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Fused Pyridine Derivatives from the Wittig Reaction of some Fluorinated Amides

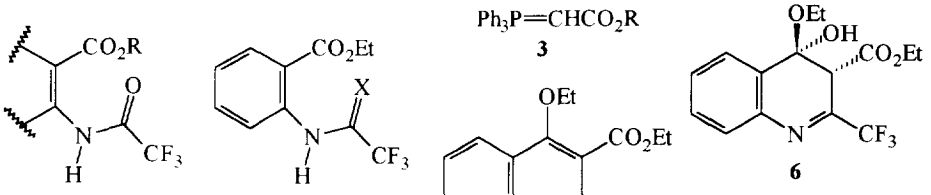
Elliot J. Latham, Steven M. Murphy and Stephen P. Stanforth*

Department of Chemical and Life Sciences, University of Northumbria at Newcastle, Newcastle upon Tyne, NE1 8ST, UK.

Abstract: Compound **2** reacted with phosphorane **3** (R = Et) giving the quinoline derivative **5** whereas thiophenes **7** and **9** gave enamines **8** and **10** respectively with the appropriate phosphorane **3** (R = Me or Et). Pyridine derivative **11** yielded only ethyl 2-aminonicotinate with phosphorane **3** (R = Et). Compounds **8** and **10** gave the fused pyridine derivatives **14** and **15** respectively when treated with sodium hydride.

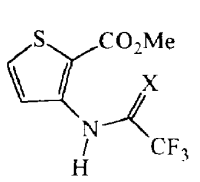
The Wittig reaction[1] of compounds other than aldehydes and ketones,[2] for example anhydrides and imides[3] has been extensively studied and in many cases has provided a useful method for the preparation of heterocyclic molecules. In contrast, the Wittig reaction of amides has received little attention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

We were interested in investigating the Wittig reaction of fluorinated amide derivatives represented by the general structure **1** in which the trifluoroacetamido substituent is located adjacent to an ester group on an aromatic ring. We reasoned that the amide carbonyl group in structure **1** should be sufficiently electron deficient in these compounds to allow them to participate in a Wittig reaction. Thus, both the mesomeric association of the nitrogen lone pair with the ester group together with the inductive effect of the trifluoromethyl group should enhance the electrophilicity of the amide carbonyl group. If the Wittig reaction of compounds **1** were successful, the resulting enamines may then participate in an intramolecular cyclisation reaction with the adjoining ester group yielding fused pyridine derivatives.

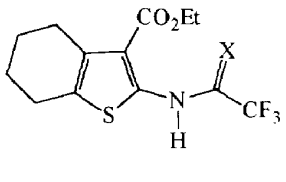


When ethyl 2-trifluoromethylamidobenzoate **2** was heated in the melt (180 - 200°) with carboethoxymethylenetriphenylphosphorane **3** (R = Et), the enamine **4** was not isolated but the quinoline derivative **5** was produced in 30 % yield.[6] Enamine **4** is evidently produced in the reaction but it undergoes

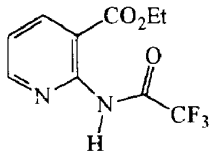
an intramolecular cyclisation with the ethyl ester group giving the intermediate **6** in which the most bulky C3 and C4 substituents *ie* the carboethoxy and ethoxy group respectively adopt an anti-relationship. Elimination of water (rather than ethanol) from intermediate **6** therefore follows giving the observed product **5**. At lower reaction temperatures (toluene at reflux) this reaction was slow and forcing conditions were therefore necessary to ensure an adequate reaction rate.



7; X = O
8; X = $CHCO_2Me$



9; X = O
10; X = $CHCO_2Et$



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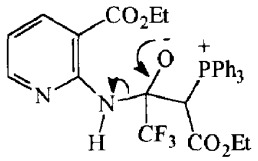

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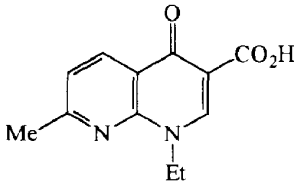
We next investigated the reaction of methyl 3-trifluoromethylamidothiophene-2-carboxylate **7** with carbomethoxymethylenetriphenylphosphorane **3** (R = Me). In contrast to the transformation **2** → **5** described above, thiophene derivative **7** and phosphorane **3** (R = Me) reacted in toluene at reflux yielding the Wittig reaction product **8** (65 % yield). Only one geometrical isomer was produced in this reaction but we do not know whether it is the *E* isomer (with the most bulky substituents in a *trans* relationship) or the *Z* isomer (which can be associated with intramolecular hydrogen bonding between the >NH group and the alkenyl ester substituent). Similarly, the tetrahydrobenzo[b]thiophene derivative **9** reacted with phosphorane **3** (R = Et) in toluene at reflux yielding compound **10** (32 % yield). The difference in reactivities of amides **7** and **9** compared to amide **2** is probably a consequence of an increased association of the nitrogen lone pair with the ester group in the thiophene systems thus creating a more electrophilic amide carbonyl group in compounds **7** and **9**.

