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Preparation of *N*-Benzylsulfonamido-1,2-Dihydroisoquinolines and Their Reaction with Raney Nickel. A Mild, New Synthesis of Isoquinolines

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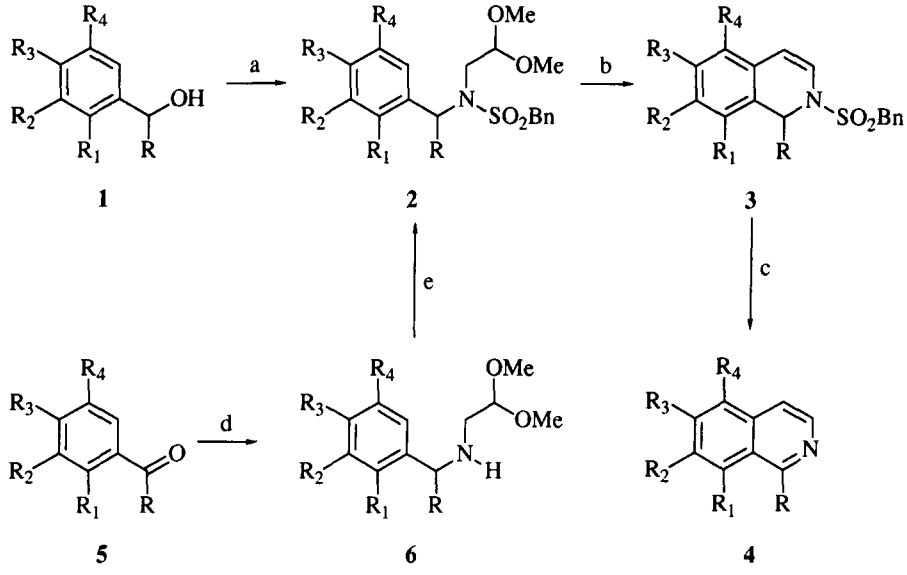
Abstract: *N*-benzylsulfonamido-1,2-dihydroisoquinolines react with Raney nickel to provide isoquinolines in excellent yields and under mild, neutral conditions. © 1997 Elsevier Science Ltd.

One of the most useful variations of the Pomeranz-Fritsch synthesis of isoquinolines is that developed by Jackson and co-workers,[1] which has been used as a synthetic tool of importance in the elaboration of these and related heterocyclic compounds.[2] The original procedure and its several modifications require the preparation of *N*-tosyl-1,2-dihydroisoquinolines and their subsequent detosylation, which must be carried out under harsh conditions employing prolonged reflux periods with mineral acids or strong bases.[3] Although only tosyl derivatives have been synthesized to date, the success of the Jackson protocol has been attributed to the stabilizing effect of the sulfonyl group, due to its electron withdrawing properties.

During the course of our program on the design of useful extentions of the Jackson cyclization and their use in the synthesis of natural products,[4] we observed that *N*-tosyl-1,2-dihydroisoquinolines, known to be photosensitive,[1b] were smoothly transformed into several products including the corresponding isoquinolines, upon irradiation at 254 nm.

Based on the above observation, it was envisioned that sulfonyl groups other than tosyl could yield isoquinolines under mild conditions following the Jackson strategy, provided they are susceptible to radical cleavage. Benzylsulfonamide, a readily available but seldom used amino protecting group, easily removed by Raney nickel[5] and photolysis,[6] fulfilled the above requirement. Interestingly, benzyl sulfonyl chloride has long ago been suggested as an alternative to tosyl chloride in the Hinsberg test of amines.[7]

