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# The Wittig reaction of fluorinated amides: formation of enamine and imine tautomers

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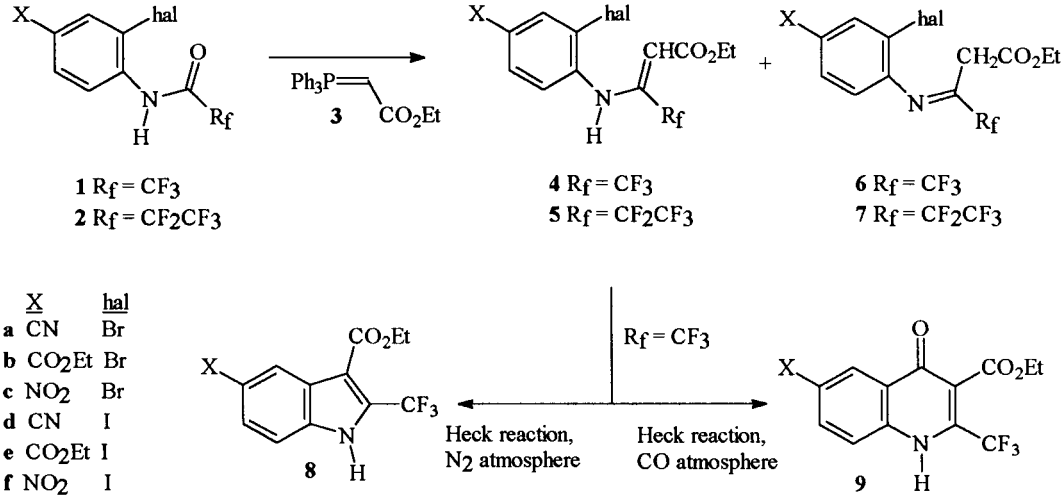
**Abstract**—Amides **1a–f** reacted with phosphorane **3** at room temperature giving a mixture of enamine **4a–f** and imine **6a–f** tautomers in excellent yields. These tautomers were formed in competing reaction pathways. Silica gel promoted the conversion of **4d** into **6d**. Amides **1d** and **1f** reacted with the methyl analogue of phosphorane **3** giving tautomers **11a,b/12a,b**. The β-amino acid derivatives, **13a,b**, were formed from sodium borohydride reduction of imines **12a,b**. 

## 1. Introduction

We have shown recently that fluorinated amides **1a–f** reacted with phosphorane **3** in boiling toluene solution giving the enamines **4a–f** after column chromatography (Scheme 1).[1,2] These enamines were precursors of indole derivatives **8** and quinolone derivatives **9**. However, when amides **2a,c** and **d** were reacted with phosphorane **3** in boiling toluene solution, an inseparable mixture of the enamine **5a,c** and **d** and imine tautomers **7a,c** and **d** were isolated by column chromatography, with the imine tautomers generally being the major reaction product.[3]

The formation of both enamine **5a,c** and **d** and imine **7a,c** and **d** tautomers has been rationalised by the mechanism shown in Scheme 2 in which the putative oxaphosphetane intermediate **10** can give the products in competing reaction pathways. Alternatively, only one of the products might be formed initially via intermediate **10** and subsequent tautomerism would yield the other product. Intuitively, tautomerism of enamines **5** giving imines **7** seemed unlikely because the nitrogen lone pair in enamines **5** can be mesomerically associated with both the carbonyl and X-groups. In Scheme 2, the intermediate **10** has been depicted with the ethoxycarbonyl and arylamine groups in a *cis* relationship because we believe the enamine **4/5** products are the *Z* geometrical isomers.[2]




**Scheme 1.**

*Keywords*: Wittig reaction; fluorinated amides; tautomerism.

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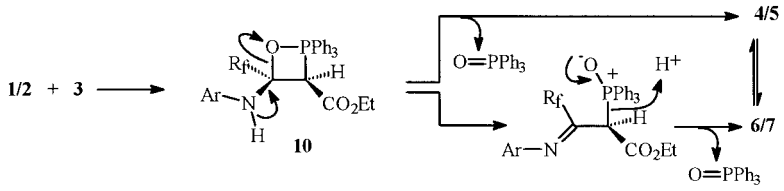



**Scheme 2.**

In view of the formation of substantial quantities of imine products **7a**,**c** and **d** from the Wittig reaction of amides **2a**,**c** and **d**, we decided to reinvestigate the Wittig reaction of the amides **1a**–**f** to ascertain whether imine products **6a**–**f** had also been formed, and if this was the case, to eludicate whether competing or sequential reaction pathways were involved.

