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Cyclisation of Tryptamine Enaminones to Functionalised Tetrahydro-β-carbolines Induced by [Bis(trifluoroacetoxy)iodo] benzene.

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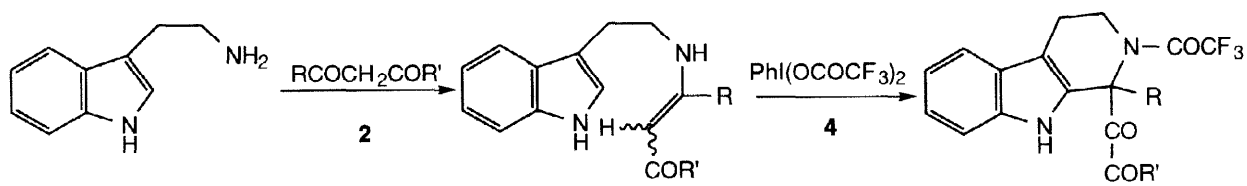
Abstract: The reaction of enamino carbonyl derivatives of tryptamine with [bis(trifluoroacetoxy)iodo]benzene provides an easy route to 1,1-bis-functionalised-*N*-trifluoroacetylated-β-carbolines. The reaction proceeds through Pictet-Spengler-type cyclisation, trifluoroacetylation and oxidation steps.

The Pictet-Spengler reaction has long been known as an important method toward the preparation of indole and isoquinoline alkaloids. Its application on tryptophan and tryptamine derivatives has been established as the principal method for the formation of 1,2,3,4,-tetrahydro-β-carbolines.[1]

Since the interest for the preparation of functionalised tetrahydro-β-carbolines keeps growing,[1,2] we considered of the possibility of cyclising enamino carbonyl compounds of type **3**, easily prepared[3] from a condensation reaction of tryptamine, **1**, with β-dicarbonyl compounds **2**. As cyclisation agents we used hypervalent iodine reagents for which we have a permanent interest in synthetic applications.[4] We expected some kind of oxidative cyclisation, since analogous reactions of other nitrogen compounds have been reported.[5a,b]

The reaction of enamino ester **3a** with [hydroxy(tosyloxy)iodo]benzene and (diacetoxyiodo)-benzene was sluggish and no cyclisation product was isolated. On the contrary, [bis(trifluoracetoxy)-iodo]benzene, **4**, reacted with **3a** at 0 °C to room temperature to afford 2-trifluoroacetyl-1-[(ethoxycarbonyl)carbonyl]-1-methyl-1,2,3,4-tetrahydro-β-carboline, **5a**, in 35% yield.



1 **3** **5**

2,3,5 **a** R = Me, R' = OEt **c** R = Ph, R' = Me

b R = Me, R' = Me **d** R = Pr, R' = OEt

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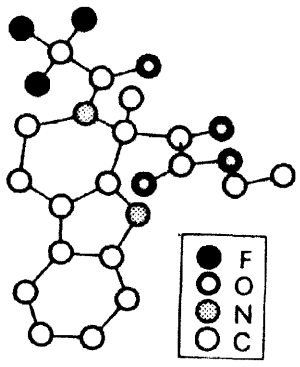
Structure elucidation of **5a** was based on spectroscopic and analytical data.[6] An X-ray analysis corroborated the proposed structure,[7] as it is shown in the clinographic projection given below.



Clinographic projection of **5a**.

Enamino carbonyl compounds **3b-d**, prepared by the condensation reaction of tryptamine with the corresponding β-dicarbonyl derivatives **2b-d**, gave with [bis(trifluoroacetoxy)iodo]benzene **4** the analogous cyclisation products **5b-d** in 9%, 33% and 7% yield respectively. No attempts to optimize these yields have been made. On the contrary, no cyclisation product was isolated from the reaction with **4** of the enaminone derived from tryptamine and dimedone, the only isolable product being some starting dimedone.

The above results indicate that this oxidative cyclisation, despite moderate or low yields, offers an easy access to 1,1-bis-functional β-carbolines in two steps starting from tryptamine. The trasformation is rather complicated, since reactions involving cyclisation, trifluoroacetylation and oxidation take place successively, and will be further investigated.

References and Notes

1. Cox, E.D.; Cook, J.M. *Chem. Rev.* **1995**, *95*, 1797.
2. Tietze, L.F.; Wichmann, J. *Liebigs Ann. Chem.* **1992**, 1063 and references cited therein.
3. Sucari, M.A.; Vernon, J.M. *Tetrahedron* **1983**, *39*, 793.
4. Varvoglis, A.; Spyroudis, S. *SynLett.*, in press.
5. a. Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*, VCH, New York, 1992.
   b. Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179.
6. Typical procedure for the preparation of **5** : [Bis(trifluoroacetoxy)iodo]benzene (1 mmol) was added to a stirred solution of **3a** (1 mmol) in $CHCl_3$ (20 mL) at °C under argon. The reaction mixture was allowed to reach room temperature and after all enaminone was consumed (3 h) it was concentrated and chromatographed on column (SiO_2, hexanes-ethyl acetate) to afford, after iodobenzene, **5a** as yellow crystals in 35% yield, mp 201-202 °C. IR (Nujol): 3350, 1735, 1710,1655, 1195 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.19 (t, J = 7 Hz, 3H), 1.93 (s, 3H), 3.01 (m, 1H), 3.22 (m, 1H), 3.55 (m, 1H), 4.12 (m, 2H), 4.44 (m, 1H), 7.10-7.25 (m, 2H) 7.35 (d, J = 8 Hz, 1H), 7.52 (d, J = 8 Hz, 1H) 8.24 (s, br, 1H); ^{13}C NMR ($CDCl_3$): δ 13.60, 20.64, 21.09, 42.77 (q, J = 4 Hz), 62.44, 66.28, 110.58, 11.59, 116.00 (q, J = 285 Hz), 118.71, 120.26, 123.25, 126.10, 127.48, 136.75,157.10 (d, J = 36 Hz), 158.42, 186.01; MS m/z 382 (M^+, 6), 281 (100), 183 (52), 168 (29), 153 (18). Anal. Calcd for $C_{18}H_{17}F_3N_2O_4$: C, 56.54; H, 4.48; N, 7.32. Found : C, 56.77, H, 4.51, N, 7.09.
7. Bozopoulos, A. to be published.