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The reaction of arynes with münchnones: synthesis of isoindoles and azaisoindoles

Justin M. Lopchuk, Gordon W. Gribble *

Department of Chemistry, Dartmouth College, Hanover, NH 03755-3564, USA

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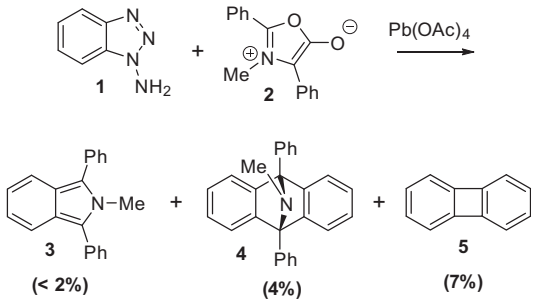
ABSTRACT

Arynes derived from silyltriflate precursors undergo a smooth 1,3-dipolar cycloaddition with münchnones to furnish isoindoles and azaisoindoles in moderate to high yields. Modification of the fluoride source, solvent, and temperature allows for the selective generation of either isoindoles or benzanthracenimines, the latter of which serve as precursors to polycyclic aromatic hydrocarbons.

Modern methods for the mild generation of arynes have facilitated their resurgence as powerful synthetic intermediates capable of engaging in a wide variety of chemistries.[1] In particular, arynes are willing partners in 1,3-dipolar cycloadditions with a variety of dipoles including azides,[2] sydnones,[3] azomethine ylides,[4] nitrones,[5] nitrile oxides,[6] and nitrosoarenes.[7] More recent efforts have demonstrated their effectiveness in natural product synthesis.[8]

As a part of our ongoing interest in the chemistry of münchnones,[9] we began to investigate the possibility of using these mesoionic heterocycles with arynes derived from silyltriflates as a mild route to isoindoles. Such a method would provide a useful alternative to traditional preparations of isoindoles which often require harsh conditions for their synthesis.[10] Kato described an initial attempt to generate isoindoles from arynes and münchnones (Scheme 1); however, the arynes were generated via the oxidative fragmentation of 1-aminobenzotriazole (**1**).[3a] These conditions proved too harsh for the münchnones and resulted in only a trace of desired isoindole **3** along with benzanthracenimine **4** and biphenylene (**5**). It is notable that the researchers successfully converted sydnones, a related and typically more stable mesoionic heterocycle, to indazoles under the same oxidative conditions.

The successful development of this reaction between arynes and münchnones is complicated by a number of factors: the münchnones are sensitive to nucleophilic conditions (which are required to generate the aryne), the newly generated isoindole will readily react with arynes, perhaps in preference to the münchnones, and isoindoles are often unstable to isolation. Despite these perceived difficulties, we now describe the successful reaction of arynes with münchnones to afford a practical synthesis of isoindoles and azaisoindoles.



Scheme 1. Reaction of arynes with münchnones (Kato).[3a]

Münchnone precursors **6**–**9** were prepared as previously described[9] and cyclized in situ by treatment with *N*,*N*′-diisopropylcarbodiimide (DIPC) in dry THF or MeCN (Scheme 2).

We began our investigations by subjecting unsubstituted aryne precursor **13** and münchnone **10** to *n*-Bu_4NF (TBAF) at room temperature. Unfortunately, after 24 h this resulted in a 1:1 mixture of isoindole **15** and benzanthracenimine **16**, along with unreacted silyltriflate **13**. A screen of fluoride sources identified CsF, TBAT, and TAS-F as the most promising since they delivered isoindole

* Corresponding author. Tel.: +1 603 646 3118; fax: +1 603 646 3946.
E-mail address: ggribble@dartmouth.edu (G.W. Gribble).

