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A SIMPLIFIED ISOQUINOLINE SYNTHESIS

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Abstract—A simple variation of the Pomeranz-Fritsch cyclization provides a short, efficient route to isoquinolines. Treatment of benzylic halides or mesylates **1** with the sodium anion of N-tosyl aminoacetaldehyde dimethyl acetal (**2**) followed by acid-catalyzed cyclization provides an effective, two-step preparation of isoquinolines **4**.

Of the many methods available for the preparation of isoquinoline alkaloids,[2-4] including the well-known Bischler-Napieralski cyclization[3a] (affords dihydroisoquinolines) and the Pictet-Spengler ring closure[3b] (yields tetrahydroisoquinolines), only the Pomeranz-Fritsch cyclization[3c] provides a general and direct method for the construction of a fully unsaturated isoquinoline. The original procedure, devised independently by Pomeranz and Fritsch,[3c] involves two steps: imine formation between an aromatic aldehyde and aminoacetaldehyde dimethyl acetal followed by acid-catalyzed cyclization, Fig. 1. The documented difficulties involved with the mineral acid catalyzed cyclization of benzylideneamino-acetals has encouraged the use of alternative cyclization agents[3d] and the investigation of related, but improved, methods. A notable two-step modification devised by Schlittler and Muller[3a] involves imine formation between a benzylamine and glyoxal semiacetal followed by acid-catalyzed cyclization, Fig. 1. Despite these and other efforts to implement effectively a two-step Pomeranz-Fritsch cyclization for the preparation of isoquinolines, the low yields, harsh conditions, and numerous side products that accompany the direct cyclization of imines has required the development of more useful procedures.

Subsequent modifications have been developed and all involve the acid-catalyzed cyclization of benzylamino-acetals[2d-f] (reduced benzylideneamino-acetals) and as such require the dehydrogenation of the resultant dihydroisoquinolines. A common problem, attenuating the low yields and unavoidable side products in these processes, is the evaluation or isolation of the cyclization product(s)—a mixture of isoquinoline, tetrahydroisoquinoline and dihydroisoquinoline. The difficulties encountered in using these procedures in the laboratory prompted Bobbit *et al.*[3f] to introduce an improved, but longer modification. Mild cyclization of benzylamino-acetals with *in situ* reduction affords the stable and isolable tetrahydroisoquinolines. Subsequent, though not always simple, dehydrogenation gives the fully unsaturated isoquinolines. Though this work has served as a cornerstone for the recent Pomeranz-Fritsch type preparation of many simple isoquinolines, the overall length of this indirect procedure detracts from its laboratory success.

In a recent attempt to minimize the side products produced in the cyclization of benzylamino-acetals, Jackson *et al.* employed N-tosyl benzylamino-acetals.[3g] Importantly, they discovered that the immediate cyclization product, N-tosyl dihydroisoquinoline, often loses

