

Preparation of quinolines from resin-bound esters using titanium reagents

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Received 7 September 2004; accepted 28 September 2004

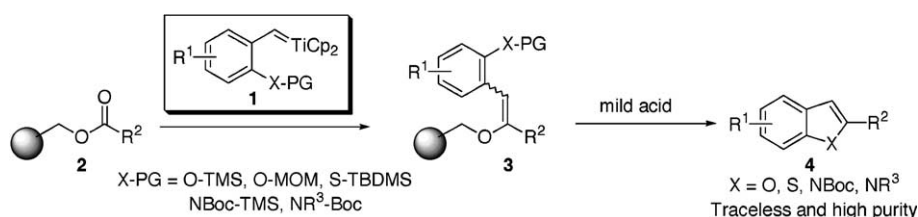
Available online 14 October 2004

Abstract—*ortho*-Amino homobenzylic thioacetals are prepared from *ortho*-nitrobenzaldehydes via homologation using an alpha-methoxy Wittig reagent. Titanium reagents are generated from the 1,3-dithianes using a low valent titanium reagent and are then used to alkylidene resin-bound esters. An *N*-silylated Boc group protects the *ortho*-amino functionality. Traceless SPS of quinolines is completed by treating the resulting resin-bound enol ethers with TFA and then oxidizing with manganese dioxide to give 2-substituted quinolines in high purity without the need for chromatography.

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Quinolines are found in many medicinally interesting compounds¹ and for this reason researchers have continued to improve traditional methods and develop new strategies for their construction.² However, in spite of the importance of solid-phase synthesis (SPS),³ few methods for the construction^{4,5} or decoration⁶ of quinolines on solid-phase have been developed. Of these, only Levacher and co-workers' adaptation⁵ of the Friedländer synthesis is traceless.⁷ Here we describe a method for terminating traditional SPS in a traceless way by conversion of an ester linker into a range of quinolines using novel titanium reagents. This is the first time that titanium alkylidenes⁸ have been used in the construction of quinolines, and the method has potential as in theory a diverse range of esters could be synthesized by standard split and mix techniques prior to our termination sequence.

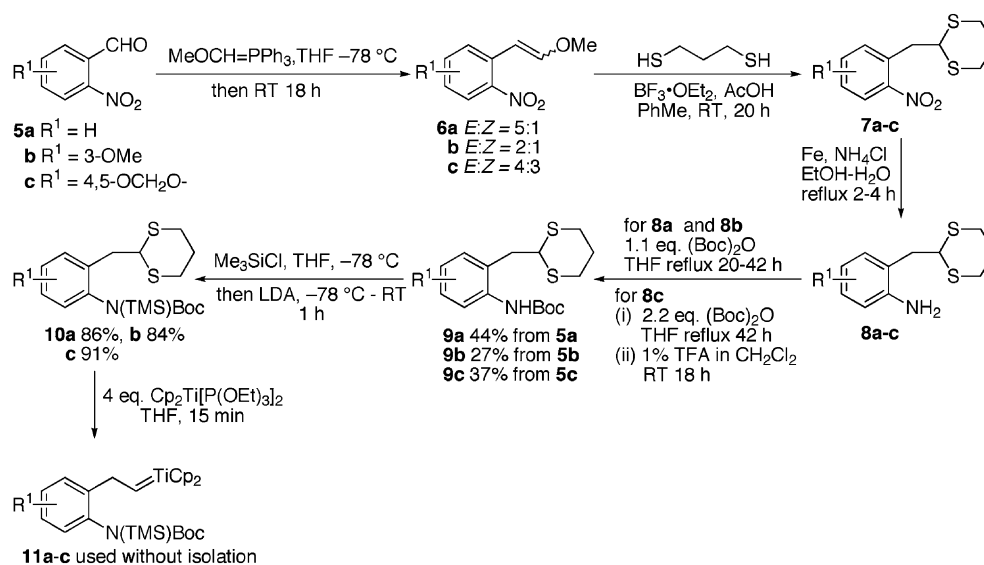
We have recently shown that titanium benzylidene reagents^{9–13} **1** (Scheme 1) bearing a protected oxygen, nitrogen or sulfur nucleophile in the *ortho* position are easy to generate from thioacetals using low valent titanium species, Cp₂Ti[P(OEt)₃]₂, and will benzylidene resin-bound esters **2** to give resin-bound enol ethers **3**. A range of functionality is tolerated in the titanium benzylidenes **1**, including boronate, acetal, fluoro and some amino and carbamate groups. Treating the enol ethers **3** with acid then yields 2-substituted benzofurans^{9–11} indoles^{11,12} or benzothiophenes¹³ **4** in high purity because the nature of the linker has been switched from an acid-stable ester to an acid-sensitive enol ether, ensuring that no products arise from unreacted resin-bound esters **2**. Furthermore, there is no trace in the products of where the resin had been attached. Thus, the reagents allow traceless termination of an SPS to form a range of



Scheme 1.