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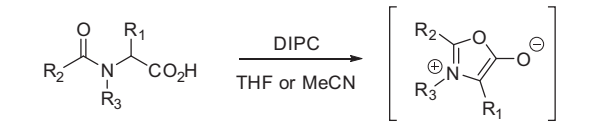
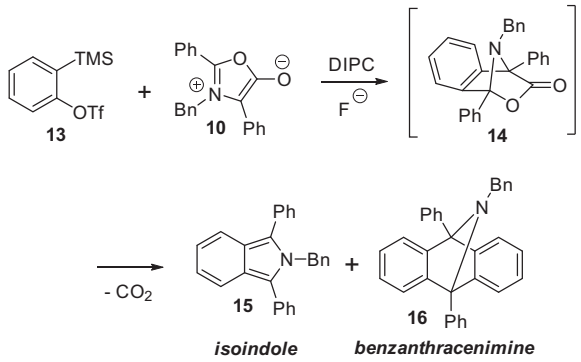


6: $R_1 = R_2 = Ph$, $R_3 = Bn$
7: $R_1 = R_2 = Ph$, $R_3 = Me$
8: $R_1 = Me$, $R_2 = Ph$, $R_3 = Bn$
9: $R_1 = Ph$, $R_2 = Me$, $R_3 = Bn$

10: $R_1 = R_2 = Ph$, $R_3 = Bn$
2: $R_1 = R_2 = Ph$, $R_3 = Me$
11: $R_1 = Me$, $R_2 = Ph$, $R_3 = Bn$
12: $R_1 = Ph$, $R_2 = Me$, $R_3 = Bn$

Scheme 2. Cyclization of münchnone precursors **6**–**9**.



Scheme 3. Reaction of arynes with münchnones (this work).

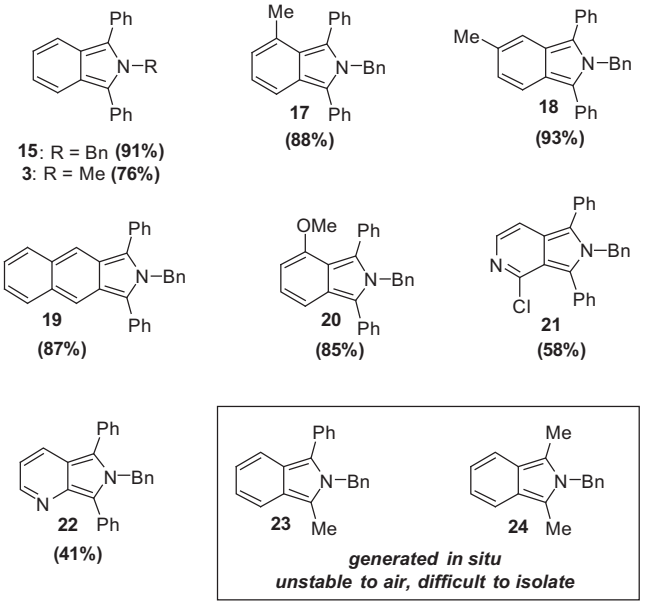


Figure 1. Scope of isoindole and azaisoindole synthesis.

15 in high yields with only minor amounts of benzanthracenimine **16** (Scheme 3).[11]

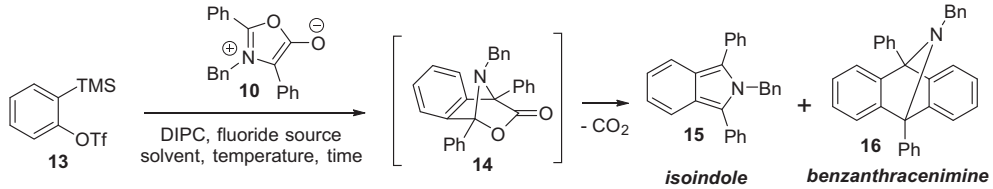
Conditions were also optimized to provide exclusive formation of the benzanthracenimines (Table 1, entries 4 and 7); these compounds are known to serve as useful precursors to polyaromatics via deamination reactions.[12]

The reaction was successful for all arynes and münchnones tested; isoindoles were obtained in high yields, while azaisoindoles **21** and **22** were synthesized in moderate yields from the corresponding pyridyne precursors (Fig. 1).[13]

Since naphthalene derivative **19** was fairly unstable, it was characterized by conversion to dione **26** under air or silica gel or alternatively by trapping with a second equivalent of **25** to yield adduct **27** (Scheme 4). Isoindoles **23** and **24** were generated in situ, but decomposed rapidly upon any purification attempts. As such, **23** was trapped with dimethyl acetylenedicarboxylate (DMAD) to furnish **28** in 78% from münchnone **11** and 51% from münchnone **12** (Scheme 5).