## 2. Discussion

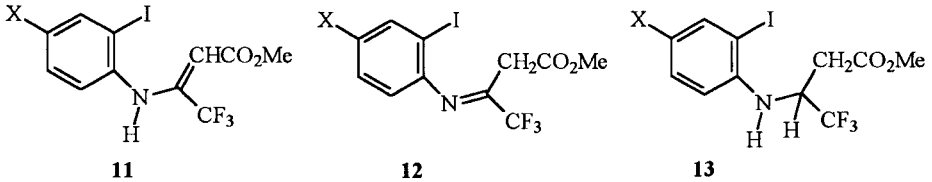
When the Wittig reactions of compounds **1d**–**f** with phosphorane **3** were performed in $d_8$-toluene solution and monitored by $^1$H NMR spectroscopy, we quickly established that the reaction proceeded at *room temperature* giving a mixture of enamine **4d**–**f** and imine **6d**–**f** products in the ratios shown in Table 1. Furthermore, after the reaction was complete, there were no significant changes in these ratios over several days. This suggested that either these products were formed in (a) competing pathways, or (b) that after formation of enamines **4d**–**f** in a relatively slow reaction, a rapid equilibrium between the enamines **4d**–**f** and imines **6d**–**f** was then established.

On a preparative scale in toluene solution, the room temperature Wittig reaction of compounds **1a**–**f** gave, after chromatography over silica gel, an inseparable mixture of the enamine **4a**–**f** and imine **6a**–**f** products. The ratios of enamine **4a**–**f** and imine **6a**–**f** products and reaction yields are reported in Table 1. With the exception of the reaction of amide **1b**, these Wittig reactions proceeded in a significantly better yield at room temperature than in boiling toluene solution and were also free from other by-products. Enamine **4d** and imine **6d** were prepared in slightly different ratios on two occasions and reasons for this are discussed below. We also prepared, on a preparative scale, the derivatives **11a/12a** (80:20) in quantitative yield and **11b/12b** (90:10) in 74% yield from the appropriate amides and the methyl ester analogue of phosphorane **3**.

Enamines **4a**–**f** and **11a**,**b**/imines **6a**–**f** and **12a**,**b** were all isolated as oils after chromatography. The enamine/imine ratios reported in Table 1 reflect the composition of these oils. However, on standing the cyano derivatives **4d/6d** and **11a/12a** crystallised quickly. When the $^1$H NMR spectra of the crystalline materials were determined in $CDCl_3$ solution, only the enamine tautomers **4d**, mp 90–91°C and **11a**, mp 79–80°C were present indicating that in the absence of solvent tautomerism of the imines to the corresponding enamines had occurred. After standing for several days in $CDCl_3$ solution, no change in the $^1$H NMR spectra was detected showing that enamines **4d** and **11a** were stable in $CDCl_3$ solution and did not undergo tautomerism to their corresponding imine tautomers. This enamine to imine tautomerism in the absence of solvent would explain the different enamine/imine ratios mentioned above.

Now that we had pure samples of enamines **4d** and **11a** we were able to demonstrate next that the enamine and imine products depicted in Scheme 2 were probably formed in competing reactions. Thus, the room temperature Wittig reaction between amide **1d** and phosphorane **3** gave, after chromatography, an oil that had an enamine **4d**/imine **6d** ratio of 70:30 by $^1$H NMR spectroscopy ($CDCl_3$). This solution was allowed to stand for two days at room temperature and after this time there was no change in the enamine **4d**/imine **6d** ratio. A sample of pure enamine **4d** was then added giving a new enamine **4d**/imine **6d** ratio of 80:20. When the spectrum was re-determined after a further three days, no significant change in the latter ratio was observed indicating that tautomerism had not occurred. If an equilibrium had been established between enamine **4d** and imine **6d** then the ratio of these tautomers should have changed from 80:20 to 70:30. Additionally, when a sample of triphenylphosphine oxide was added to a $CDCl_3$ solution of the pure methyl ester **11a**, there was no change in the $^1$H NMR spectrum after several days. This excluded triphenylphosphine oxide as a potential catalyst in enamine/imine tautomerism.

