A Short Efficient Route to Acronycine and Other Acridones

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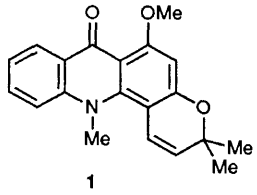
A Fries type of rearrangement of *N*-tosyl-*o*-iodobenzanilides, triggered by lithium–iodine exchange at low temperature is the key step in a general, regiospecific synthesis of acridones.

Acronycine **1**, a tetracyclic antitumour acridone alkaloid[1,2] is a well-known example of this group of natural products[3] isolated from species of plants belonging to the *Rutaceae* family. Acridones are always synthesized from benzenoid starting materials either by Ullman reaction to form the diphenylamine, followed by Friedel–Crafts cyclization[2,4] or by what is commonly regarded as a 'biomimetic' route where the benzoylation to produce a benzophenone precedes an intramolecular nucleophilic substitution.[5] In one instance[6] both steps were combined by the expedient tactic of adding *N*-lithioanthranilates to benzynes; a short, convergent synthesis of **1** was achieved in this way. In all these procedures, the question of regiocontrol in the benzoylation (or cyclization) step was not specifically addressed with suitably substituted substrates. In most cases, one of the aromatic nuclei of the acidrone synthesized carried no substituents.

Our recent successful application[7] of the anionic Fries rearrangement to regiospecific xanthone synthesis led us to enquire whether an analogous process could be employed for production of acridones with similar regiocontrol. Preliminary experiments carried out with *o*-iodobenzamide **2** (as its sodium salt) and **3** resulted in deiodinated products **4** and **5** only, when the appropriate amount of *n*-butyllithium was added at −100 °C tetrahydrofuran (THF)–diethyl ether–hexane and the solution allowed to reach 0 °C over two hours. Initially, this was surprising because the *o*-bromoanilide **6** had been reported[8] to rearrange under similar conditions and because the rearrangement of *o*-iodophenyl benzoates had required at least one methoxyl group *ortho* to the carbonyl for its success.[7] Rotational barriers in *N*,*N*-dimethylbenzamides have been determined[9] and it is quite clear from these results that the presence of an *ortho*-substituent significantly increases the free energy of activation ($\Delta G^{\ddagger}$) for the rotation about the C–N bond (for *o*-H, *o*-F, *o*-OMe, $\Delta G^{\ddagger}$ = 65.2, 73.9, 76.0 kJ mol^{-1}, respectively,[9a] or 64.41, 73.49, 75.51 kJ mol^{-1}, respectively[9b]). These increases in $\Delta G^{\ddagger}$ have been ascribed to the existence of a steric effect which prevents coplanarity and conjugation between the carbonyl group and the benzene ring



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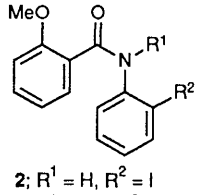
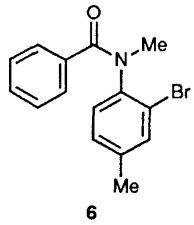


2; R^1 = H, R^2 = I
3; R^1 = Me, R^2 = I
4; R^1 = R^2 = H
5; R^1 = Me, R^2 = H



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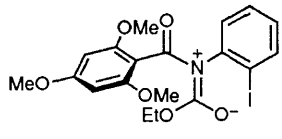

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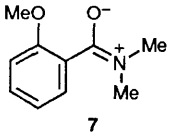

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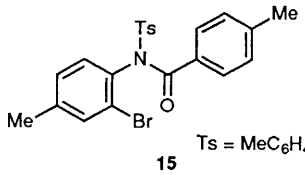

Ts = $MeC_6H_4SO_2$

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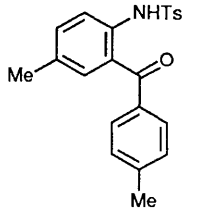