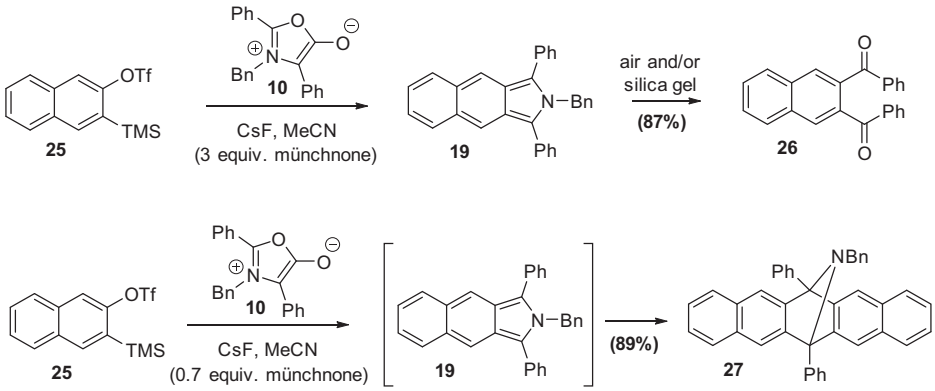
In summary, we have developed a mild synthesis of isoindoles and azaindoles from the reaction of arynes and münchnones in moderate to high yields. Despite the potential difficulties, the reaction is made possible by the use of anhydrous conditions and a mild nucleophile in fluoride which is both compatible with the münchnone and able to generate the aryne; furthermore, an excess of münchnone and room temperature conditions allow for the selective formation and isolation of the labile isoindoles. It is also noteworthy that the reaction conditions can be tuned to deliver either the isoindole or benzanthracenimine by the choice of fluoride source and solvent.

Table 1
Optimization of the reaction between silyltriflate **13** and münchnone **10**[14–25]

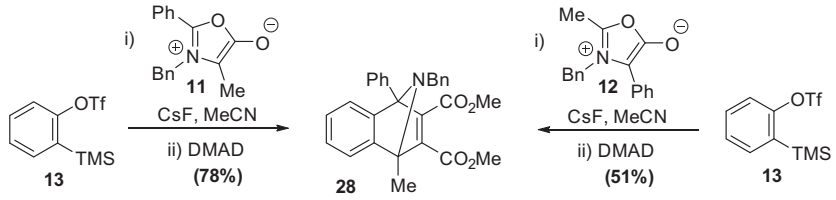


Entry	Münchnone (equiv)	Fluoride[a]	Solvent	Temp	Time (h)	Isoindole[b] (%)	Benzanthracenimine[b] (%)
1	3	TBAF (s)	THF	rt	24	23	22
2	3	TBAF (l)	THF	rt	24	54	11
3	3	CsF	THF	rt	24	45	7
4	3	TBAF (l)	THF	70 °C	24	0	61
5	3	CsF	THF	70 °C	24	48	2
6	3	KF/18-c-6	MeCN	rt	24	73	11
7	0.7	TBAF (l)	THF	rt	24	0	68
8	0.7	CsF	THF	rt	24	14	48
9	3	CsF	MeCN	rt	24	91	4
10	3	CsF	MeCN	70 °C	12	85	11
11	1.5	CsF	MeCN	rt	24	17	78
12	3	TBAF (l)	MeCN	70 °C	24	45	19
13	3	TBAT	MeCN	rt	12	90	5
14	3	TAS-F	MeCN	rt	12	91	3

[a] TBAF = tetra-*n*-butylammonium fluoride; TBAT = tetrabutylammonium difluorotriphenylsilicate; TAS-F = tris(dimethylamino)sulfonium difluorotrimethylsilicate.
[b] Yields based on isolated products after column chromatography.



Scheme 4. Conversion of **19**–**26** and **27**.



Scheme 5. Trapping of isoindole **23** with DMAD.

