The Wittig Reaction of Fluorinated Amides: an Unusual Fragmentation of Oxaphosphetane Intermediates

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The fluorinated amides **1a–e** reacted with phosphorane **2** in toluene at reflux yielding a tautomeric mixture of enamines **5a–e** and imines **6a–e** *via* a putative oxaphosphetane intermediate **3**.

The Wittig reaction[1] of compounds other than aldehydes and ketones,[2] for example anhydrides and imides[3] has been extensively studied and in many cases has provided a useful method for the synthesis of heterocyclic compounds. In contrast, the Wittig reaction of amides has received relatively little attention although the reaction of *N,N*-dialkyltrifluoroacetamides with phosphoranes yielding trifluoromethylated enamines has been studied by Bégué *et al.*[4,5]

In our work on the Wittig reaction of amides, we have recently reported the synthesis of trifluoromethylated indoles and quinolones from amides **1** (R = CN, NO_2, CO_2Et; X = Br or I; $R_f = CF_3$) and phosphorane **2** using a combination of Wittig and Heck methodologies.[6,7] Thus, these amides gave the corresponding isolable enamines **5** which gave trifluoromethylated indoles in an intramolecular Heck reaction and trifluoromethylated quinolones related to Nalidixic acid in a tandem carbonylation-Heck reaction. We had tentatively assigned the *Z* stereochemistry to the isolable enamine derivatives **5**, which can be associated with intramolecular hydrogen bonding between the amine and ester moieties, and this implied the relative stereochemistry depicted in the corresponding putative oxaphosphetane intermediates **3**. Additionally, we have also prepared other trifluoromethylated heterocycles using similar Wittig reactions.[8,9]

Since our previous investigations of the Wittig reaction of fluorinated amides had concentrated on the reaction of trifluoromethylated amides, we were interested in investigating whether this reaction could be extended to the homologous fluorinated amides **1** ($R_f = CF_2CF_3$ and $CF_2CF_2CF_3$) and in this paper we report our unexpected observations of the reactions of amides **1a–e** with phosphorane **2** (Scheme 1). Amides **1a–e** were prepared (63–83%) by heating the appropriate aniline and fluorinated anhydride derivatives in dichloromethane at reflux.

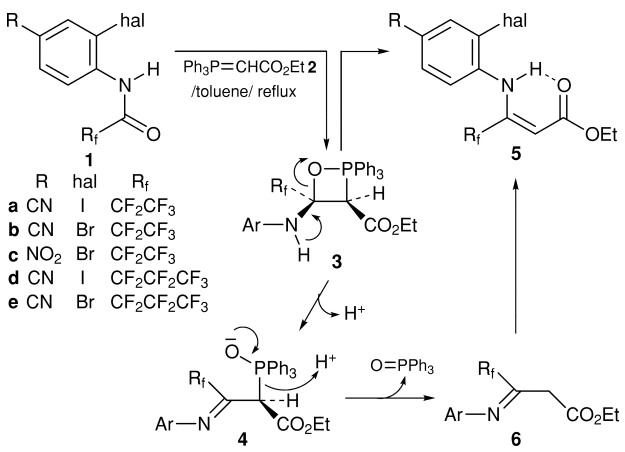
When amides **1a–e** were reacted with an excess of phosphorane **2** in boiling toluene for 5–7 hours, an inseparable mixture of the corresponding enamines **5a–e** and another product, to which we have assigned the tautomeric imine structures **6a–e**, were isolated after column chromatography with the imines generally being the major products. The enamines **5**:imines **6** ratios were typically in the range 25:75 to 50:50. When $R_f = CF_2CF_3$ the yields of the mixture of tautomers were generally moderate to good (45–75%) but with $R_f = CF_2CF_2CF_3$ the yields were only moderate (30–42%).

The ^1H NMR spectra ($CDCl_3$, 270 MHz) of these mixtures exhibited two singlets which were attributed to the alkenyl (δ 5.88–6.00) and methylene protons (δ 3.37–3.40) in these two products respectively. Two distinct sets of aromatic signals were also observed corresponding to the aromatic moieties of products **5a–e** and **6a–e** and the methyl and methylene protons of the ester groups in each of these products had co-incident chemical shifts. A broad singlet (δ 7.7–8.3) was also observed which was assigned to the >NH proton in compounds **5a–e**. In the case of tautomers **5c/6c**, a ^{13}C NMR spectrum confirmed the presence of methylene protons: the signal at δ 36.1 which was assigned to the methylene carbon atom was observed as a triplet in the proton-coupled spectrum.

The effect of acid on the enamine **5c**–imine **6c** tautomeric mixture has also been studied by ^1H NMR spectroscopy. Thus, to a solution of this mixture of compounds in $CDCl_3$ was added a drop of trifluoroacetic acid. After 1 hour there was relatively little change in the spectrum but after 24 hours the quantity of the methylene tautomer **6c** had diminished considerably. The major product was not however the *Z* alkene **5c**, but the corresponding *E* alkene which showed a signal at δ 5.7. The upfield location of the *E* enamine alkenyl proton suggests that we have correctly assigned the stereochemistry in compounds **5a–e** and in our previously reported trifluoromethylated compounds.[6,7]

It seemed unlikely that the enamines **5a–e** had tautomerised to the imines **6a–e** under the reaction conditions because this would involve loss of conjugation of the nitrogen lone pair with both the ester group and the cyano or nitro substituents. Thus, we consider that these two sets of tautomers **5a–e** and **6a–e** are probably formed in either competing reaction pathways or that imines **6a–e** are formed initially and these imines **6a–e** then tautomerise giving the corresponding enamines **5a–e**. Imines **6a–e** are presumed to have been formed by fragmentation of the oxaphosphetane **3** giving the intermediate **4** which then eliminates triphenylphosphine oxide as shown in Scheme 1.

We have therefore demonstrated that fluorinated amides can participate in the Wittig reaction giving the anticipated enamine products together with unexpected imine products.



Scheme 1

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Techniques used: ^{1}H NMR, IR, chromatography

Schemes: 1

References: 9

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