When the pyridine derivative **11** was reacted with phosphorane **3** (R = Et) in the melt (180°), only ethyl 2-aminonicotinate was isolated. In this reaction, the betaine intermediate **12** eliminates an aminopyridine moiety (arrows, formula **12**) in preference to triphenylphosphine oxide extrusion. Thus, the relatively electron deficient pyridine ring behaves as a leaving group in this reaction.



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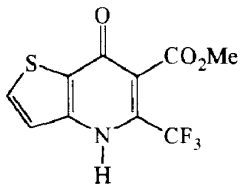

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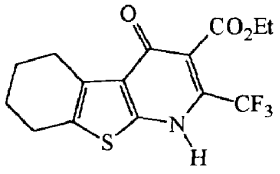

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Nalidixic acid **13** and related compounds are important anti-bacterial agents which have attracted considerable interest.[7,8] Treatment of thiophene derivatives **8** and **10** with sodium hydride yielded the fused

pyridine derivatives **14** (56 % yield) and **15** (32 % yield) respectively which are structually related to nalidixic acid **13**.

We have thus demonstrated a range of reactivities of compounds **1** towards phosphoranes **3** in the Wittig reaction. Some of these compounds have been transformed into nalidixic acid **13** analogues.

EXPERIMENTAL

Proton nmr were recorded at 90 MHz in $CDCl_3$ solution and infra-red spectra were obtained from KBr discs. Chromatography was performed using silica gel.

2-Trifluoromethyl-3-carboethoxy-4-ethoxyquinoline **5**. Ethyl 2-trifluoromethylamidobenzoate[9] **2** (0.5 g) (prepared from ethyl anthranilate and trifluoroacetic anhydride) and phosphorane **3** (R = Et) (1.3 g) were heated (180 - 200°, oil-bath temperature) under a nitrogen atmosphere (10 hours). Purification of the reaction mixture by column chromatography (eluent ether: hexane, 1:19) afforded compound **5** (0.16 g, 30 %) as white needles, m.p. 111-113°. Found: C, 57.65; H, 4.4; N, 4.6. $C_{15}H_{14}F_3NO_3$ requires C, 57.5; H, 4.5; N, 4.5 %. ν_{max} 2990, 1740, 1565, 1500, 1380, 1350, 1250 1150 and 1030 cm^{-1}. δ 8.20 (2H, dd, J 9 and 2 Hz, Ar<u>H</u>), 7.72 (2H, m, Ar<u>H</u>), 4.42 (4H, q, J 7 Hz, 2 x -OC<u>H</u>$_2$CH$_3$) and 1.35 (6H, t, J 7 Hz, 2 x -OCH$_2$C<u>H</u>$_3$).

Methyl N-*(2-Carbomethoxy-3-thienyl)-3-amino-4,4,4-trifluorobutenoate* **8**. Compound **7** (0.75 g)[10] and phosphorane **3** (R = Me) (2.0 g) were heated at reflux (9 hours) in toluene (30 ml) under a nitrogen atmosphere. After cooling to room temperature the toluene was evaporated and the residue was purified by column chromatography (eluent: CH_2Cl_2) giving compound **8** (0.59 g, 65 %) as a white powder, m.p. 58-60° (from methanol). Found: C, 42.9; H, 3.1; N, 4.45. $C_{11}H_{10}F_3NO_4S$ requires C, 42.7; H, 3.3; N, 4.5 %. ν_{max} 3075, 2950, 2900, 1680, 1620, 1550, 1440, 1420, 1200 and 820 cm^{-1}. δ 11.16 (1H, broad s, >N<u>H</u>), 7.40 (1H, d, J 6 Hz, Ar<u>H</u>), 7.02 (1H, d, J 6 Hz, Ar<u>H</u>), 5.56 (1H, s, =C<u>H</u>-), 3.90 (3H, s, -OC<u>H</u>$_3$) and 3.78 (3H, s, -OC<u>H</u>$_3$).

Ethyl 2-Trifluoromethylamido-4,5,6,7-tetrahydrobenzo[b]thienyl-3-carboxylate **9**. Compound **9** (89 %) was obtained as cream needles, m.p. 129-131° (from ethanol) by a similar method to that described above for compound **7**. Found: C, 48.85; H, 4.6; N, 4.3. $C_{13}H_{14}F_3NO_3S$ requires C, 48.6; H, 4.4; N, 4.4 %. ν_{max} 3160, 2940, 1715, 1655, 1565, 1450, 1380 and 1230 cm^{-1}. δ 12.25 (1H, broad s, >N<u>H</u>), 4.38 (2H, q, J 8 Hz, -OC<u>H</u>$_2$CH$_3$), 2.94-2.55 (4H, m, 2 x -C<u>H</u>$_2$-), 1.91-1.68 (4H, m, 2 x -C<u>H</u>$_2$-) and 1.39 (3H, t, J 8 Hz, -OCH$_2$C<u>H</u>$_3$).