When the enamine **4d**–**f**/imine **6d**–**f** ratios from the preparative scale reactions were compared with those from the $^1$H NMR experiments, it was apparent that the proportion of imine products was significantly greater in the preparative scale reactions. This suggested that during column chromatography the enamine tautomer might have been converted to some extent to the imine tautomer. This




**a**, X = CN; **b**, X = $NO_2$

**Table 1.**

| Amide | Yield (%)[a] | **4**:**6**[b] Preparative scale | **4**:**6**[c] $^1$H NMR scale |
|---|---|---|---|
| **1a** | 84 (69) | 95:5 | – |
| **1b** | 90 (95) | 90:10 | – |
| **1c** | 86 (63) | 80:20 | – |
| **1d** | 93 (63) | 80:20/70:30[d] | 85:15 |
| **1e** | 84 (58) | 75:25 | 85:15 |
| **1f** | 95 (54) | 70:30 | 90:10 |

[a] Values in parenthesis are yields previously obtained in toluene at reflux.[2]
[b] Ratios determined by $^1$H NMR spectroscopy ($CDCl_3$) after column chromatography.
[c] Reaction performed in an NMR-tube in $d_8$ toluene solution; the products were not isolated.
[d] Two reactions.

was confirmed as follows. A sample of pure enamine **4d** was dissolved in $CDCl_3$ and the $^1$H NMR spectrum recorded. The $^1$H NMR spectrum was re-recorded after several days but no significant change had taken place. The solution was added to a small portion of silica-gel in a sample tube and allowed to stand at room temperature for two days. After removal of the silica gel by filtration, the $^1$H NMR spectrum was re-determined. The enamine **4d**/imine **6d** ratio was now 80:20, indicating that silica gel could catalyse the interconversion of compounds **4d** and **6d** (Scheme 3). Protonation of enamine tautomers has been postulated as a step in the hydroylsis of enamine/imine tautomers.[4] α,β-Unsaturated α-amino acids have also been shown to undergo hydrolysis via their imine tautomers.[5]

Having established that enamine/imine tautomerism does not occur under neutral conditions but can be promoted by silica gel, we next investigated the $NaBH_4$ reduction of pure enamines **11a**,**b** in methanol solution. If an enamine **11a**,**b**/imine **12a**,**b** equilibrium could be established under these conditions, then reduction of the imines **12a**,**b** would yield the saturated ester derivatives **13a**,**b**. When compounds **11a** and **b** were treated with $NaBH_4$ at room temperature, the β-amino acid derivatives **13a** and **b** were isolated in 80 and 34% yields, respectively.

## 3. Conclusions

We have demonstrated that the room temperature Wittig reaction of amides **1a**–**f** with phosphorane **3** gave excellent yields of enamine **4a**–**f**/imine **6a**–**f** products, with the enamine tautomer as the major product. Enamines and imines are probably formed in competing reactions. Silica gel has also been shown to catalyse enamine/imine tautomerism and enamines **11a**,**b** could be reduced with $NaBH_4$ giving β-amino acid derivatives **13a**,**b**.

## 4. Experimental

### 4.1. Wittig reactions amides 1a–f

A solution of the amide **1a**–**f**[2] (1.0 mmol) and phosphorane **3** (or its methyl analogue as appropriate) (1.4 mmol) in toluene (5 mL) was allowed to stand at room temperature for 7–9 days. In the case of the preparation of **11a**,**b**/**12a**,**b** a mixture of toluene (5 mL) and dichloromethane (2 mL) was used to ensure complete solubility of the reactants. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, eluent $CH_2Cl_2$) giving a mixture of **4a**–**f**/**6a**–**f** or **11a**,**b**/**12a**,**b** in the ratios and yields reported in Table 1 and the text. $^1$H NMR data for compounds **4a**–**f** have been reported previously.[2] $^1$H NMR (270 MHz, $CDCl_3$) data for compounds **6a**–**f**.

**4.1.1. Compounds 6a–f. 6a.** δ 7.92 (1H, d, *J*=2 Hz, C3–*H*), 7.63 (1H, dd, *J*=8, 2 Hz, C5–*H*), 7.01 (1H, d, *J*=8 Hz, C6–*H*), 4.18 (2H, q, *J*=7 Hz, $-CH_2CH_3$), 3.37 (2H, s, $>CH_2$), 1.25 (3H, t, *J*=7 Hz, $-CH_2CH_3$).