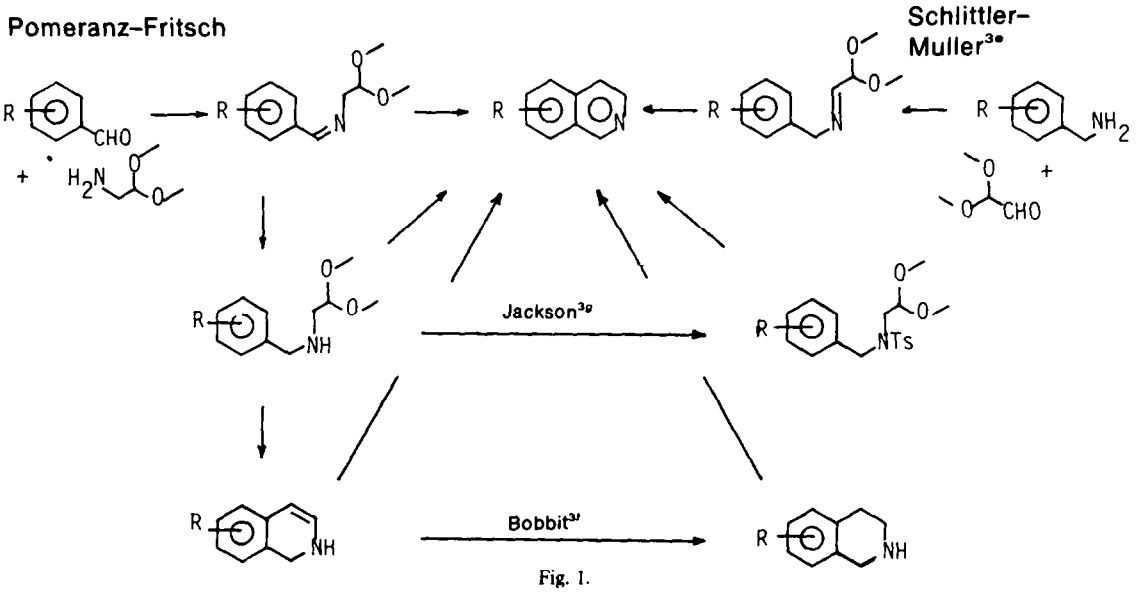


Fig. 1.

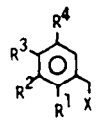
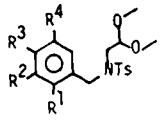
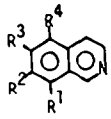
p-toluenesulfonic acid under the reaction conditions and affords directly the desired isoquinoline. A complete investigation of the acid-catalyzed cyclization of N-tosyl benzylamino-acetals revealed the generality of this procedure.[3g]

However, in the process of improving the original Pomeranz–Fritsch synthesis of isoquinolines (two steps, low yields), the modified sequences, Fig. 1, now entail 4–5 steps/reactions and several days for execution countering the improved yields.

Our current interest in the preparation of isoquinoline alkaloids[5] and an evaluation of this past work has led us to devise and develop a practical, *two-step* preparation of isoquinolines. This process is outlined in Scheme 1.

Treatment of benzylic halides or mesylates **1** with the sodium anion of N-tosyl aminoacetaldehyde dimethyl acetal (**2**) followed by the acid-catalyzed cyclization of **3** provides an efficient preparation of isoquinolines **4**. Typical results are detailed in Table 1. Benzylic mesylates[6] and iodides are sufficiently reactive to be displaced by the sodium anion of **2** in tetrahydrofuran at 25°; benzylic bromides react slowly, though the rate may be accelerated by the addition of sodium iodide, and benzylic chlorides are unreactive under these conditions.

Table 1. A simple isoquinoline synthesis

Benzylic halide or mesylate	Product 3 Yield[a] (conditions)	Isoquinoline 4 Yield[a] ( )[b], time
		
1a: R^1=H, R^2=R^3=R^4=OCH_3, X=Br	94% (1 h, DMF, 25°C) 77% (96 h, THF, 25°C)[c] 85% (24 h, THF, 1.5 equiv NaI, 25°C)[c]	**4a**, 80% (98), 24 h
1b: R^1=H, R^2=R^3=R^4=OCH_3, X=I	85% (12 h, THF, 25°C)	
1c: R^1=Br, R^2=R^3=R^4=OCH_3, X=OMs	96% (3 h, THF, 25°C)[d,e]	**4c**,[e] 83%[f]
1d: R^1=Br, R^2=R^3=R^4=OCH_3, X=Br	92% (2 h, DMF, 25°C)[c] 71% (72 h, THF, 25°C)[c]	
1e: R^1=R^4=H, R^2=R^3=OCH_3, X=Br	79% (2 h, DMF, 25°C)[d]	**4e**, 81% (90), 24 h
1f: R^1=R^4=H, R^2=R^3=OCH_3, X=Cl	72% (1 h, DMF, 25°C) 0% (48 h, THF, 25°C)	
1g: R^1=R^4=H, R^2/R^3=OCH_2O, X=Br	95% (1.5 h, DMF, 25°C)[c]	**4g**, 84% (85), 24 h
1h: R^1=R^3=H, R^2=R^4=OCH_3, X=Br	80% (1 h, DMF, 25°C)[c]	**4h**, 73% (91), 24 h
1i: R^1=R^2=OCH_3, R^3=R^4=H, X=Br	90% (1 h, DMF, 25°C)[c]	**4i**, (88)

[a] Yield of purified product isolated by chromatography (SiO_2). All products exhibited the reported or expected spectral and physical characteristics: ^{1}H-NMR, IR, and MS, mp. The recorded characteristics for known compounds may be found in reference 3g. New compounds gave satisfactory C, H, N analysis (±0.40%).

