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Convenient Syntheses of Benzo-Fluorinated Dibenz[*b*,*f*]azepines: Rearrangements of Isatins, Acridines, and Indoles

Emma-Claire Elliott,[†] Elizabeth R. Bowkett,[†] James L. Maggs,[‡] John Bacsa,[†,§] B. Kevin Park,[‡] Sophie L. Regan,[‡] Paul M. O'Neill,[†] and Andrew V. Stachulski*[,†]

Robert Robinson Laboratories, Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, U.K., and MRC Centre for Drug Safety Science, Institute of Translational Medicine, University of Liverpool, Ashton Street, Liverpool, U.K.

andrew.stachulski@bioch.ox.ac.uk

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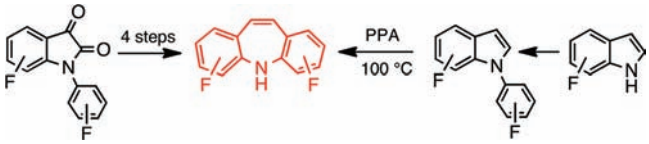
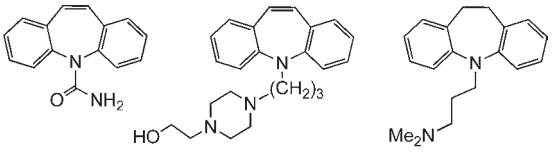
ABSTRACT



Efficient procedures for the synthesis of benzo-fluorinated dibenz[*b*,*f*]azepines (iminostilbenes) from fluorinated isatins or indoles using a number of ring-expansion reactions are described. A range of mono- and difluorinated analogues is accessible, and the syntheses can deliver gram quantities of the final products, which are precursors of fluoro analogues of the important anticonvulsant carbamazepine.

The tricyclic heterocycles dibenz[*b*,*f*]azepine (iminostilbene) and its 10,11-dihydro derivative iminodibenzyl are important synthons for the synthesis of various therapeutic agents. Thus (Figure 1), the anticonvulsant carbamazepine **1** and the antidepressants opipramol **2** and imipramine **3** have been widely used. In particular, **1**,[1] introduced by Geigy in 1960, is still one of the most widely used anticonvulsants and is increasingly prescribed in the treatment of other disorders including trigeminal neuralgia. Nevertheless, its use is associated with frequent incidences of idiosyncratic[2] side effects including hypersensitivity. Carbamazepine has a complex but well-characterized metabolic fate, forming in particular (Figure 2) the 10,11-epoxide **4**,[3] the associated 10,11-diol **5**, and various nuclear-hydroxylated



1 **2** **3**

Figure 1. Tricyclic therapeutic agents structurally related to dibenz[*b*,*f*]azepine and 10,11-dihydrodibenz[*b*,*f*]azepine.

structures arising from P450-catalyzed metabolism. It is also subject to phase 2 metabolism, forming the *N*-glucuronide **6**.[4] The epoxide **4**, once considered relatively unreactive, has been shown to form GSH and protein adducts.[5] The idiosyncratic toxicity of **1** has been linked hypothetically to metabolites formed by oxidation of a benzo ring.[6]

[†] Department of Chemistry.
[‡] Institute of Translational Medicine.
[§] Current addres: X-ray Crystallography Center, Atwood Chemistry Center, 216C Emory University, Atlanta, GA 30322.

(1) *The Merck Index*, 13th ed; Merck & Co.: Boca Raton, 2001; p 298; Schindler, W. (Geigy AG) US Patent 2,948,718, 1960.

(2) The idiosyncratic toxicity has been postulated to originate from an arene oxide, a highly electrophilic, protein-reactive species: Piromohamed, M.; Kittringham, N. R.; Guenthner, T. M.; Breckenridge, A. M.; Park, B. K. *Biochem. Pharmacol.* **1992**, *43*, 1675–1682. See also: Ju, C.; Uetrecht, J. P. *J. Pharmacol. Exper. Ther.* **1999**, *288*, 51–56.

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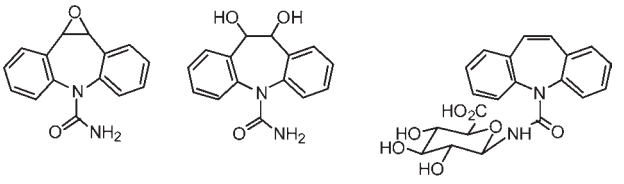


Figure 2. Major metabolites of carbamazepine.