**6b.** δ 8.31 (1H, d, *J*=2 Hz, C3–*H*), 8.00 (1H, dd, *J*=8, 2 Hz, C5–*H*), 6.94 (1H, d, *J*=8 Hz, C6–*H*), 4.36 (2H, q, *J*=7 Hz, $-CH_2CH_3$), 4.18 (2H, q, *J*=7 Hz, $-CH_2CH_3$), 3.38 (2H, s, $>CH_2$), 1.38 (3H, t, *J*=7 Hz, $-CH_2CH_3$), 1.25 (3H, t, *J*=7 Hz, $-CH_2CH_3$).

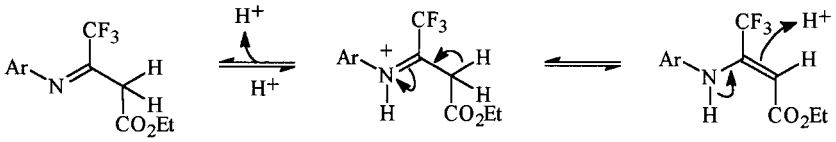
**6c.** δ 8.52 (1H, d, *J*=2 Hz, C3–*H*), 8.12 (1H, dd, *J*=8, 2 Hz, C5–*H*), 7.04 (1H, d, *J*=8 Hz, C6–*H*), 4.18 (2H, q, *J*=7 Hz, $-CH_2CH_3$), 3.39 (2H, s, $>CH_2$), 1.25 (3H, t, *J*=7 Hz, $-CH_2CH_3$).

**6d.** δ 8.12 (1H, d, *J*=2 Hz, C3–*H*), 7.63 (1H, dd, *J*=8, 2 Hz, C5–*H*), 6.95 (1H, d, *J*=8 Hz, C6–*H*), 4.18 (2H, q, *J*=7 Hz, $-CH_2CH_3$), 3.36 (2H, s, $>CH_2$), 1.25 (3H, t, *J*=7 Hz, $-CH_2CH_3$).

**6e.** δ 8.57 (1H, d, *J*=2 Hz, C3–*H*), 8.03 (1H, dd, *J*=8, 2 Hz, C5–*H*), 6.94 (1H, d, *J*=8 Hz, C6–*H*), 4.38 (2H, q, *J*=7 Hz, $-CH_2CH_3$), 4.18 (2H, q, *J*=7 Hz, $-CH_2CH_3$), 3.36 (2H, s, $>CH_2$), 1.38 (3H, t, *J*=7 Hz, $-CH_2CH_3$), 1.25 (3H, t, *J*=7 Hz, $-CH_2CH_3$).

**6f.** δ 8.76 (1H, d, *J*=2 Hz, C3–*H*), 8.25 (1H, dd, *J*=8, 2 Hz, C5–*H*), 7.00 (1H, d, *J*=8 Hz, C6–*H*), 4.20 (2H, q, *J*=7 Hz, $-CH_2CH_3$), 3.38 (2H, s, $>CH_2$), 1.25 (3H, t, *J*=7 Hz, $-CH_2CH_3$).

**4.1.2. Compounds 11a/12a.** Compounds **11a/12a** were obtained in quantitative yield as a colourless oil which crystallised on standing giving pure **11a** as a cream solid, mp 79–80°C. Found: C, 36.0; H, 1.7; N, 7.0. $C_{12}H_8F_3IN_2O_2$




**Scheme 3.**

requires C, 36.4; H, 2.0; N, 7.1%; IR (KBr) 2229, 1684, 1627, 1589, 1294, 1191 and 1134 $cm^{-1}$; $^1H$ NMR **11a** $\delta$ (270 MHz, $CDCl_3$) 9.68 (1H, broad s, >N*H*), 8.14 (1H, d, *J*=2 Hz, C3–*H*), 7.61 (1H, dd, *J*=8, 2 Hz, C5–*H*), 7.25 (1H, d, *J*=8 Hz, C6–*H*), 5.64 (1H, s, alkene–*H*), 3.80 (3H, s, –C$H_3$).

$^1H$ NMR **12a** $\delta$ (270 MHz, $CDCl_3$) 8.16 (1H, d, *J*=2 Hz, C3–*H*), 7.64 (1H, dd, *J*=8, 2 Hz, C5–*H*), 6.95 (1H, d, *J*=8 Hz, C6–*H*), 3.70 (3H, s, –C$H_3$), 3.38 (2H, s, >C$H_2$).

