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Preparation of 1,2,3,4-Tetrahydroisoquinolines Lacking Electron Donating Groups - An Intramolecular Cyclization Complementary to the Pictet-Spengler Reaction

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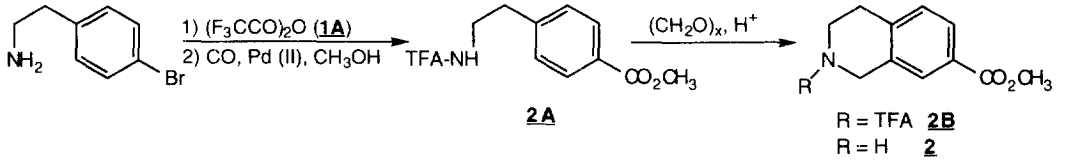
Abstract: The synthesis of 1,2,3,4-tetrahydroisoquinolines via an intramolecular cyclization of N-trifluoroacylated phenethylamines devoid of electron donating groups, with paraformaldehyde mediated by acetic/sulfuric acid milieu is described. Copyright © 1996 Elsevier Science Ltd

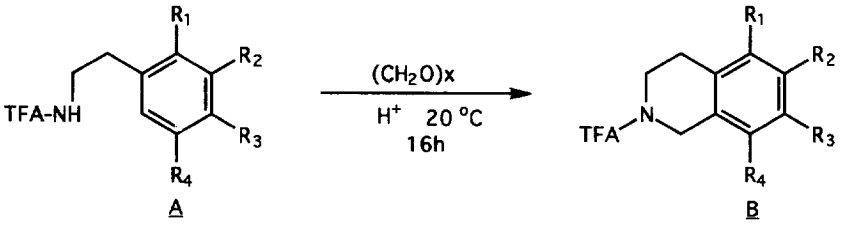
In the course of one of our recent projects we required multigram quantities of methyl 1,2,3,4-tetrahydroisoquinoline-7-carboxylate **2**. The only previously reported synthesis of **2** appeared in the patent literature and was prepared from starting materials not readily available.[1] One of the most direct methods of tetrahydroisoquinoline formation is the Pictet-Spengler type reaction, however, it usually requires alkoxy or hydroxy groups on the aromatic ring[2] and thus is not suitable for the synthesis of **2**. The Friedel-Crafts-type reaction of α-amido alcohols with aromatic rings, a special case of the Mannich reaction, has been reviewed.[3] An intramolecular version of this reaction is described in this letter wherein the α-amido alcohols were prepared *in situ* using paraformaldehyde and the requisite N-trifluoroacylated phenethylamines (Scheme 1).[4,5]

Scheme 1



In contrast to the Pictet-Spengler reaction, the use of paraformaldehyde in an acetic-sulfuric acid milieu on the acylated amine provided the appropriate tetrahydroisoquinoline in good yield when electron withdrawing substituents are present (**1-9**, Table 1). With no or slight activation, the isolated yield of the tetrahydroisoquinolines was only moderate (**10-12**), while activated rings (**15-17**) gave only products identified as those resulting from hydroxymethylation of the aromatic ring to form bisarylmethylenes, trimers and cyclotetramers (calix[4]arenes). The paraformaldehyde could successfully be replaced by s-trioxane without diminution in yield; however, attempts to extend the utility of this reaction by the use of paracetaldehyde, alkyl or aromatic aldehydes to obtain 1-substituted derivatives were unsuccessful.

Table 1



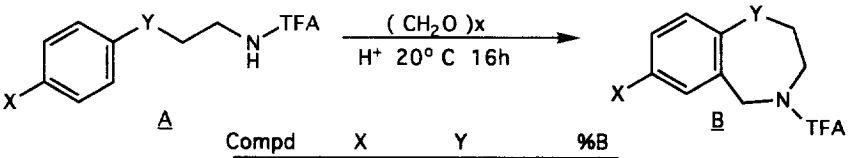
Compd	R1	R2	R3	R4	%H_2SO_4 in HOAc	% yield of B[a]
1	H	H	Br	H	40	94
2	H	H	CO_2CH_3	H	60	92[b]
3	H	H	NO_2	H	60	85
4	H	H	$SO_2N=C(N(CH_3)_2)H$	H	60	79[c]
5	Cl	H	H	H	40	87
6	Cl	H	Cl	H	60	48[d]
7	H	Cl	H	H	40	86[e]
8	H	Cl	Cl	H	60	90
9	H	CF_3	H	H	60	89[e]
10	H	H	H	H	40	45[f]
11	H	H	CH_3	H	20	51[g]
12	H	H	$NHCOCF_3$	H	40	40[h]
13	OCH_3	H	H	Br	40	39
14	OCH_3	H	H	CO_2CH_3	60	0[b]
15	H	OCH_3	H	H	20	0
16	H	OH	H	H	10	0
17	H	H	OCH_3	H	20	0

[a]All compounds were fully characterized by NMR and MS. [b]Starting methyl ester was prepared by Pd (II) catalyzed carbonylmethylation of correspond bromo **A** (**1** or **13**). [c]Sulfonyliminomethylamine was formed using DMF as solvent during trifluoramide formation of **A** from the aminosulfonyl. [d] 0% yield with 40% sulfuric acid. [e]Mixture formed by closure ortho and para. [f]80% yield with 20% sulfuric acid after 120h. [g]After 120h;<5% in a complex mixture with 40% sulfuric acid. [h]After 96h.