Acknowledgements

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14. *General procedure for the synthesis of isoindoles:* A round bottomed flask was charged with the münchnone precursor **6**–**9** (3 equiv), silyltriflate (1 equiv), and MeCN under nitrogen. DIPC (3 equiv) was added via syringe and the mixture stirred 5–10 min. The fluoride source—all yields below use CsF—(2.5 equiv) was added and the mixture stirred 12–24 h until the silyltriflate was consumed. The reaction mixture was concentrated and purified directly by flash chromatography (silica gel, 0–10% ethyl acetate in pentane) to afford the isoindole. Note the CsF was oven-dried overnight (>120 °C) prior to use.
15. *2-Benzyl-1,3-diphenyl-2H-isoindole* (**15**): Orange solid (91%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, 2H, J = 2.9, 6.6 Hz), 7.45–7.31 (m, 10H), 7.09–7.07 (m, 3H), 6.98 (dd, 2H, J = 2.9, 6.6 Hz), 6.60–6.56 (m, 2H), 5.54 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 132.6, 130.7, 128.9, 128.6, 128.1, 127.4, 126.3, 125.7, 123.4, 122.3, 119.9, 49.7; HRMS (ESI$^+$) calcd for $C_{27}H_{22}N$ (MH^+) 360.1752, found 360.1755.
16. *11-Benzyl-9,10-diphenyl-9,10-dihydro-9,10-epimino-anthracene* (**16**): White solid (68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, 4H, J = 7.1 Hz), 7.43–7.30 (m, 10H), 7.10–7.04 (m, 4H), 6.83–6.78 (m, 3H), 6.58–6.55 (m, 2H), 3.53 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 140.8, 134.4, 130.8, 128.6, 128.5, 128.0, 127.3, 125.6, 125.4, 123.5, 82.0, 48.5; HRMS (ESI$^+$) calcd for $C_{33}H_{26}N$ (MH^+) 436.2065, found 436.2067.
17. *2-Methyl-1,3-diphenyl-2H-isoindole* (**3**): Colorless oil (76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (dd, 2H, J = 3.2, 6.6 Hz), 7.35 (d, 4H, J = 7.3 Hz), 7.22 (t, 4H, J = 7.8 Hz), 7.12–7.07 (m, 2H), 7.03 (dd, 2H, J = 3.2, 6.6 Hz), 3.26 (s, 3H); known compound.[22]
18. *2-Benzyl-4-methyl-1,3-diphenyl-2H-isoindole* (**17**): Pale yellow oil (88%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, 3H, J = 1.7, 8.3 Hz), 7.48 (t, 3H, J = 7.1 Hz), 7.44–7.36 (m, 6H), 7.17 (dd, 2H, J = 2.2, 4.9 Hz), 6.98 (dd, 1H, J = 6.6, 8.7 Hz), 6.80 (d, 1H, J = 6.6 Hz), 6.67–6.64 (m, 2H), 5.40 (s, 2H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 134.9, 134.2, 134.1, 132.8, 130.8, 128.9, 128.5, 128.3, 127.8, 127.4, 127.3, 126.3, 124.6, 124.0, 123.3, 122.9, 122.1, 121.9, 117.8, 49.4, 21.2; HRMS (ESI$^+$) calcd for $C_{28}H_{24}N$ (MH^+) 374.1909, found 374.1910.
19. *2-Benzyl-5-methyl-1,3-diphenyl-2H-isoindole* (**18**): Pale yellow oil (93%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.28 (m, 12H), 7.08–7.05 (m, 3H), 6.84 (d, 1H, J = 8.8 Hz), 6.58–6.56 (m, 2H), 5.51 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 136.4, 132.6, 131.5, 130.6, 130.5, 128.8, 128.5, 128.4, 127.3, 127.2, 127.1, 126.2, 125.2, 124.8, 123.9, 123.6, 122.6, 119.7, 117.7, 49.6, 22.2; HRMS (ESI$^+$) calcd for $C_{28}H_{24}N$ (MH^+) 374.1909, found 374.1909.
20. *2-Benzyl-4-methoxy-1,3-diphenyl-2H-isoindole* (**20**): Pale yellow semisolid (85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.27 (m, 11H), 7.15 (d, 1H, J = 8.5 Hz), 7.06 (dd, 2H, J = 2.0, 5.0 Hz), 6.89 (t, 1H, J = 7.3 Hz), 6.54–6.51 (m, 2H), 6.23 (d, 1H, J = 7.3 Hz), 5.38 (s, 2H), 3.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 138.7, 133.5, 132.7, 132.0, 130.7, 128.7, 128.4, 127.4, 127.3, 127.1, 126.2, 124.9, 124.7, 124.5, 122.2, 112.2, 109.9, 98.4, 55.1, 49.4; HRMS (ESI$^+$) calcd for $C_{28}H_{24}NO$ (MH^+) 390.1858, found 390.1850.
21. *2-Benzyl-4-chloro-1,3-diphenyl-2H-pyrrolo[3,4-c]pyridine* (**21**): Yellow oil (58%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, 1H, J = 6.1 Hz), 7.44–7.31 (m, 10H), 7.28 (d, 1H, J = 6.1 Hz), 7.14–7.12 (m, 3H), 6.55 (d, 2H, J = 7.1 Hz), 5.35 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.2, 137.5, 136.1, 134.4, 132.9, 132.4, 130.6, 129.9, 129.1, 129.0, 128.9, 128.8, 128.7, 128.4, 128.3, 128.0, 127.6, 126.2, 113.1, 49.8; HRMS (ESI$^+$) calcd for $C_{26}H_{20}N_2Cl$ (MH^+) 395.1315, found 395.1309.
22. *6-Benzyl-5,7-diphenyl-6H-pyrrolo[3,4-b]pyridine* (**22**): Yellow oil (41%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, 1H, J = 7.3 Hz), 7.64–7.08 (m, 16H), 5.13 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 149.0, 141.2, 137.6, 137.0, 132.9, 132.0, 129.9, 129.0, 129.0, 128.9, 128.8, 128.4, 127.9, 124.5, 115.5, 48.8; HRMS (ESI$^+$) calcd for $C_{26}H_{21}N_2$ (MH^+) 361.1705, found 361.1701.