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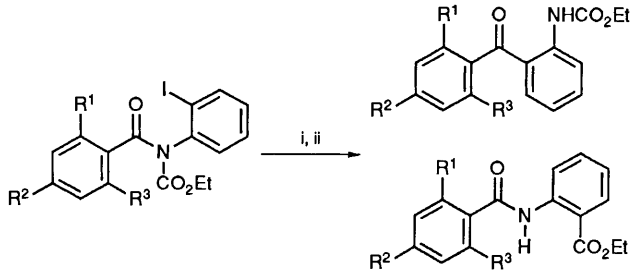


Scheme 1 *Reagents and conditions*: i, Bu^{n}Li, −100 °C; ii, −70 °C, NH_4Cl

Table 1

Carbamate	Isolated yield (%) Benzophenone	Benzamide
8 R^1 = OMe, R^2 = R^3 = H	89	0
9 R^1 = R^2 = R^3 = H	85	0
10 R^1 = R^3 = H, R^2 = F	60[a]	0
11 R^1 = R^2 = OMe, R^3 = F	18	67
12 R^1 = OMe, R^2 = H, R^3 = F	0	91
13 R^1 = R^2 = R^3 = OMe	0	0

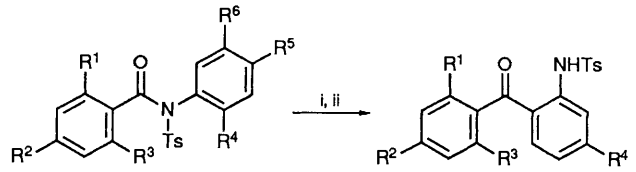
[a] An additional 28% of the product was the tertiary alcohol resulting from addition of n-butyllithium to the benzophenone.

thus increasing the significance of amide resonance (i.e. **7**). Thus, in **2** and **3** the rearrangement triggered by lithium–iodine exchange would have to proceed through a 4-*endo-trig* addition to the iminium bond rather than a 4-*exo-trig* addition to the carbonyl group.

Since the ultimate aim of this research was the development of a new route to natural acridones it was necessary to preserve the offending *ortho*-methoxy substituent and to find another way of overcoming the problem posed by amide resonance. To this end a series of carbamates† were examined (Scheme 1, Table 1) and it was gratifying to observe that the rearangement that failed with **2** and **3** proceeded smoothly with **8** to yield the benzophenone exclusively. This was also the case with the compounds **9** and **10** but with increasing *ortho* substitution (**11** and **12**) the rearrangement pathway tilted towards the second product, the amide ester. The results of Table 1 show that the rearrangement is a finely balanced process, extremely sensitive to even slight changes in electron density and double bond character in the imide (OC–N–CO) region. The failure of the 2,4,6-trimethoxybenzamide **13** to rearrange by either pathway (deiodinated starting material was recovered) must be due to the major increase in electron density at C-1. The ^{13}C NMR chemical shifts of C-1 and the carbonyl group in twelve *para*-substituted *N,N*-dimethylbenzamides have been correlated by means of a dual substituent parameter Hammett equation.[10] The $\rho_R : \rho_I$ ratios for C-1 ($\rho_R : \rho_I = 3.43$) and the carbonyl group ($\rho_R : \rho_I = 0.75$) indicate that the substituent effect experienced at the latter site is greatly decreased in comparison with the former and this is interpreted in terms of non-coplanarity of the carbonyl and phenyl moieties. Thus, in the trimethoxybenzamide **13** this electronic excess at C-1 decreases the reactivity of the adjacent carbonyl to nucleophilic attack and also forces the carbamate into the unreactive iminium structure **14**.

The synthetic utility of the rearrangement is obviously compromised by the existence of two separate pathways but a solution was promised by the solitary observation recorded

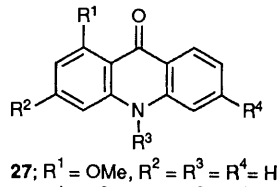
† Prepared (in 80–90% yield) by the reaction of the *o*-iodoanilide with sodium hydride and ethyl chlorocarbonate at −78 °C and warming to room temperature.