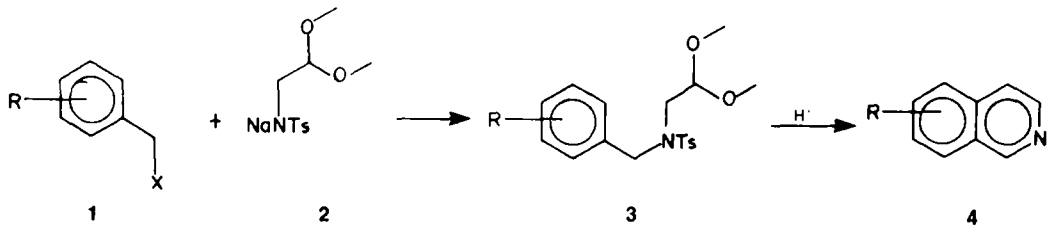
[b] The yield recorded in parenthesis represents that reported previously for this cyclization, see reference 3g.

[c] Benzyl bromides were prepared by brief treatment (ca. 10 min) of benzene solutions of the corresponding benzyl alcohols with HBr gas. Yields recorded are based on the use of the crude benzyl bromides.

[d] Yield is based on the use of crude mesylate prepared as described in reference 6.

[e] Spectral and physical characteristics for this compound are listed in reference 7.

[f] Yield after exposure to acidic cyclization conditions (2 h), see experimental, followed by base catalyzed elimination (potassium *t*-butoxide/*t*-butanol, 10 h, 25°C), see text.



1 2 3 4

Scheme 1.

Since the documented instability of benzylic mesylates[6] and the lability of benzylic iodides often make them unattractive intermediates, an optimal and practical procedure for the use of benzylic bromides was developed. Rapid, clean alkylation of benzylic bromides *and* chlorides occurs in dimethylformamide (DMF) at 25°, 1–3 hr, Table 1. The ease with which benzylic bromides may be prepared or handled and their efficient alkylation of the sodium salt of **2** in dimethylformamide makes this the practical procedure of choice.

Although the acid-catalyzed cyclization of N-tosyl benzylamino-acetals has been carefully investigated[3g] a few comments are in order. Our first attempts to reproduce this work on a 100–200 mg scale (6 N aqueous HCl/dioxane—two phase system) resulted in erratic yields. Subsequently, we discovered that all reactions run at or above the scale described[3g] (2 g) reproducibly afford the isoquinolines in high yield. Our problems on the smaller scale arose presumably from an ineffective mixing of the two phases. Additionally, in one instance, **3c**, the loss of *p*-toluenesulfonic acid required unusually long reaction times and resulted in a diminished yield of isoquinoline **4c**. This was remedied by exposure of **3c** to the acidic cyclization conditions (2 hr, 6 N HCl/dioxane, 110°, **3c** → N-tosyl dihydroisoquinoline) followed by base catalyzed elimination of *p*-toluenesulfonic acid (potassium t-butoxide/t-butanol, 10 hr) to give isoquinoline **4c** in 83% overall yield.

Aside from the practical improvements in yield and convenience resulting from this two-step variation of the Pomeranz–Fritsch cyclization, there is a covert improvement in the flexibility of the methodology. All current, reliable Pomeranz–Fritsch type isoquinoline preparations involve catalytic reduction of an imine, thus limiting functionality that may be present in the substrate. For instance, olefins, enones, benzylic alcohols, -amines, -ethers, or -sulfides, and aromatic halides potentially interfere with this reduction. This newly developed methodology, which does not depend on a catalytic reduction, circumvents these problems and opens new opportunities in our current investigations.

EXPERIMENTAL

N - (2,2 - *Dimethoxyethyl*) - p - *toluenesulfonamide*(2,N - *tosyl aminoacetaldehyde dimethyl acetal*)

Aminoacetaldehyde dimethyl acetal (5.25 g, 50 mmole), *p*-toluenesulfonyl chloride (11.44 g, 60 mmole) and Na_2CO_3 (106 g, 1 mole) were added sequentially to 400 ml dry THF and the resulting slurry was stirred for 3 days (25°) under N_2. After filtration (CH_2Cl_2 wash), the filtrate was washed with water, satd NaCl aq, dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography (25 × 1000 mm mplc, 60:40 ether:hexane eluant) afforded 12.32 g (95% yield) of pure **2** as a white powder; m.p. 45–47°. IR ($CHCl_3$): 3370, 3020, 2930, 2830, 1596, 1320, 1145, 1075, 790 cm^{-1}; ^1H NMR ($CDCl_3$, ppm): 7.6 and 7.12 (two d, J = 8 Hz, 4H), 4.75 (broadened t, 1H, –NH–), 4.25 (t, J = 5 Hz, 1H), 3.30 (s, 6H), 2.95 (t, J = 5 Hz, 2H), 2.40 (s, 3H); MS *m/e* (rel. intensity): 230 (24), 228 (–OCH_3, 7), 171 (10), 155 (17), 139 (34), 91 (63), 76 (31), 75 (100), 65 (27). (Found: C, 50.84; H, 6.54; N, 5.24. Calc. for $C_{11}H_{17}NO_4S$: C, 50.95; H, 6.61; N, 5.40.)

