Synthesis of indoles and quinolones by sequential Wittig and Heck reactions

Elliot J. Latham and Stephen P. Stanforth*

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

***N*-Trifluoroacetylanilines 6 and 7 undergo a Wittig reaction with phosphorane 2 (R = Et) giving enamine derivatives 9 and 10 respectively which are precursors to indoles 4 and quinolones 5.**

In two recent publications,[1,2] we have shown that the Wittig reaction of aryltrifluoroacetamido derivatives **1** (R = Me or Et) with phosphorane **2** (R = Me or Et) in toluene under reflux or in the melt (180 °C) yielded enamines **3** which were precursors to fused trifluoromethylated pyridine derivatives by either thermal or base initiated cyclisation at the adjacent arylester group (Scheme 1). Here we report an extension to this methodology which enables the preparation of the novel 5-substituted ethyl 2-trifluoromethylindole-3-carboxylate derivatives **4**[3] and also of the 6-substituted ethyl 2-trifluoromethylquinol-4-one-3-carboxylates **5** from common intermediates. Heterocycles **5** are structurally related to the quinolone antibacterial agents.[4]

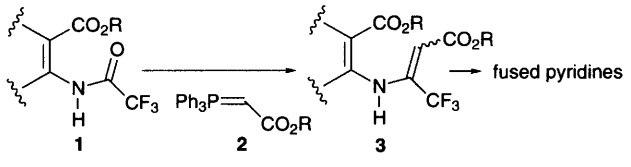
When *N*-trifluoroacetyl 2-bromo-4-cyanoaniline **6a**[5] was heated with phosphorane **2** (R = Et) in toluene under reflux, the corresponding enamine **9a** was isolated as a pale yellow oil in 70% yield as a mixture of *Z*- and *E*-isomers after chromatography. Similarly, aniline derivatives **6b**[6] and **6c**[7] yielded compounds **9b** (95% yield) and **9c** (67% yield) respectively as yellow oils. Cyclisation of compound **9a** giving indole derivative **4a** was achieved by an intramolecular Heck reaction presumably *via* the corresponding intermediates **11a** and **12a** (Scheme 2).[8–10] Thus, when compound **9a** was heated in DMF at 120 °C in the presence of a catalytic quantity of palladium acetate and triphenylphosphine with tripropylamine as the base, indole **4a** (54% yield), mp 221–225 °C (decomp.) was isolated after chromatography together with enamine **8a** (28% yield). In a similar manner, enamine **9b** gave a mixture of indole **4b** (68% yield), mp 186–188 °C and enamine **8b** (25% yield). Enamine **9c** however, failed to give indole **4c** under these conditions.

The origin of the byproducts **8a** and **8b** might be explained by invoking protonation of the palladium intermediates **11a** and **11b** by tripropylamine hydrobromide (Scheme 3). Such a protonation reaction would however generate palladium(II) which would then have to be reconverted into palladium(0). We therefore reasoned that by replacing tripropylamine with sodium hydrogen carbonate as base, formation of these byproducts could be avoided as the proton source would be removed. Thus, the Heck reaction of compound **9b** gave only indole derivative **4b** although the yield of this compound (44%) was now reduced.

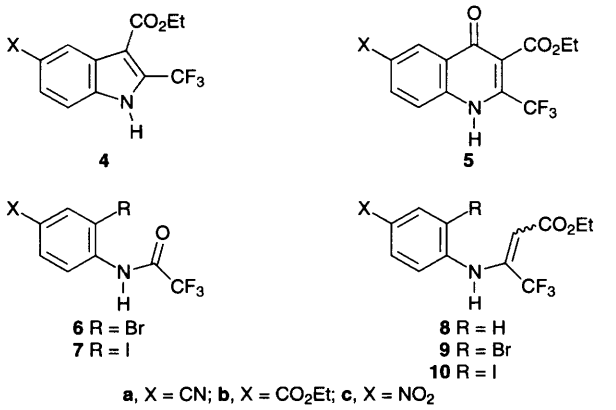
In view of the failure of enamine **9c** to give indole **4c**, we decided to prepare enamine **10c** and investigate its reaction under Heck conditions. Thus, compound **7c** and phosphorane **2** (R = Et) afforded enamine **10c** (54% yield) which cyclised giving the required indole derivative **4c** (44% yield), mp 177–179 °C, in a Heck reaction using sodium hydrogen carbonate as base. Enamines **10a** (64% yield) and **10b** (58% yield) were also prepared from compounds **7a** and **7b** respectively. This series of enamines **10a–c** were then used in the synthesis of quinolones **5a–c** as described below.