Through an ongoing program,[7] we aim to identify by synthesis and biological testing analogues of **1** which show more favorable metabolic profiles and reduced hypersensitivity. We have already prepared some *N*-substituted and halogenated derivatives of **1**: our early results have shown that the *N*-substituent and 10,11-substitution are both factors influencing hypersensitivity.[7]

We are currently preparing a portfolio of nuclear-substituted analogues of **1** in order selectively to modify its metabolic profile and to define more precisely both the steric requirements of the T-cell receptor and the influence of the substitution pattern.

In any program of analogues, fluorine substitution holds a special place. Fluorine substitution combines a minimum steric influence with a profound electronic effect and is known to have a strong effect on nuclear P450-mediated hydroxylation.[8] Thus fluorine may block oxidation directly at the site of substitution;[9] moreover the overall rate of reaction of the benzene π-orbitals with P450s is reduced.[10] P450-mediated hydroxylation may still occur at positions adjacent to C−F and may be accompanied by an NIH shift of fluorine or oxidative defluorination.[11]

We are aware of only two reports of a fluorinated analogue of **1**, namely the 10-F analogue.[12] We now present the first convenient syntheses of mono- and dibenzo-fluorinated dibenz[*b*,*f*]azepines, employing fluorinated precursors and utilizing a number of rather efficient rearrangements of heterocyclic systems leading, in a few steps, to the desired products.

We first attempted direct fluorination of dibenz[*b*,*f*]-azepine **7**, iminodibenzyl **8**, and their *N*-substituted analogues (*N*-CHO, *N*-Ac, *N*-Me; Figure 3) using SelectFluor,[6,13]

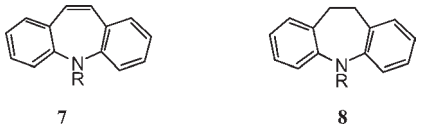
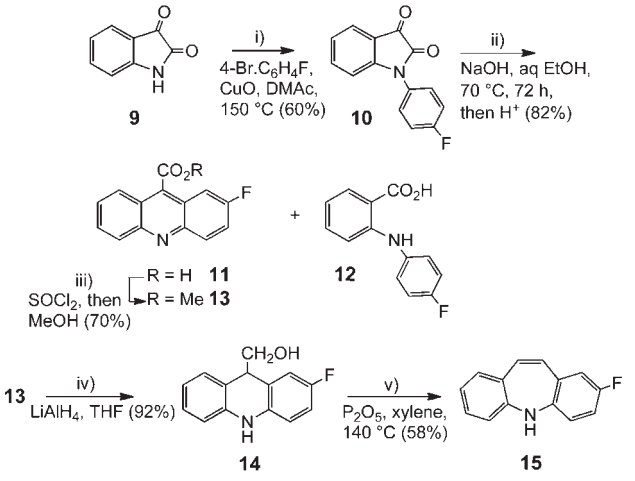


Figure 3. Dibenz[*b*,*f*]azepines and their 10,11-dihydro derivatives, potential intermediates for fluoro analogues. R = H, CHO, COMe, Me.

without any success. This was not a reagent problem as our batch of SelectFluor reacted with acetanilide to give a mixture of *o*- and *p*-fluoroacetanilide as reported.[13b] There is a literature report[14] of a synthesis of 2-fluorodibenz-[*b*,*f*]azepine from 2-fluoro-9-methylacridine, via the corresponding 9-chloro compound, but no synthetic details for the latter derivative are given. We considered that the 9-acridinemethanol intermediate in that synthesis could be conveniently accessed from the corresponding carboxylic acid, which itself could be obtained by base-catalyzed rearrangement of an *N*-aryl isatin. The latter rearrangement was, we believe, first reported by Stolle[15] and has since been used by others.[16]

Scheme 1. Synthesis of 2-Fluorodibenz[*b*,*f*]azepine



Our synthesis of **15**, the 2-F analogue of **7** (R = H), is shown in Scheme 1. We slightly modified Coppola's procedure[17] for the *N*-arylation of isatin **9**, using *N*,*N*-dimethylacetamide as the solvent and a reaction time of 8 h (longer times led to slow degradation).