Keywords: Quinolines; Titanium and compounds; Solid-phase synthesis; Thioacetals; Wittig reaction.

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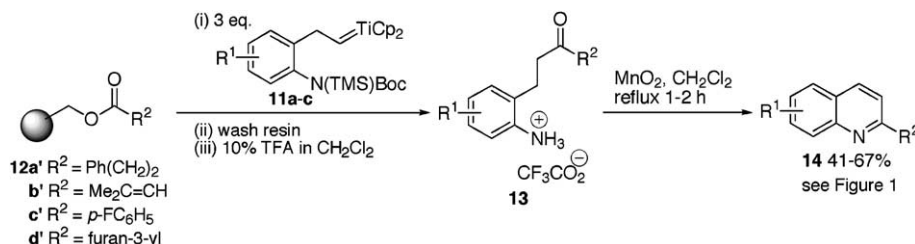
Scheme 2.

heterocycles from resin-bound esters, and this has great potential in SPS where a diverse range of esters may be prepared using automation. At first sight, access to quinolines using related chemistry would seem more demanding: the necessary homobenzylic titanium reagents would be expected to be more difficult to generate; the silylated carbamate protecting groups successful in the indole series might be less stable towards a titanium alkylidene tethered by a more flexible chain; and a post-cleavage oxidation step would be required to aromatize to the quinolines. However, we here report the success of this strategy.

The necessary dithiane substrates **10** for titanium alkylidene formation were prepared from commercially available 2-nitrobenzaldehydes **5** as shown in Scheme 2. Reaction with the Wittig reagent derived from meth-

oxymethyl triphenylphosphonium chloride¹⁴ gave predominantly *E*-enol ethers¹⁵ **6** with the *E*-selectivity decreasing with increasing electron-donating ability of the aromatic ring, which is surprising but consistent with the *E*:*Z* ratios reported for similar reactions.¹⁶ Enol ethers **6** were converted into thioacetals **7** directly following work-up of the Wittig reaction. Reduction¹⁷ to the amines **8** and Boc protection gave carbamates **9**, which were purified by recrystallization so that no chromatography was used to prepare these in four or five steps from aldehydes **5**. Silylation of the carbamate groups was followed by reduction of the dithianes **10** to give the active alkylidenating agents, presumably titanium alkylidenes **11**.

A selection of quinolines^{18,19} **14** (Scheme 3 and Fig. 1) were then prepared in high purity from Merrifield-resin-



Scheme 3.

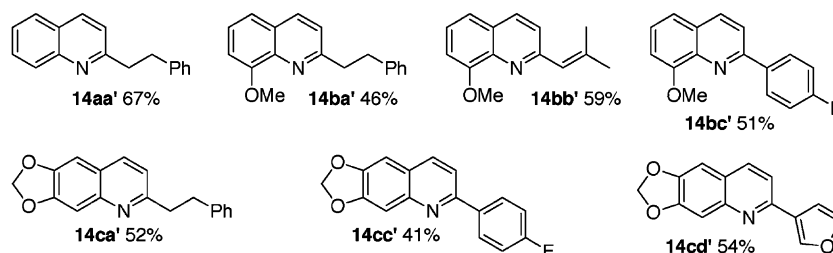


Figure 1.

bound esters **12a'–d'** by treating the latter with the titanium alkylidenes **11a–c**, washing the resin, releasing the arylammonium salts **13** under acid conditions and oxidizing to give the quinolines **14**. A solid oxidant was chosen so that it could be removed simply by filtration.

Acknowledgements

EPSRC and GSK for funding.