When the trifluoroacetyl moiety was replaced with acetyl the yield was unaffected but the rate was considerably reduced. In contrast, the use of the benzoyl derivative produced no cyclized product. Replacement of the acetic-sulfuric acid milieu with trifluoracetic or formic acid was ineffectual for ring closure.

The reaction could not be extended to the formation of isoindolines, benzazepines, benzoxazepines or benzthiazepines. However, moderate success was obtained for the preparation of unsubstituted benzodiazepine **18** (Scheme 2).

Scheme 2

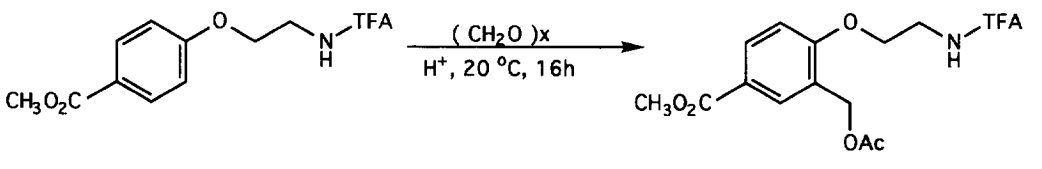


A B

Compd	X	Y	%B
18	H	N-TFA	50
19	Br	N-TFA	0
20	H	O	0

In an attempt to reduce the nucleophilicity of the alkoxyphenyl ring in **20A**, a methoxycarbonyl group was introduced (**21A**).[7] In this case the only product isolated was the acyloxymethyl derivative (**21B**, Scheme 3).

Scheme 3



21A 21B

In conclusion, we have reported a simple, relatively mild, and rapid method for the synthesis of 1,2,3,4-tetrahydroisoquinolines containing electron deficient moieties, complementary to the Pictet-Spengler reaction.

Acknowledgement

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References and Notes:

1. Austel, V.; Eisert, W.; Himmelsbach, F.; Linz, G.; Mueller, T.; Pieper, H.; Weisenberger, J. Eur. Pat. 528 369 A2 (1992).
2. Kametani, T. J.; Fukumoto, K. *Chem. Heterocycl. Compd.* **1981**, *38(1)*, 139-274.
3. Zaugg, H. E., *Synthesis* **1984**, *2*, 85-110.
4. Typical amidation procedure: 4-bromophenethylamine (3.12 mL 20 mmol) was added dropwise to trifluoroacetic anhydride (12 mL) at ~5 °C with vigorous stirring. After stirring for 30 min. the reaction was poured into ice-water (250 mL). After stirring the aqueous mixture for 30 min. the white powder was filtered off, washed well with H_2O and dried to give the amide (5.88 g, 19.8 mmol) mp. 115-117°C; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 2.85 (2H, t, *J* = 8 Hz), 3.60 (2H, q, *J* = 8 Hz), 6.35 (1H, bs), 7.05 (2H, d, *J* = 7.8 Hz), 7.45 (2H, d, *J* = 7.8 Hz). MS (FAB) (M+H): Found, 297, Calc'd for $C_{10}H_9BrF_3NO$ (M+H), 297.
5. Typical cyclization procedure: a mixture of methyl 4-[2-(trifluoroacetylamino)ethyl]benzoate[6] (2.5 g, 9.15 mmol) and paraformaldehyde (450 mg, 14.4 mmol) was added to a solution of acetic acid (10 mL) in sulfuric acid (15 mL) at ambient temperature. After stirring for 16 h the clear colorless solution was poured into cold water (200 mL). The gummy residue was extracted into EtOAc (200 mL) and the organic layer was washed with sat. $NaHCO_3$ (50 mL), H_2O (2 x 100 mL), dried ($MgSO_4$), and evaporated. The oily residue crystalized on standing to provide **2B** (2.42 g, 8.46 mmol, 92% yield), mp 54-56 °C as a mixture of rotational isomeric amides; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 3.00 (t, 2H, *J* = 4 Hz) minor, 3.018 (t, 2H, *J* = 4 Hz) major, 3.87 (t, 2H, *J* = 5.6 Hz) major, ~ 3.91 (obscure t, 2H, *J* = ~ 5.6 Hz) minor, 3.92 (3H, s), 4.79 (2H, s) minor, 4.84 (2H, s) major, 7.22 - 7.27 (H, m), 7.82 - 7.92 (2H, m). MS (FAB) (M + H): Found 288, Calc'd for $C_{13}H_{12}F_3NO_3$ (M+ H): 288.
6. Typical methoxycarbonylation procedure: Carbon monoxide was bubbled slowly through a solution of the bromide (3.3 g, 11 mmol), in MeOH (30 mL) and DMSO (15 mL) containing $Pd(OAc)_2$ (150 mg), dppp (300 mg) and triethylamine (3.5 ml) at 80°C for 7 h. The MeOH was evaporated and the residue was chromatographed on silica gel (7:1 Hexane/EtOAc) to afford ester (2.52 g, 9.17 mmol, 80% yield); ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 2.96 (2H, t, *J* = 8 Hz), 3.65 (2H, q, *J* = 8 Hz), 3.92 (3H, s), 7.28 (2H, d, *J* = 7.8 Hz), 8.02 (2H, d, *J* = 7.8 Hz).
7. Starting methyl ester was prepared by Pd(0) catalyzed carbonylmethylation of the corresponding iodide which was prepared as in Kajigaeshi, S., Kakinami, T., Moriwaki, M., Watanabe, M., Fugisaki, S., Okamoto, T. *Chem. Lett.* **1988**, *5*, 795.

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