After careful chromatography, the product **10** was obtained in satisfactory yield; direct recrystallization of

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crude product, in contrast, failed to remove trace impurities, which hindered the next step. Base-catalyzed rearrangement of **10** was effected by prolonged heating with NaOH in aq EtOH, affording acid **11** in good yield after acidification. A byproduct from this step (ca. 10%) was the *N*-arylanthranilic acid derivative **12**, which we believe was formed by the action of adventitious HO_2^- on **10**; a similar reaction of an isatin with basic H_2O_2 was observed by Newman and Powell.[16b]

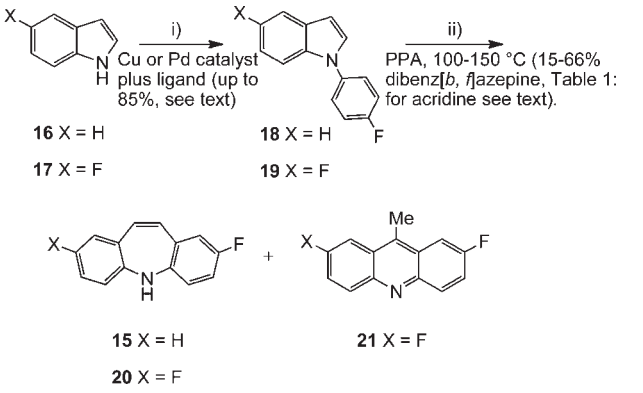
It was possible to reduce acid **11** directly, but better results were obtained after conversion to methyl ester **13**, which also usefully removed trace impurities from **11**. Reduction of **13** with $LiAlH_4$ gave alcohol **14** in excellent yield, showing a distinctive A_2B ^1H NMR pattern for $HOCH_2CHAr_2$ and major differences in the ArH region (see the Supporting Information). Insufficient reduction led to the 9-acridinemethanol without reduction of the central ring. Alcohol **14** was sensitive to air oxidation but could be stored at 0 °C under N_2 for extended periods.

Figure 4. Crystal structure of 2-fluorodibenz[*b*,*f*]azepine **15**. The molecule is disordered, and the atoms of the second component (not shown here) are related to this component by the symmetry operation x, $1/2 - y$, z.

The dihydro-9-acridinemethanol to dibenz[*b*,*f*]azepine rearrangement has been well documented;[18] P_2O_5 appears as satisfactory a reagent as any. We used a slight variation, by adding a xylene solution of **14** to a well-stirred, gently refluxing suspension of P_2O_5 in xylene, and obtained a very satisfactory yield of the desired product **15**[14] whose structure was confirmed by a single-crystal X-ray determination, Figure 4. The pronounced puckering of the tricyclic system is noteworthy. In fact, this molecule is disordered and packs with the F atoms oriented in opposite directions: the asymmetric unit consists of the averaged structure shown, but refined bond distances and angles are chemically meaningful.

A similar synthesis commencing with 5-F isatin came into consideration for the synthesis of a difluoro analogue of **1**. However, despite its scientific interest, the route is quite long, and in fact, a much shorter route is available for both mono- and difluorodibenz[*b*,*f*]azepines, based on a published acid-catalyzed rearrangement of *N*-aryl indoles.[19] The authors reported that the method gave low or zero yields when electron-withdrawing substituents (NO_2, CF_3, Cl) were present in the *N*-aryl group, but in fact the method proved fully satisfactory for fluoro analogues, Scheme 2. Again, the unique character of fluorine plays a part here, probably by back-donation from its lone pairs and stabilization of the cationic intermediates in a way that is far less efficient for, e.g., chlorine.

Scheme 2. Fluorodibenz[*b*,*f*]azepines from Indoles



N-Arylindoles are interesting compounds in their own right, and a number of synthetic methods, mainly based on *N*-arylation, have been reported. We initially treated indole **16** or 5-F indole **17** with 4-bromofluorobenzene or 4-fluoroiodobenzene under Cu/CuI catalysis at ca. 150 °C in PEG 400. The *N*-arylindoles **18** and **19** were obtained in 60% and 72% yield, respectively, but these results were not easy to reproduce or to scale up.[20] High catalyst loadings (20 mol %) were required for reasonable reaction times and extraction of the product from PEG 400 was difficult on a large scale.

An alternative was the Pd-catalyzed route of Old et al.[21] After some optimization, we were able to achieve a 90% yield of **18** in small-scale (ca. 1 mmol) reactions employing $Pd(OAc)_2$ with PBu^t_3 as ligand. On scale up, we obtained products of varying yield and purity, however, and significant amounts of 3-aryl products were observed. Instead we reverted to Cu catalysis, this time with proline as ligand,[22] and obtained desired products **18** and **19** in up to 85% yield on a multigram scale.