23. *Naphthalene-2,3-diylbis(phenylmethanone)* (**26**): White solid (87%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 2H), 7.96–7.93 (m, 2H), 7.83–7.80 (m, 4H), 7.69–7.65 (m, 2H), 7.55 (t, 2H, J = 7.3 Hz), 7.42 (t, 4H, J = 7.3 Hz). Known compound.[23]
24. *15-Benzyl-6,13-diphenyl-6,13-dihydro-6,13-epiminopentacene* (**27**): Pale orange solid (89%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, 4H, J = 7.3 Hz), 7.85 (s, 4H), 7.77 (dd, 4H, J = 3.2, 6.2 Hz), 7.51 (t, 4H, J = 7.8 Hz), 7.44 (dd, 6H, J = 3.2, 6.2 Hz), 6.86–6.84 (m, 3H), 6.65–6.63 (m, 2H), 3.63 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 140.7, 137.8, 134.5, 132.5, 130.8, 128.8, 128.3, 128.0, 127.4, 126.3, 125.5, 122.1, 80.9, 48.6; HRMS (ESI$^+$) calcd for $C_{41}H_{30}N$ (MH^+) 536.2378, found 536.2378.
25. *Dimethyl 9-benzyl-1-methyl-4-phenyl-1,4-dihydro-1,4-epiminonaphthalene-2,3-dicarboxylate* (**28**): After completion of isoindole formation, the reaction was cooled to 0 °C and DMAD (10 equiv) was added via syringe. Stirred 1 h, concentrated in vacuo, and directly purified by flash chromatography. Clear oil (78% for münchnone **87**; 51% for münchnone **88**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59–7.09 (m, 14H), 5.01 (s, 2H), 3.75 (s, 3H), 3.70 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 137.5, 136.0, 132.7, 131.3, 129.8, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.3, 128.2, 128.0, 127.7, 110.1, 78.8, 74.0, 52.4, 49.5, 26.7; HRMS (ESI$^+$) calcd for $C_{28}H_{25}NO_4$ (MH^+) 440.1862, found 440.1860.