Scheme 2 *Reagents and conditions*: i, Bu^{n}Li, −100 °C; ii, −70 °C, NH_4Cl

Table 2

Sulphonamide	Benzophenone Isolated yield (%)
17 R^1 = OMe, R^3 = F, R^4 = I, R^2 = R^5 = R^6 = H	**22** (83)
18 R^1 = R^2 = OMe, R^3 = F, R^4 = I, R^5 = R^6 = H	**23** (94)
19 R^1 = R^2 = R^3 = OMe, R^4 = I, R^5 = R^6 = H	**24** (35)
20 R^1 = R^6 = OMe, R^2 = H, R^3 = F, R^4 = R^5 = I	**25** (84)
21 R^1 = R^2 = R^6 = OMe, R^3 = F, R^4 = R^5 = I	**26** (66)



27; R^1 = OMe, R^2 = R^3 = R^4 = H
28; R^1 = R^2 = OMe, R^3 = R^4 = H
29; R^1 = R^2 = OMe, R^3 = Me, R^4 = H
30; R^1 = R^4 = OMe, R^2 = R^3 = H
31; R^1 = R^2 = R^4 = OMe, R^3 = H

earlier[8] that the bromosulphonamide **15** did rearrange in moderate yield to the benzophenone **16** when treated with *tert*-butyllithium in the presence of lithium perchlorate. We therefore attempted the rearrangement with several similar sulphonamides‡ (**17–21**) with n-butyllithium (−100 °C to −70 °C, 15 min) and no lithium perchlorate. We were very pleased to discover that the reactions proceeded in high yield to a single product (Scheme 2, Table 2), the benzophenones **22–26**, respectively. It was particularly gratifying from a practical point of view that the sulphonamides **17**, and **18** and **19**, which have identical substitution as the carbamates of entries **11**, **12** and **13** (Table 1) behaved in such exemplary fashion, although the rearrangement of the electron rich trimethoxy analogue **19** was much slower and proceeded in lower yield than **17** or **18**. Both **22** and **23** were hydrolysed and cyclised in one step to the corresponding acridones **27** and **28** (NEt_4OH, THF, methanol, reflux, 70–75%) with complete regiospecificity in the cyclisation step; only the fluorine and not the equivalently situated methoxyl was replaced and the yield is also much better than yields recorded[11] for methoxy nucleophilic substitution. The acridone **28** was methylated (sodium hydride, methyl iodide, 80%) to the *N*-methyl derivative **29** which had been previously converted[12] to acronycine **1** in two steps and 81% yield.

In order to illustrate the versatility of this route to acridones, especially those with substituents in both aromatic rings, we looked for oxygenated *o*-iodoanilines for use as starting materials. *ortho*-Iodination of primary aromatic amines is not generally feasible, especially when the aromatic nucleus is further activated by methoxyl or other oxygen substituents. However, the commercially available *m*-anisidine could be diiodinated in 94% yield with benzyltrimethyl-

‡ Prepared by reaction of the iodoanilide with sodium hydride and tosyl chloride (−78 to +25 °C). The unreacted starting material was recovered and recycled (80% overall yield of sulphonamide).

ammonium dichloroiodate by the published[13] procedure to 2,4-diiodo-5-methoxyaniline and this could be converted to sulphonamides **20** and **21** in the usual way. Treatment of these compounds with two molar proportions of butyllithium under the same conditions as before gave excellent yields of deiodinated benzophenones **25** and **26** which were cyclised regiospecifically as before to acridones **30** and **31** (37 and 39% overall, respectively from the amine and acid starting materials).

The simple expedient of *N*-tosylation thus alters the electronic environment of the amide function to make it behave just like the corresponding esters did[7] in this rearrangement. This fact by itself is hardly surprising, but in practical terms it permits the development of a general, efficient route to a variety of acridones carrying oxygen substituents in both benzene rings.[16]§

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§ Satisfactory spectral and analytical data were obtained for all new compounds. Full details will be published later.

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