Conditions for the acid-catalyzed rearrangement of the *N*-arylindoles were based on those of Tokmakov and Grandberg.[19] The use of PPA is fully satisfactory (though fresh reagent is important for high yields), but careful temperature control is important. Eventually, we obtained the monofluorinated dibenz[*b*,*f*]azepine **15** in around 50% yield on a gram scale. In a similar manner, the difluoro precursor **19** was converted into **20** (up to 66%); ^{19}F NMR confirmed a change from two fluorine environments to one because of the symmetry of the product.

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Dibenz[*b*,*f*]azepines correspond to relatively shallow energy minima on the reaction profile. Longer reaction times, or higher temperatures, lead to the formation of 9-methylacridines such as **21** (not discussed in ref 19) in significant amounts. A reasonable mechanism for this type of rearrangement was proposed by Ledwith et al.[18a] The ratio is critically temperature dependent. When difluoro precursor **19** is the substrate, acridine **21** is by far the major product at 150 °C, but a very satisfactory yield of the iminostilbene **20** is obtained at 100 °C (Table 1).

Table 1. Effect of Temperature on the **20**:**21** Product Ratio in the Rearrangement of **19**

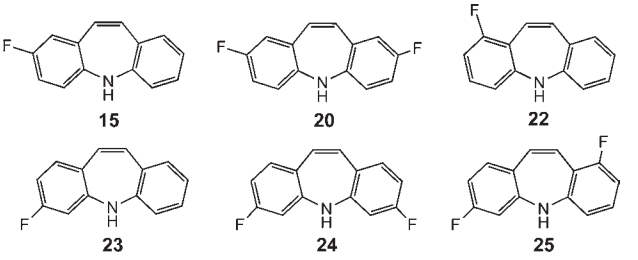
		yield,[a] %	
temp, °C	time, h	**20**	**21**
150	72	15	43
130	72	22	30
100	72	66	5
90	>96	32	0

[a] Yields refer to pure, isolated products.

Below 100 °C, only **20** can be isolated, but the reaction becomes very slow. A previous synthesis of 2,8-difluoroiminodibenzyl[23] required seven steps, and for our purposes, the final product would still require the reintroduction of the 10,11-double bond.

The reaction may usefully be extended to other fluoro *N*-arylindoles (Schemes 2 and 3): we found the reaction is relatively unaffected by the position of the F atom(s) in either ring. Tokmakov and Grandberg[19] isolated only the 3-methyl product on rearrangement of *N*-(*m*-tolyl)indole, possibly reflecting steric hindrance. By contrast, rearrangement of *N*-(3-fluoro)phenylindole gave after separation useful quantities of both 1-F and 3-F dibenz[*b*,*f*]azepine products **22** and **23** in a virtually 1:1 ratio. A range of fluorinated dibenz[*b*,*f*]azepines made by this method is shown in Scheme 3. The use of benzo-fluorinated indole precursors allows more options: thus, in the examples illustrated, 6-fluoroindole is a precursor of **23**–**25**. See the Supporting Information for full details of all these compounds: yields of dibenzo[*b*,*f*]azepines as single or combined isomers are from 40 to 60%.

Scheme 3. Range of Fluorodibenz[*b*,*f*]azepines Synthesized



In conclusion, we have demonstrated effective syntheses of both mono- and difluorinated dibenz[*b*,*f*]azepines from readily accessible nitrogen heterocycles. In particular, (2-fluoro)dibenz[*b*,*f*]azepine is available from either isatin or indole: the latter synthesis requires just two steps. The *N*-arylindole synthesis is also more flexible, allowing access to a range of regioisomeric fluorinated products. In a future publication, we shall report on the structure–metabolism relationships of a number of halogenated carbamazepines, including fluoro analogues derived from these precursors.

While our work was being written up, an alternative synthesis of fluorinated dibenzo[*b*,*f*]azepines from 2-bromostyrene and 2-chloroanilines was reported.[24] Two monofluoro examples were included. We believe that both approaches are valuable, depending on accessibility of intermediates and substitution pattern required.

Acknowledgment. We are grateful to the EPSRC (DTA studentships to E.R.B. and E.E.) and BBSRC (studentship to S.L.R.) for financial support and to the EPSRC mass spectroscopy service for HRMS data.

Supporting Information Available. Experimental details for synthetic procedures, characterization of new compounds, and NMR spectra of compounds **10**, **11**, **13**–**15**, and **18**–**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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