**4.1.3. Compounds 11b/12b.** Compounds **11b/12b** (74%) were obtained as an oil that crystallised giving pure **11b** as a pale yellow solid, mp 83–85°C. Found: C, 31.8; H, 1.55; N, 6.7. $C_{11}H_8F_3IN_2O_4$ requires C, 31.75; H, 1.9; N, 6.7%; IR (KBr) 3086, 1685, 1637, 1582, 1519, 1350, 1300, 1221, 1193 and 1135 $cm^{-1}$; $^1H$ NMR **11b** $\delta$ (270 MHz, $CDCl_3$) 9.65 (1H, broad s, >NH), 8.75 (1H, d, *J*=2 Hz, C3–*H*), 8.25 (1H, dd, *J*=8, 2 Hz, C5–*H*), 7.24 (1H, d, *J*=8 Hz, C6–*H*), 5.70 (1H, s, alkene–*H*), 3.81 (3H, s, –C$H_3$).

$^1H$ NMR **12b** $\delta$ (270 MHz, $CDCl_3$) 8.77 (1H, d, *J*=2 Hz, C3–*H*), 8.23 (1H, dd, *J*=8, 2 Hz, C5–*H*), 6.98 (1H, d, *J*=8 Hz, C6–*H*), 3.71 (3H, s, –C$H_3$), 3.38 (2H, s, >C$H_2$).

**4.1.4. Compounds 13a and b.** To a stirred solution of compound **11a** (0.20 g, 0.51 mmol) in methanol (5 mL) at room temperature was added $NaBH_4$ (0.03 g, 0.79 mmol) portionwise over 2 min. The mixture was stirred (1 h) at room temperature and then evaporated. Water and $CH_2Cl_2$ were added to the residue. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated giving compound **13a** as a yellow oil (0.16 g, 80%), which solidified upon standing. Recrystallisation from heptane gave white needles, mp 99°C. Found: C, 36.3; H, 7.1; N, 2.4. $C_{12}H_{10}F_3IN_2O_2$ requires C, 36.2; H, 7.0, N, 2.6%; IR (KBr) 3372, 2225, 1733 and 1593 $cm^{-1}$; $^1H$ NMR $\delta$ (270 MHz, $CDCl_3$) 7.95 (1H, d, *J*=2 Hz, C3–*H*), 7.53 (1H, dd, *J*=8, 2 Hz, C5–*H*), 6.79 (1H, d, *J*=8 Hz, C6–*H*), 5.08 (1H, d, *J*=9 Hz, >N*H*), 4.58 (1H, m, >C*H*$CF_3$), 3.74 (3H, s, –C$H_3$), 2.84 (2H, m, –C$H_2CO_2$Me). Similarly compound **13b** was prepared in 34% yield (the formation of a transient deep red solution was noted after the addition of $NaBH_4$). Compound **13b** was obtained as a pale yellow oil which solidified on standing. Recrystallisation from heptane gave yellow needles, mp 85–87°C. Found: C, 31.6; H, 2.1; N, 6.6. $C_{11}H_{10}FI_3N_2O_4$ requires C, 31.6; H, 2.4; N, 6.7%; IR (KBr) 3346, 1728, 1588, 1507, 1328 and 1128 $cm^{-1}$; $^1H$ NMR $\delta$ (270 MHz, $CDCl_3$) 8.61 (1H, d, *J*=2 Hz, C3–*H*), 8.17 (1H, dd, *J*=8, 2 Hz, C5–*H*), 6.80 (1H, d, *J*=8 Hz, C6–*H*), 5.32 (1H, d, *J*=9 Hz, >N*H*), 4.60 (1H, m, >C*H*$CF_3$), 3.75 (3H, s, –C$H_3$), 2.87 (2H, m, –C$H_2CO_2$Me).

## References

1. Latham, E. J.; Stanforth, S. P. *Chem. Commun.* **1996**, 2253.
2. Latham, E. J.; Stanforth, S. P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2059.
3. Boulard, S.; Gordon, P.; Stanforth, S. P. *J. Chem. Res. (Synop.)* **1998**, 728.
4. Coward, J. K.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 5329. Guthrie, J. P.; Jordan, F. *J. Am. Chem. Soc.* **1972**, *94*, 9132. Jordan, F. *J. Am. Chem. Soc.* **1974**, *96*, 825. Capan, B.; Wu, Z.-P. *J. Org. Chem.* **1990**, *55*, 2317.
5. Lu, S. P.; Lewin, A. H. *Tetrahedron* **1998**, *54*, 15097.