbon-based nucleophiles undergo smooth reaction with indolyne **4**, which indeed functions as an electrophilic indole surrogate. Treatment of silyltriflate **17** with either *p*-cresol or aniline, in the presence of CsF, led to the formation of products **19a**,**b** and **20a**,**b** (entries 1 and 2, respectively).[20] In addition, indolyne formation in the presence of *p*-methylthiophenol afforded sulfur-containing products **21a**,**b** (entry 3). With respect to carbon-based nucleophiles, a cyclic β-enaminoketone could be used to prepare monosubstituted indole products **22a**,**b** (entry 4),[21] whereas employment of potassium cyanide afforded cyanoindoles **23a**,**b** (entry 5). The latter result is notable because cyanide has rarely been used in nucleophilic addition reactions to arynes.[22]

Indolyne precursor **17** could also be used in a variety of formal cycloaddition processes to access several unique 4,5-disubstituted indole derivatives. For instance, reaction of benzylazide and silyltriflate **17**, in the presence of TBAF, provided access to indolyltriazoles **24a**,**b** in 86% yield, using a formal aryne [3 + 2] cycloaddition (Table 1, entry 6).[23] Moreover, a formal [2 + 2] cycloaddition provided indolylcyclobutanones **25a**,**b** (entry 7), whereas a variant involving cycloaddition followed by fragmentation provided ketoesters **26a**,**b** (entry 8).[24]

Several salient features of the reactions shown in Table 1 should be noted: (a) the diverse collection of compounds synthesized demonstrates the potential to utilize silyltriflate **17** as a common precursor to a library of substituted indole derivatives; (b) many of the products obtained would not be readily accessible by conventional means; (c) the C3 position in all products remains unfunctionalized, and thus could be easily substituted if so desired; (d) high-yielding access to these compounds is only made possible by the mild reaction conditions employed; most of the trapping agents and products shown in Table 1 would not be stable to more basic butyllithium or amide base conditions for indolyne generation; and (e) each of the examples shown reflect an interesting general preference for initial nucleophilic attack at C5 of the presumed indolyne intermediate **4** with selectivity as high as 12.5:1 (entry 2).

With the goal of accessing additional 4,5-disubstituted indole products, the propensity of indolyne **4** to participate in Diels−Alder reactions was investigated (Table 2). We were delighted to find that *N*-Boc-pyrrole and cyclopenta-

Table 1. Synthetic Applications of Indolynes

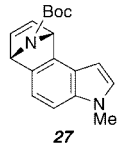
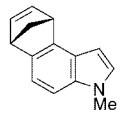
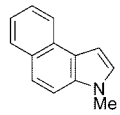
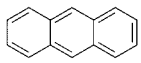
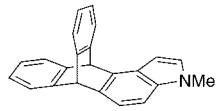
entry	trapping agent	products	yield (ratio)
1[a]		 **19a** **19b**	*80% yield* (3:1)
2[a]		 **20a** **20b**	*91% yield* (12.5:1)
3[a]		 **21a** **21b**	*88% yield* (2:1)
4[b]		 **22a** **22b**	*58% yield* (10:1)
5[a]	KCN	 **23a** **23b**	*85% yield* (3.3:1)
6[c]	N_3−Bn	 **24a** **24b**	*86% yield* (2.4:1)
7[d]		 **25a** **25b**	*86% yield* (5.5:1)
8[e]		 **26a** **26b**	*68% yield* (2:1)

[a] Conditions: **17**, CsF, CH_3CN, 50 °C. [b] Conditions: **17**, CsF, CH_3CN, 40 °C. [c] Conditions: **17**, TBAF, CH_3CN, 23 °C. [d] Conditions: **17**, CsF, CH_3CN, 23 °C. [e] Conditions: **17**, CsF, CH_3CN, 80 °C.

(20) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198–3209.
(21) Ramtohul, Y. K.; Chartrand, A. *Org. Lett.* **2007**, *9*, 1029–1032.
(22) Scardiglia, F.; Roberts, J. D. *Tetrahedron* **1958**, *3*, 197–208.
(23) (a) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409–2412. (b) Campbell-Verduyn, L.; Elsinga, P. H.; Mirfeizi, L.; Dierckx, R. A.; Feringa, B. L. *Org. Biomol. Chem.* **2008**, *6*, 3461–3463.
(24) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340–5341.

diene could also be used to trap indolyne **4**, thus affording adducts **27** and **28** (entries 1 and 2). In addition, reaction in the presence of α-pyrone produced benzoindole **29** (entry 3), presumably via a Diels−Alder/retro-Diels−Alder process with concomitant loss of CO_2. Finally, trapping of indolyne **4** with anthracene furnished indolyltriptycene **30** in good yield (entry 4).

Table 2. Diels−Alder Reactions of Indolyne **4**

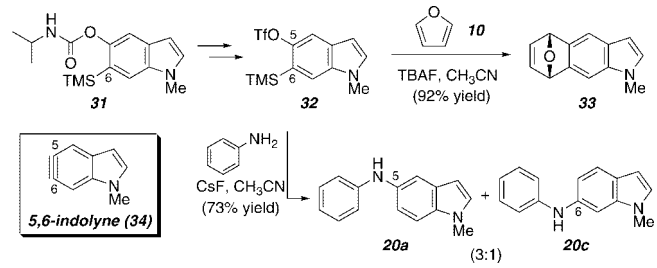
entry	trapping agent	products	yield
1[a]		 **27**	*83% yield*
2[a]		 **28**	*65% yield*
3[b]		 **29**	*85% yield*
4[c]		 **30**	*72% yield*

[a] Conditions: **17**, TBAF, CH_3CN, 23 °C. [b] Conditions: **17**, CsF, CH_3CN, 100 °C. [c] Conditions: **17**, CsF, CH_3CN, 80 °C.

The potential to synthesize 5,6-indolyne **34** was also explored as a means to further study the generation and reactivity of indolynes (Scheme 2). Fortunately, it was possible to access indolyne precursor **32** from silyl carbamate **31** in a straightforward manner.[25] With silyltriflate **32** available, we investigated formation of indolyne **34**. Upon treatment of **32** with TBAF in the presence of furan (**10**), Diels−Alder reaction took place to provide cycloadduct **33** in 92% yield. Additionally, reaction of silyltriflate **32** with CsF and aniline resulted in the formation of a 3:1 mixture of **20a** and **20c**, reflecting a curious preference for attack of aniline at C5 of indolyne **34**. That a preference is observed in this case suggests that the origin of selectivity in the attack of indolynes is likely not controlled strictly by steric factors. The subtle factors that govern the observed selectivity are currently under active investigation in our laboratory.

(25) See the Supporting Informationfor details.

Scheme 2. Preparation of 5,6-Indolyne **34** and Related Studies



In summary, we have developed an efficient new method for accessing a variety of substituted indole derivatives. Our strategy relies on the generation of highly reactive indolyne intermediates, which function as electrophilic indole surrogates. These studies have shown, for the first time, that nucleophilic addition to 4,5- and 5,6- indolynes occurs with a general preference for attack at C5. Studies geared toward the synthesis of complex molecules using indolynes as surrogates for electrophilic indoles are currently underway in our laboratory, as are efforts to obtain a fundamental understanding of selectivity in nucleophilic addition reactions to indolynes.

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Supporting Information Available: Detailed experimental details and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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