We report in this letter the synthesis of *N*-benzylsulfonamides **3a-f** and the results of their reaction with W-2 Raney nickel, which provides a novel entry into simple isoquinolines. As depicted in the Scheme, the elaboration of **3a-f** was accomplished in two steps by Mitsunobu amination of benzylic alcohols **1a-f**[8] with *N*-benzylsulfonamidoacetaldehyde dimethyl acetal (**7**),[3a] followed by reaction of the resulting sulfonamides **2a-f** with 6 N HCl in refluxing dioxane.[9] Tetramethylazodicarboxamide-tributyl phosphine[10] was employed as the Mitsunobu coupling agent for the more congested secondary alcohols, giving in those cases better yields than the classical DEAD-PPh_3 couple, which was used for the primary alcohols **1a** and **1b**.



a R= H, R_1= R_2= OMe, R_3= R_4= H
b R= H, R_1= H, R_2= R_3= R_4= OMe
c R= Me, R_1= R_4= H, R_2= R_3= OMe
d R= Et, R_1= R_4= H, R_2= R_3= OMe
e R= Ph, R_1= R_4= H, R_2= R_3= OMe
f R= 4-MeO-C_6H_4-CH_2, R_1= R_4= H, R_2= R_3= OMe

Scheme. *Reagents and conditions:* a) $BnSO_2NHCH_2CH(OMe)_2$ (7, 3 equiv.), PBu_3 (3 equiv.), TMAD (3 equiv.), benzene, RT, 3 h (60 - 84%); b) 6 N HCl, dioxane, reflux (77 - 85%); c) W-2 Raney nickel, EtOH, reflux (61 - 99%); d) $H_2NCH_2CH(OMe)_2$ (5 equiv.), AcOH (4.5 equiv.), $NaCNBH_3$, EtOH, reflux (90-97%); e) $BnSO_2Cl$, 2 M Na_2CO_3, toluene, RT (82-86%, **6a** and **6b**).

Noteworthy, compounds **2a** and **2b** could be obtained in comparable yields by reductive amination of aldehydes **5a** and **5b**, followed by exposure of the resulting secondary amines to benzylsulfonyl chloride in toluene-aqueous Na_2CO_3 media; however, the same reaction to form **2c** could not be completed and no reaction was observed when the syntheses of **2d-f** were attempted, presumably because of steric hindrance.

Finally, **3a-f** reacted with Raney nickel, affording the related isoquinolines **4a-f** in good to excellent yields, as reported in the Table. Fast formation of **4c**, **4d** and **4f** occurred at room temperature, while heating under reflux shortened the reaction time without seriously affecting yields. Although reactions were usually run in ethanol, it was shown that other solvents such as dioxane were useful. Compounds **3a** and **3b**, unsubstituted on C-1, required longer reaction periods and gave lower yields of product, while the congested **3e** gave a 2:1 mixture of **4e** and the related *N*-ethyl tetrahydroisoquinoline when the reaction was run in ethanol, and 76% of **4e** when dioxane was employed as solvent. Interestingly, no rearranged product (3-benzylisoquinoline) was observed during the synthesis of benzylisoquinoline **4f**, demonstrating the ability of the benzylsulfonyl group to advantageously substitute the tosyl moiety.[3b, 3c]

Fortunately, under the mild reaction conditions employed for this synthesis, isoquinolines were not hydrogenated with Raney nickel,[11] which contributed to the obtention of high yields. In addition, compared with the original strategy of Jackson,[1] reaction products were more easily and more efficiently isolated, by filtration and solvent removal.

Table. Synthesis of isoquinolines by reaction of Raney nickel with *N*-benzylsulfonamido-1,2-dihydroisoquinolines.

Compound N°	Reaction time (h)	Solvent	Temperature	Product (Isoquinoline)	Yield (%)
3a	3.0	EtOH	Reflux	**4a**	62
3a	3.0	Dioxane	Reflux	**4a**	75
3b	2.7	EtOH	Reflux	**4b**	61
3c	0.1	EtOH	Reflux	**4c**	99
3c	1.0	EtOH	25°C	**4c**	99
3d	0.1	EtOH	Reflux	**4d**	99
3d	1.0	EtOH	25°C	**4d**	99
3e	0.1	EtOH	Reflux	**4e**	92
3e	1.6	EtOH	25°C	**4e**	95
3f	3.0	EtOH	Reflux	**4f**	69[a]
3f	3.0	Dioxane	Reflux	**4f**	76

a. In addition, 1-phenyl-2-ethyl-6,7-dimethoxytetrahydroisoquinoline (28%), was isolated.