General procedure for the preparation of isoquinolines is illustrated with 6,7-methylenedioxyisoquinoline (**4g**)

N - (2,2 - *Dimethoxyethyl*) - N - [(3,4 - *methylenedioxyphenyl)methyl*] - p - *toluenesulfonamide* (**3g**). Compound **2** (3.24 g, 12.5 mmole, 1.05 equiv) in 20 ml dry DMF was added to a suspension of NaH (60% oil dispersion, 0.5 g, 12.5 mmole, 1.05 equiv) in 10 ml dry DMF under N_2 at 25°. After H_2 evolution ceased (5 min), piperionyl bromide (2.56 g, 11.9 mmole) in 20 ml dry DMF was added and the resulting mixture was stirred for 2 hr (25°) under N_2 before being poured onto water and extracted with ether (3x). The combined etheral layers were washed with satd NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography (25 × 250 mm mplc, 40:60 ether:hexane eluant) afforded 4.33 g (93% yield) of pure **3g** as a white solid identical in all respects to that previously reported.[3g]

6,7-*Methylenedioxyisoquinoline* (**4g**).[3g] A soln of **3g** (2.0 g, 5.1 mmole) in 48 ml dioxane was treated with 6 N HCl (3.7 ml) and the resulting mixture was warmed at reflux under N_2 in the dark for 24 hr before being cooled and poured onto water. The aqueous phase was washed with ether (2x), CH_2Cl_2 (2x) and made alkaline with the addition of 10% NaOH aq and extracted with ether (2x) and CH_2Cl_2 (2x). The combined organic phase (from the latter extractions) were washed with satd NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography (25 × 250 mm mplc, ether eluant) afforded 0.72 g (81% yield) of pure **4g**[3g] identical in all respects to that reported previously.

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[3a]Bischler–Napieralski cyclization, see: Ref. 2*a*; 2*b*, pp. 4–34; 2*c*, pp. 4–6; 2*e*; [b]Pictet–Spengler cyclization, see: Ref. 2*a*; 2*b*, pp. 34–58; 2*c*, pp. 2–4; [c]Pomeranz–Fritsch cyclization: C.

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[7]N-Tosyl benzylamine acetal **3c**: m.p. 66–68°; IR ($CHCl_3$): 2940, 1475, 1388, 1317, 1145, 1092, 991, 905, 790, 633 cm^{-1}; ^1H NMR ($CDCl_3$, ppm): 7.70 and 7.22 (two d, J = 8 Hz, 4H), 6.81 (s, 1H), 4.47 (s, 2H), 4.37 (t, J = 5 Hz, 1H), 3.87, 3.78 (two s, 9H), 3.26 (s and d, 8H), 2.38 (s, 3H); MS *m/e* (rel. intensity) 519 (0.7, M + 2), 517 (0.6, M^+), 456 (0.7), 454 (0.7), 364 (2), 261 (5), 259 (5), 181 (22), 75 (100). (Found: C, 48.47; H, 5.35; N, 2.54. Calc. for $C_{21}H_{28}BrNO_7S$: C, 48.65; H, 5.44; N, 2.70%). 8-bromo-5,6,7-trimethoxyisoquinoline (**4c**); m.p. 64–67°; IR ($CHCl_3$): 2960, 1579, 1455, 1393, 1372, 1347, 1271, 1227, 1090, 1017, 982, 818 cm^{-1}; ^1H NMR ($CDCl_3$, ppm): 9.22 (s, 1H), 8.27, 7.58 (two d, J = 5 Hz, 2H), 3.90 (s, 6H), 3.85 (s, 3H); MS *m/e* (rel. intensity) 299 (100, M + 2), 297 (100, M^+), 285 (8), 284 (50), 282 (50), 269 (8), 267 (8), 256 (19), 254 (21), 241 (22), 239 (22), 175 (22), 160 (18). (Found: C, 48.66; H, 4.17; N, 4.55. Calc for $C_{12}H_{12}BrNO_3$: C, 48.34; H, 4.03; N, 4.70%).