A New Approach to Tritium Labelling; the Synthesis of [^{3}H]Ibogaine

Herbert H. Seltzman,* Denise F. Odear, F. Ivy Carroll and Christopher D. Wyrick

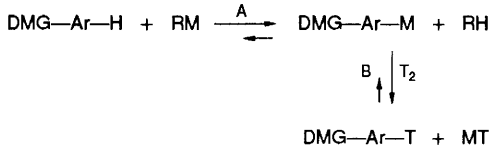
Organic and Medicinal Chemistry, Research Triangle Institute, Research Triangle Park, NC 27709, USA

Tritium labelled ibogaine, for pharmacological studies as an anti-addiction treatment for cocaine abuse, is prepared by a new method for the tritiation of aryl compounds involving *ortho* metallation followed by facile reduction of the carbon–metal bond.

A novel and potentially general approach to the incorporation of tritium into aryl compounds has been developed. Standard methods[1] for the preparation of tritiated compounds typically employ catalytic tritiation of an olefin or halide derivative of the target compound. Both methods require the prior synthesis of the derivative which can involve most of the overall effort. Furthermore, functionalities in the target molecule may suffer unwanted reduction under catalytic tritiation conditions, which limits the application of the method. In this paper we introduce a new approach for the tritiation of aryl compounds that requires neither prior derivatization of the compound to be labelled nor the use of a catalyst and results in introduction of tritium of high specific activity. The method combines directed *ortho* metallation with the facile reduction of the carbon–metal bond.

The first of the two reaction steps (A), Scheme 1, that provide the basis of the new tritiation procedure is directed *ortho* metallation[2–4] by metal–hydrogen exchange. Aryl compounds with a wide variety of heteroatom substituents such as sulfonamide, amide, carbamate, ether and amine moieties, are readily metallated in the *ortho* position by treatment with n-butyllithium. Similar treatment with n-butylpotassium affords the corresponding arylpotassium compound with greater facility. The metallation step is an equilibrium process between the alkyl- and the aryl-metal compounds that favours formation of the more electronegative aryl derivative by a 95 : 5 ratio in simple cases.[4–6]

The second reaction step (B) utilizes the remarkably facile reduction of the carbon–metal bond by hydrogen to afford a C–H bond and the corresponding metal hydride.[5,7] These reactions proceed at −25 to 35° C in the absence of a hydrogenation catalyst for organopotassium[8] and organolithium[7] compounds. Furthermore, the nature of the metal influences the ease and rate of the reduction. The potassium–carbon bond is reduced significantly faster than the corresponding lithium–carbon bond.[7] By employing the above sequence of reactions, a one flask approach to the tritiation of a broad class of underivatized aryl compounds can be envisaged.



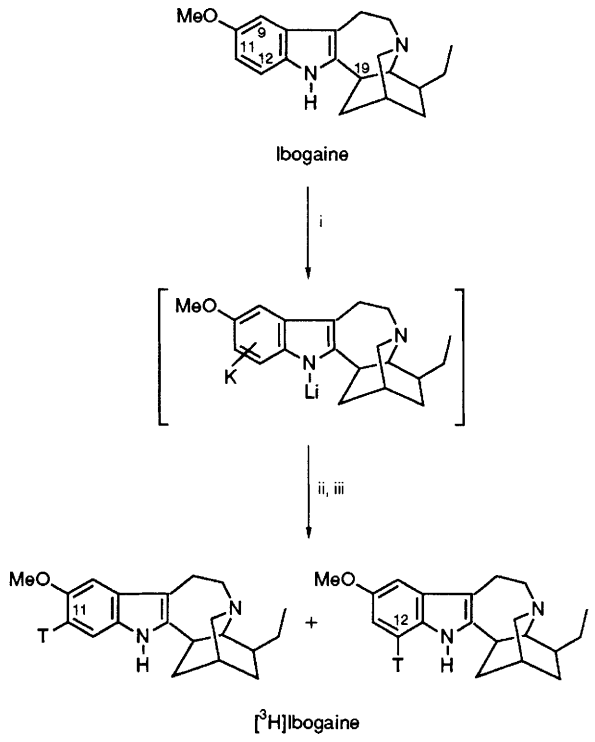
Scheme 1 Metallation/reduction of aryl compounds (DMG = *ortho*-directed metallation group)

This new approach is demonstrated for the synthesis of [^{3}H]ibogaine. Ibogaine[9] is an indole alkaloid that has received recent attention as a potential anti-addiction treatment for cocaine abuse.[10] A tritiated analogue was needed for metabolism, distribution and binding studies and cannot be conveniently prepared by the usual tritiation methods. For the method of synthesis of [^{3}H]ibogaine, the chemistry of the metallation of indoles also needs to be considered. Specifically, indoles with an unsubstituted nitrogen metallate only on the nitrogen when n-butyllithium is the base.[11] However, with n-butylpotassium prepared *in situ* from n-butyllithium and potassium *tert*-butoxide, indoles can be dimetallated.[12] This suggested that ibogaine could be employed as a substrate for tritiation without derivatization or protection, by the use of n-butylpotassium.

Treatment of ibogaine with 2 equiv. each of n-butyllithium and potassium *tert*-butoxide in anhydrous diethyl ether (−30 °C → room temp., 15 min) followed by tritium gas (−20 °C, 2 h → room temp., 2 h) afforded tritiated ibogaine as predominantly a single component (TLC-radioscan, HPLC) which was purified by HPLC (Scheme 2). Potential metallation/reduction sites on ibogaine are C-9 and C-11 *ortho* to the methoxy[11] and C-12 *ortho*[13] and C-19 β[12] to the indole nitrogen. Tritium NMR spectroscopy of the product was especially revealing as it unambiguously demonstrated the sites of labelling as the C-11 and C-12 aromatic positions.† From the absence of tritium–tritium coupling it was also clear that the product was a 1 : 1 mixture of mono-C-11 and mono-C-12 tritiated ibogaine and not 11,12-ditritiated ibogaine. The presence of two labelled sites ensures the maintenance of label in the vast majority of metabolites while the specific activity of 13.8 Ci mmol^{-1} (1 Ci = 3.7 × 10^{10} Bq) enables a variety of pharmacological studies to be conducted.

The C-11 and C-12 incorporation demonstrates the directing effect of the methoxy and indole nitrogen groups

† Tritiation (5%) also occurred in the C-9 position.



Scheme 2 *Reagents and conditions*: i, Bu^nLi–Bu^tOK, −30 °C to room temp.; ii, T_2, −20 °C; iii, EtOH

respectively. The lack of incorporation at C-19 can reasonably be attributed to the poor acidity of the benzylic methine proton relative to a benzylic methyl[14] and the fact that the resulting carbanion at C-19 would also be conformationally restricted from overlap stabilization with the aryl system.[12,13] This would make metallation of the C-19 benzylic hydrogen β to the indole nitrogen anion less favourable than that of the C-12 aryl hydrogen *ortho* to the same nitrogen.

This new approach of metallation/reduction for aryl tritiation has been demonstrated for the preparation of high specific activity [^{3}H]ibogaine. Since the method employs chemistry which demonstrates a widee scope, it is expected that this approach will have applicability to the tritiation of a broad class of aryl compounds.

This work was supported by the National Institute on Drug Abuse on Contract No. 271-91-7311. The tritium NMR spectra were obtained by Kevan Gaetano.

Received, 29th July 1992; Com. 2/04078F

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