The reaction mechanism of this transformation is uncertain. We have detected the production of toluene (HPLC) and have observed that the reaction does not proceed with aged or inactive Raney nickel nor with the ethanol used as solvent to suspend and store the reagent, and that when *N*-tosyl-1,2-dihydroisoquinolines were employed, only double bond hydrogenation was observed.[12] Therefore, the possibility of a base-catalyzed sulfonamide elimination mechanism should be discarded.

In addition, since experiments were carried out under a dry and oxygen-free Argon atmosphere, it seems unlikely that the reaction could proceed *via* conventional desulfonylation to the 1,2-dihydroisoquinolines followed by oxidation to the corresponding isoquinolines.

Probably the deoxygenation of tertiary alcohols with Raney nickel in toluene and the use of this reagent for the oxidation of secondary alcohols without hydrogen acceptor, described by Kraft,[13] offer a good analogy with the transformation reported in this work.

In conclusion, we have found that the treatment of *N*-benzylsulfonyl-1,2-dihydroisoquinolines with freshly prepared W-2 Raney nickel, gives isoquinolines in high yield under mild, neutral conditions, involving the unprecedented formation of a C-N double bond concurrent with the desulfonylation. This resulted in new synthetic approaches to isoquinoline natural products such as isobackebergine (**4a**), isonortehuanine (**4b**), nigellimine (**4c**), and 1-benzylisoquinoline **4f**,[14] as well as bioactive synthetic isoquinolines **4d** and **4e**.[15]

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References and Notes

1. (a) Jackson, A. H.; Stewart, G. W. *J. Chem. Soc., Chem. Commun.* **1971**, 149; (b) Charnock, S. A.; Jackson, A. H.; Martin, J. A.; Stewart, G. W. *J. Chem. Soc., Perkin Trans. 1*, **1974**, 1911-1920; (c) Birch, A. J.; Jackson, A. H.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1*, **1974**, 2185-2190.
2. (a) Birch, A. J.; Jackson, A. H.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1*, **1974**, 2190-2194;

(b) de la Fuente, M. C.; Castedo, L.; Dominguez, D. *Tetrahedron*, **1996**, *52*, 4917-4924; (c) García, A.; Castedo, L.; Dominguez, D. *Tetrahedron*, **1995**, *51*, 8585-8598.