Ethyl N-*(3-Carboethoxy-4,5,6,7-tetrahydrobenzo[b]thienyl)-3-amino-4,4,4-trifluorobutenonate* **10**. Compound **10** (83 %) was obtained as a yellow powder, m.p. 42-45° (from acetonitrile) from compound **9** and phosphorane **3** (R = Et) using a similar method to that described above for the preparation of compound **8**. Found: C, 52.5; H, 5.45; N, 3.45. $C_{17}H_{20}F_3O_4NS$ requires C, 52.2; H, 5.2; N, 3.6 %. ν_{max} 3100, 2965, 1710, 1625, 1565 and 1210 cm^{-1}. δ 10.49 (1H, broad s, >N<u>H</u>), 5.48 (1H, s, =C<u>H</u>-), 4.50-4.02 (4H, m, 2 x -OC<u>H</u>$_2$CH$_3$), 2.95-2.30 (4H, m, 2 x -C<u>H</u>$_2$-), 1.95-1.68 (4H, m, 2 x -C<u>H</u>$_2$-) and 1.42-1.15 (6H, m, 2 x -OCH$_2$C<u>H</u>$_3$).

Ethyl 2-Trifluoroamidonicotinate **11**. A mixture of ethyl 2-aminonicotinate (1.5 g) and trifluoroacetic anhydride (4.0 g) in dichloromethane (40 ml) was stirred (12 hours) at room temperature. The mixture was washed with sodium hydrogen carbonate solution and then with water, dried ($MgSO_4$) and evaporated

giving compound **11** (1.09 g, 46 %) as white needles, m.p. 137-139° (from ethanol). Found: C, 43.05; H, 4.1; N, 10.2. $C_{10}H_9F_3N_2O_3.H_2O$ requires C, 42.9; H, 4.0; N, 10.0 %. ν_{max} 3350, 3070, 2970, 1715, 1680, 1610, 1560, 1425, 1370, 1280 and 720 cm^{-1}. δ 12.04 (1H, broad s, >NH), 8.52 (1H, dd, J 7 and 2 Hz, ArH), 8.04-7.86 (1H, m, ArH), 6.91-6.70 (1H, m, ArH), 4.42 (2H, q, J 7 Hz, $-OCH_2CH_3$) and 1.41 (3H, t, J 7 Hz, $-OCH_2CH_3$).

Reaction of Compound **11** *with Phosphorane* **3** *(R = Et).* A mixture of compound **11** (0.75 g) and phosphorane **3** (R = Et) (2.0 g) was heated (15 hours) in toluene (25 ml) at reflux under a nitrogen atmosphere. Very little reaction had taken place (tlc) after this time. The toluene was evaporated and the residue was heated (10 hours) in the melt (180°, oil bath temperature). The reaction mixture was purified by column chromatography (eluent: petroleum ether, ethyl acetate 1:1) giving ethyl 2-aminonicotinate (0.3 g, 63 %), identical with an authentic sample.

Methyl 2-Trifluoromethyl-4,7-dihydro-7-oxo-thieno[3,2-b]pyridine-6-carboxylate **14**. A mixture of compound **8** (0.4 g) and sodium hydride (80% dispersion in oil, 0.1 g) in dry tetrahydrofuran (20 ml) was heated under reflux (14 hours) under a nitrogen atmosphere and then allowed to cool to room temperature. Water was then added cautiously and the mixture was extracted with dichloromethane. The organic layer was dried ($MgSO_4$) and evaporated giving compound **14** (0.20 g, 56 %) as white needles, m.p. 183-184.5° (from acetonitrile). Found: C, 43.6; H, 2.0; N, 5.1. $C_{10}H_6F_3NO_3S$ requires C, 43.3; H, 2.19; N, 5.05 %. ν_{max} 3210, 3050, 2920, 1720, 1620, 1555, 1515, 1415, 1300, 1190 and 780 cm^{-1}. δ 7.96 (1H, d, J 8 Hz ArH), 7.61 (1H, d, J 8 Hz, ArH) and 4.06 (3H, s, $-OCH_3$). The >NH signal was too broad to locate.

Ethyl 2-Trifluoromethyl-1,4,5,6,7,8-hexahydro-4-oxo-[1]benzothieno[2,3-b]pyridine-3-carboxylate **15**. Compound **15** (32 %) was obtained as a white powder, m.p. 80-81° (from ethanol) in a similar manner as described above for the preparation of compound **14**. Found: C, 52.5; H, 3.85; N, 3.9. $C_{15}H_{14}F_3NO_3S$ requires C, 52.2; H, 4.1; N, 4.1 %. ν_{max} 2980, 2910, 1665, 1580, 1500, 1475, 1300, 1180 and 1125 cm^{-1}. δ 12.18 (1H, broad s, >NH), 4.50 (2H, q, J 8 Hz, $-OCH_2CH_3$), 3.25-2.72 (4H, m, 2 x $-CH_2-$), 2.08-1.78 (4H, m, 2 x $-CH_2-$) and 1.42 (3H, t, J 8Hz, $-OCH_2CH_3$).

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