References and notes

- Recent reviews: (a) Du, W. *Tetrahedron* **2003**, *59*, 8649–8687; (b) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 476–493.
- Recent methods for the preparation of 2-substituted quinolines include: (a) Sangu, K.; Fuchibe, K.; Akiyama, T. *Org. Lett.* **2004**, *6*, 353–355; (b) Cho, C. S.; Kim, B. T.; Choi, H.-J.; Kim, T.-J.; Shim, S. C. *Tetrahedron* **2003**, *59*, 7997–8002; (c) Du, W.; Curran, D. P. *Org. Lett.* **2003**, *5*, 1765–1768; (d) McNaughton, B. R.; Miller, B. L. *Org. Lett.* **2003**, *5*, 4257–4259; (e) Song, S. J.; Cho, S. J.; Park, D. K.; Kwon, T. W.; Jenekhe, S. A. *Tetrahedron Lett.* **2003**, *44*, 255–257; (f) Huma, H. Z. S.; Halder, R.; Kalra, S. S.; Das, J.; Iqbal, J. *Tetrahedron Lett.* **2002**, *43*, 6485–6488.
- (a) Recent reviews of SPS of heterocycles: Dolle, R. E. *J. Comb. Chem.* **2004**, *6*, 623–679; (b) Dolle, R. E. *J. Comb. Chem.* **2003**, *5*, 693–753; (c) Bräse, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem.* **2002**, *10*, 2415–2437; (d) Krchnák, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61–91.
- (a) Demaude, T.; Knerr, L.; Pasau, P. *J. Comb. Chem.* **2004**, *6*, 768–775; (b) Gopalsamy, A.; Pallai, P. V. *Tetrahedron Lett.* **1997**, *38*, 907–910; (c) Ruhland, T.; Künzer, H. *Tetrahedron Lett.* **1996**, *37*, 2757–2760.
- Patteux, C.; Levacher, V.; Dupas, G. *Org. Lett.* **2003**, *5*, 3061–3063.
- (a) Cironi, P.; Tulla-Puche, J.; Barany, G.; Albericio, F.; Alvarez, M. *Org. Lett.* **2004**, *6*, 1405–1408; (b) Hoemann, M. Z.; Melikian-Badalian, A.; Kumaravel, G.; Hauske, J. R. *Tetrahedron Lett.* **1998**, *39*, 4749–4752.
- For discussions of traceless synthesis see: (a) Gil, C.; Bräse, S. *Curr. Opin. Chem. Biol.* **2004**, *8*, 230–237; (b) Blaney, P.; Grigg, R.; Sridharan, V. *Chem. Rev.* **2002**, *102*, 2607–2624.
- For a review of titanium alkylidenes see Hartley, R. C.; McKiernan, G. J. *J. Chem. Soc., Perkin Trans 1* **2002**, 2763–2793.
- Guthrie, E. J.; Macritchie, J.; Hartley, R. C. *Tetrahedron Lett.* **2000**, *41*, 4987–4990.
- McKiernan, G. J.; Hartley, R. C. *Org. Lett.* **2003**, *5*, 4389–4392.
- Macleod, C.; McKiernan, G. J.; Guthrie, E. J.; Farrugia, L. J.; Hamprecht, D. W.; Macritchie, J.; Hartley, R. C. *J. Org. Chem.* **2003**, *68*, 387–401.
- Macleod, C.; Hartley, R. C.; Hamprecht, D. W. *Org. Lett.* **2002**, *4*, 75–78.
- Roberts, C. F.; Hartley, R. C. *J. Org. Chem.* **2004**, *69*, 6145–6148.
- Sukenik, C. N.; Bergman, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 6613–6623.
- The ratio of geometrical isomers was determined from the vicinal coupling between signals for the alkene protons in the ¹H NMR spectra of the crude mixtures. The *E* isomers produced two 12.8 Hz doublets while the *Z* isomers produced two 7.2–7.3 Hz doublets with chemical shifts as follows: *E-6a* at δ_{H} 7.05 and 6.39, *E-6b* at δ_{H} 7.07 and 5.62, *E-6b* at δ_{H} 6.95 and 5.52, *Z-6a* at δ_{H} 6.31 and 5.70, *Z-6b* at δ_{H} 6.26 and 5.03, *Z-6c* at δ_{H} 6.24 and 5.83.
- Compare (a) Maehr, H.; Smallheer, J. M. *J. Org. Chem.* **1981**, *46*, 1752–1755, and (b) Wiegand, S.; Schafer, H. J. *Tetrahedron* **1995**, *51*, 5341–5350.
- Ramadas, K.; Srinivasan, N. *Synth. Commun.* **1992**, *22*, 3189–3195.