3. (a) Boger, D. L.; Brotherton, C. E.; Kelley, M. D. *Tetrahedron*, **1981**, *37*, 3977-3980; (b) García, A.; Castedo, L.; Domínguez, D. *Synlett* **1993**, 271-272.
4. (a) Kaufman, T. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 2497-2505; (b) Kaufman, T. *Tetrahedron Lett.*, **1996**, *37*, 5329-5332; (c) Ponzo, V. L.; Kaufman, T. *Tetrahedron Lett.*, **1995**, *36*, 9105-9108.
5. For a review, see Pizey, J. S. *Synthetic Reagents*, Vol. 2, Wiley, N.Y. 1974, pp. 175-311.
6. (a) Milne, H. B; Peng, C.-H. *J. Am. Chem. Soc.*, **1957**, *79*, 639-644; (b) Yoshioka, M.; Nakai, H.; Ohno, M. *ibid*, **1984**, *106*, 1133-1135; (c) Fukuda, T.; Kitada, C.; Fujino, M. *J. Chem. Soc., Chem. Commun.*, **1978**, 220; (d) Pincock, J. A.; Jürgens, A. *Tetrahedron Lett.*, **1979**, *20*, 1029-1030.
7. Marvel, C. S.; Gillespie, H. B. *J. Am. Chem. Soc.*, **1926**, *48*, 2943-2944.
8. Compounds **1a-c** are commercially available. Alcohols **1d** and **1f** were obtained by an ultrasound catalyzed Barbier reaction; see: Luche, J. L.; Damiano, J. C. *J. Am. Chem. Soc.*, **1980**, *102*, 7926-7927 and **1e** was synthesized by addition of PhMgBr to veratraldehyde.
9. Spectroscopic and analytical data of all new compounds were consistent with their assigned structures. In a typical procedure, **2c** (884 mg, 2.09 mmol) was dissolved in dioxane (10 mL), aqueous 6 N HCl (3 equiv.) was added and the reaction was stirred under reflux for 20 min. Conventional extractive work-up (AcOEt) and chromatography afforded **3c** (84%) as white needles. mp: 124-126°C (EtOH); ^{1}H NMR (δ): 1.22 (d, 3H, *J*=6.7), 3.81 (s, 3H), 3.90 (s, 3H), 4.08 (d, 2H, *J*=13.9), 4.27 (d, 2H, *J*=13.9), 4.50 (q, 1H, *J*=6.7), 5.92 (d, 2H, *J*=7.4), 6.08 (s, 1H), 6.44 (d, 2H, *J*=7.4), 6.59 (s, 1H) and 7.08-7.28 (m, 5H); Anal. Calcd. C, 63.49; H, 5.89; N, 3.90; S, 8.92 ; Obsd. C, 63.29; H, 6.01; N, 3.82; S, 8.79. Freshly prepared W-2 Raney nickel (4g/mmol) in absolute EtOH was added to an ethanolic solution of **3c** (198.5 mg, 0.55 mmol) and the mixture was stirred under a dry Argon atmosphere for 1 h at room temperature. The catalyst was separated by decantation and washed with EtOH (4 x 2 mL); the ethanolic phases were filtered through a Celite pad and concentrated *in vacuo* giving **4c** (111.4 mg, 99.2%), as a solid mp 118-119°C (Et_2O-AcOEt) which spectral data (IR, ^{1}H and ^{13}C NMR) were in complete agreement with those previously published, see Rahman, A.-U; Malik, S.; Zaman, K. *J. Nat. Prod.* **1992**, *55*, 676-678.
10. Tsunoda, T.; Yamamiya, Y.; Kawamura, Y.; Itô, S. *Tetrahedron Lett.*, **1995**, *36*, 2529-2533.
11. Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc.*, **1945**, *67*, 860-874.
12. The desulfurization of sulfonamides with Raney nickel has been studied, see for instance Pettit, G. R.; Kadunce, R. E. *J. Org. Chem.*, **1962**, *27*, 4566-4570, and references cited therein.
13. (a) Kraft, M. E.; Crooks, W. J. *J. Org. Chem.*, **1988**, *53*, 432; (b) Kraft, M. E.; Zork, B. *ibid.*, **1986**, *51*, 5482.
14. Compounds **4a**, **4b** and **4c** are ubiquitous natural products, found together in *Pachycereus weberi* ; see Roush, R. A.; Cooks, R. G.; Sweetana, S. A.; McLaughlin, J. L. *Anal. Chem.*, **1985**, *57*, 109-114; for their use as synthetic starting materials, see for example Boger, D. L.; Takahashi, K. *J. Am. Chem. Soc.*, **1995**, *117*, 12452-12459; for the isolation of **4f**, see Franca, N. C.; Giesbrech, A. M.; Gottlieb, O. R.; Magalhaes, A. F.; Maia, J. G. S. *Phytochemistry*, **1975**, *14*, 1671-1672.
15. Simon, L.; Poreszasz, J.; Gibiszer, P. K.; Talpas, S. G. *Pharmazie*, **1977**, *32*, 235-239 and 720-721.

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