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A GENERAL SYNTHESIS OF ARYL[2,3-a]QUINOLIZIN-2-ONES

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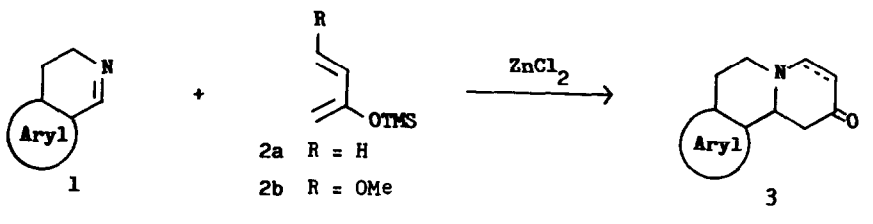
Abstract - A convenient and general synthesis of arylquinolizines utilizing a hetero Diels-Alder reaction is described.

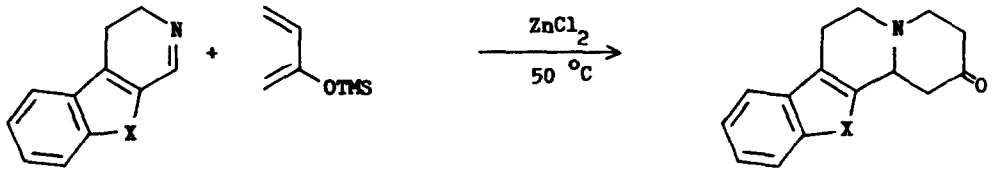
The arylquinolizine ring system, represented by **3**, is common to many naturally occurring alkaloids.[1,2] The interesting biological activity of many of these compounds and their synthetic derivatives have generated considerable effort directed toward the construction of this system.[3] Benzoquinolizines have been synthesized by the condensation of 3,4-dihydroisoquinolines with methyl vinyl ketones[4] while the corresponding indole derivative has been made from tryptamine via a lengthy sequence.[5]

We now wish to report a convenient and general synthesis of aryl[2,3-a]quinolizin-2-ones via an imino Diels-Alder reaction.[6] This approach exploits the observations by Danishefsky that acyclic imines undergo a zinc chloride catalyzed cyclocondensation with 1-methoxy-3-trimethylsiloxy-1,3-butadiene (**2b**, R = OMe) to give 5,6-dihydro-γ-pyridones.[7] We found that both 2-trimethylsiloxy-1,3-butadiene (**2a**, R = H) and its methoxy derivative **2b** reacted readily with 3,4-dihydroarylpyridines **1** and one eq. of zinc chloride in acetonitrile to yield arylquinolizin-2-ones **3**. No cyclocondensation occurs in the absence of Lewis acid.

We examined first the condensation between siloxy diene **2a** and 3,4-dihydroindolo[2,3-c]pyridine **1a**[4] in THF (50 °C) (Table I). After 5 h no reaction had occurred. When the same reaction was attempted



in acetonitrile (50 °C, 4 h) ketone **3a** was isolated in 55% yield. This solvent effect has been reported by Akiba.[8] He observed that silyl enol ethers reacted poorly with isoquinolium salts in THF while a high yield was obtained in acetonitrile. Compound **3a** has recently been converted to the natural product yohimbine by Kametani.[5] Both the benzofuran **1b**[9] (50 °C, 1 h, 41%) and the corresponding benzothiophene **1c**[10] (50 °C, 4 h, 30%) reacted in an analogous fashion with **2a** to give the novel ketones **3b** and **3c**.



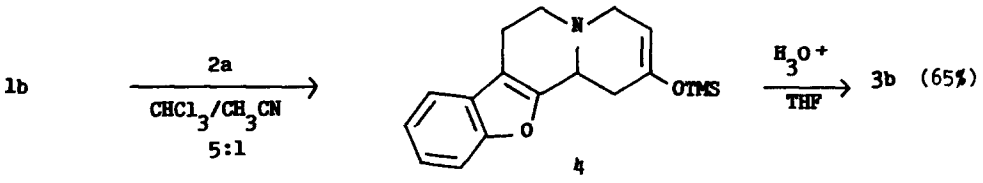
1a[4] X = NH **2a** **3a**[5] X = NH
1b[9] X = O **3b** X = O
1c[10] X = S **3c** X = S

Table 1

Arylpyr	Solvent	Rxn Time (h)	% Yield[(a),13]
1a	THF	5	—
1a	CH_3CN	4	55
1b	CH_3CN	1	41
1c	CH_3CN	4	30

[(a)]Yields are of chromatographed products.