Quinolones **5a–c** were simply prepared (54–77% yield) by heating (120 °C) a mixture of the appropriate enamine and sodium hydrogen carbonate in the presence of a catalytic quantity of palladium(II) acetate and triphenylphosphine in DMF under a carbon monoxide atmosphere (Scheme 2) presumably *via* intermediates **13a–c** and **14a–c**.

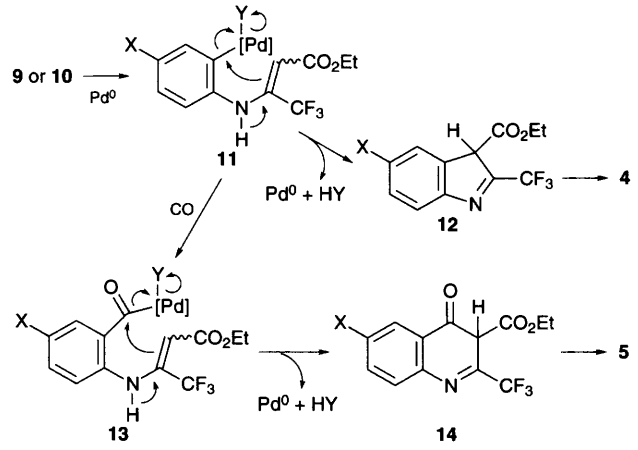
We have successfully prepared a series of enamines **9** and **10** and demonstrated that they are useful precursors to highly functionalised nitrogen containing heterocycles. All new com-



Scheme 1

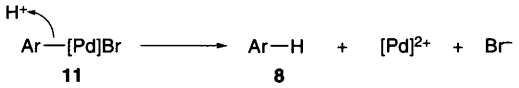


a, X = CN; **b**, X = CO_2Et; **c**, X = NO_2



11–14: **a**, X = CN; **b**, X = CO_2Et; **c**, X = NO_2; Y = Br or I

Scheme 2



Scheme 3

pounds gave satisfactory microanalytical data or high resolution mass spectral data and had ^{1}H NMR spectra which were in accordance with their proposed structures.

We thank Synthetic Chemicals Ltd. for financial assistance and Mr Lance S. Fuller for useful suggestions and encouragement.

References

1 E. J. Latham, S. M. Murphy and S. P. Stanforth, *Tetrahedron Lett.*, 1994, **35**, 3395.
2 E. J. Latham, S. M. Murphy and S. P. Stanforth, *Tetrahedron*, 1995, **51**, 10 385.
3 For a review covering the recent literature relating to the synthesis of indole derivatives see G. W. Gribble, *Contemporary Organic Synthesis*, 1994, **1**, 145.
4 D. T. W. Chu and P. B. Fernandes, 'Recent Developments in the Field of Quinolone Antibacterial Agents', in *Advances in Drug Research*, ed. B. Testa, Academic Press, New York, 1991, vol. 21, pp. 39–144.
5 C. L. Francis and A. D. Ward, *Aust. J. Chem.*, 1994, **47**, 2109.
6 J. E. Macor and M. J. Wythes, *PCT Int. Appl.* WO 92 06973, 1992 (*Chem. Abstr.*, 1992, **117**, 17 1215n).
7 R. P. Gajewski, G. D. Thompson and E. H. Chio, *J. Agric. Food Chem.*, 1988, **36**, 174 (*Chem. Abstr.*, 1988, **108**, 51209f).
8 R. F. Heck, *Organic Reactions*, 1982, **27**, 345.
9 R. F. Heck, in *Palladium Reagents in Organic Synthesis*, ed. A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Academic Press, London, 1985.
10 For some related Heck cyclisations see: T. Sakamoto, T. Nagano, Y. Kondo and H. Yamanaka, *Synthesis*, 1990, 215 and J. P. Michael, S.-F. Chang and C. Wilson, *Tetrahedron Lett.*, 1993, **34**, 8365.

Received, 2nd July 1996; Com. 6/04582K