The yield of **3b** was improved by carrying out the reaction in a mixture of chloroform/acetonitrile (5:1) at 0 °C using 1 eq. of boron trifluoride etherate as catalyst. After 5 min, the solution was poured into saturated bicarbonate and worked up[11] to give silyl enol ether **4** as the sole product. Compound **4** was converted to ketone **3b** (5% HCl/THF, 1:1, 65%).



Compounds **1a-c** also reacted with diene **2b**, and the results are summarized in Table 2. Upon comparison with **2a**, siloxybutadiene **2b** proved to be much more reactive. Reaction times were shorter and the reactions could be carried out at ambient temperature. Both THF and chloroform were suitable solvents and, as before, the cyclocondensation was facilitated by acetonitrile.

This methodology offers an expeditious route to arylquinolizines which allows for variation in both the aryl-ring and carbon framework simply by choosing the appropriate dihydroarylpyridine and butadiene.[12] A typical procedure follows.

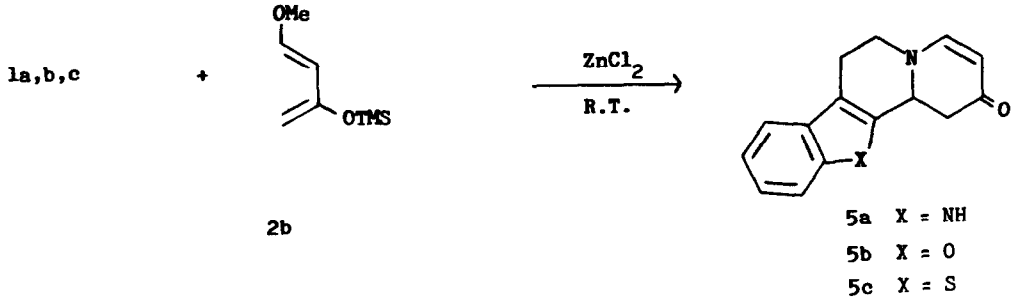


Table 2

Arylpyr	Solvent	Rxn Time	% Yield[a]
1a	THF	5 h	39
1a	CH_3CN	1 h	43
1a	CH_3CN	30 min[b]	39
1b	THF	1 h	73
1b	$CHCl_3$	1 h	71
1b	CH_3CN	5 min	65
1c	CH_3CN	1 h	62

[a]Yields are of chromatographed products.
[b]Reaction carried out at 50 °C.

To a solution of the dihydroarylpyridine in the solvent (ca. 0.1 M) is added zinc chloride (1 eq.) followed by siloxybutadiene (1.3 eq.). The reaction is stirred at the appropriate temperature and aliquots are periodically removed, worked up (see below), and monitored by TLC (EtOAc). When the reaction is complete, 5% HCl is added. The reactants are stirred for 10 min, made basic, and extracted into methylene chloride. The crude residue is chromatographed to give pure product.[13]

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13. Spectral data for: **3a** IR ($CHCl_3$) 1715 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ 8.00 (1 H), 7.5-7.0 (4 H, m), 3.53 (1 H, d, J = 12 Hz); m/e 240 (M^+), 239 (M^+-1); mp 179-180 °C (lit. mp 180-181 °C (5)). **3b** IR ($CHCl_3$) 2800, 2750, 1720 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ 7.5-7.4 (2 H, m), 7.3-7.2 (2 H, m), 3.63 (1 H, d, J = 13.5); m/e 241 (M^+); mp 107-109 °C. **3c** IR ($CHCl_3$) 1715 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ 7.8-7.1 (4 H, m), 3.70 (1 H, d, J = 12 Hz), 3.30-2.30 (10 H, m); m/e 257 (M^+), 256 (M^+-1); mp 122.5-124 °C. **5a** IR ($CHCl_3$) 1645, 1580 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ 9.76 (1 H, s), 7.55-7.0 (5 H, m), 4.97 (d, J = 7.5 Hz), 4.76 (1 H, dd, J = 15, 5 Hz); m/e 238 (M^+), 237 (M^+-1); mp 232-233 °C. **5b** IR ($CHCl_3$) 1645, 1590 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) 7.5-7.25 (4 H, m), 7.20 (1 H, d, J = 7.5 Hz), 5.10 (1 H, d, J = 7.5 Hz), 4.8 (1 H, br d, J = 15 Hz); m/e 239 (M^+); mp 107-109 °C. **5c** IR ($CHCl_3$) 1635, 1580 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ 7.83-7.3 (4 H, m), 7.13 (1 H, d, J = 7.5 Hz), 5.05 (1 H, d, J = 7.5 Hz), 4.83 (1 H, dd, J = 13, 6.5 Hz), 3.8-3.3 (2 H, m), 3.2-2.6 (4 H, m); m/e 255 (M^+); mp 182-183 °C.

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