- Titanium alkylidenes were generated and used according to the procedure that we have described for the preparation of indoles.¹¹ The solid-phase reactions were carried out in normal glassware, but with resin [particle size = 150–300 μm diameter, derived from Merrifield resin with loading 1.83 meq (of benzylic chloride) g^{-1}] contained within porous polypropylene reactors that had an internal volume of 2.4 mL and a pore size of 74 μm (IRORI macrokants, 0.30 mequiv of resin-bound ester per kan). Cleavage from resin is as previously described.¹¹ Manganese dioxide (0.09 g, 1.00 mmol) was added to a solution of each crude arylammonium salt in DCM (10 cm^3) and the reaction mixture was heated under reflux for 1–2 h. After this time, the reaction mixture was filtered through a Celite plug, washing with CH_2Cl_2 (10 cm^3). The combined organic phases were washed with saturated sodium bicarbonate (20 cm^3), dried over sodium sulfate, and concentrated to yield the desired quinolines.
- Characterization data: 2-phenethylquinoline **14aa'** (yellow oil); data in agreement with literature.^{2b} 8-Methoxy-2-phenethylquinoline **14ba'** (yellow oil); ν_{max} (thin film)/ cm^{-1} : 3060–2852, 1602, 1564, 1503; δ_{H} (400 MHz, CDCl_3): 3.14–3.18 (2H, m), 3.35–3.39 (2H, m), 4.10 (3H, s), 7.05 (1H, d, *J* 7.5), 7.09–7.31 (6H, m), 7.35–7.44 (2H, m), 8.02 (1H, d, *J* 8.4); δ_{C} (100 MHz, CDCl_3): 36.1 (CH_2), 50.0 (CH_2), 56.2 (CH_3), 107.8 (CH), 119.5 (CH), 122.0 (CH), 125.9 (CH), 126.0 (CH), 128.0 (C), 128.4 (CH), 128.5 (CH), 136.2 (CH), 139.8 (C), 141.6 (C), 155.0 (C), 161.0 (C); HRMS: M^+ requires $\text{C}_{18}\text{H}_{17}\text{NO}$, 263.1310, found 263.1308. 8-Methoxy-2-(2'-methylpropen-1-yl)-quinoline **14bb'** (yellow oil); ν_{max} (thin film)/ cm^{-1} : 3047–2835, 1649, 1600, 1556, 1498; δ_{H} (400 MHz, CDCl_3): 2.00 (3H, d, *J* 1.2), 2.14 (3H, d, *J* 1.2), 4.07 (3H, s), 6.62 (1H, m), 7.02 (1H, dd, *J* 7.5 and 1.2), 7.33–7.44 (3H, m), 8.05 (1H, d, *J* 8.5); δ_{C} (100 MHz, CDCl_3): 19.9 (CH_3), 27.3 (CH_3), 55.9 (CH_3), 107.6 (CH), 119.2 (CH), 122.7 (CH), 125.8 (CH), 126.2 (CH), 127.3 (C), 135.5 (CH), 139.8 (C), 141.4 (C), 155.2 (C), 156.6 (C); HRMS: M^+ requires $\text{C}_{14}\text{H}_{15}\text{NO}$, 213.1154, found 213.1153. 2-(4'-Fluorophenyl)-8-methoxyquinoline **14bc'** (yellow oil); ν_{max} (thin film)/ cm^{-1} : 3002–2836, 1615, 1601, 1559, 1497; δ_{H} (400 MHz, CDCl_3): 4.10 (3H, s), 7.07 (1H, d, *J* 7.4), 7.15–7.21 (2H, m), 7.39–7.47 (2H, m), 8.02 (1H, d, *J* 8.6), 8.08–8.13 (3H, m); δ_{C} (100 MHz, CDCl_3): 56.1 (CH_3), 107.2 (CH), 115.7 (d, *J* 21.4, CH), 119.1 (CH), 119.3 (CH), 126.6 (CH), 128.2 (C), 129.5 (d, *J* 8.2, CH), 135.9 (C), 136.9 (CH), 140.1 (C), 155.2 (C), 155.5 (C), 163.3 (d, *J* 249, CF); HRMS: M^+ require $\text{C}_{16}\text{H}_{12}\text{FNO}$, 253.0903, found 253.0904. 6,7-Methylenedioxy-2-phenethylquinoline **14ca'** (yellow oil); ν_{max} (thin film)/ cm^{-1} : 3032–2856, 1618, 1589, 1512, 1495; δ_{H} (400 MHz, CDCl_3): 3.10–3.15 (2H, m), 3.19–3.24 (2H, m), 6.09 (2H, s), 7.02 (1H, s), 7.03 (1H, d, *J* 8.3), 7.17–7.30 (5H, m), 7.38 (1H, s), 7.85 (1H, d, *J* 8.3); δ_{C} (100 MHz, CDCl_3): 36.1 (CH_2), 40.6 (CH_2), 101.6 (CH_2), 102.6 (CH), 105.5 (CH), 119.7 (CH), 123.5 (C), 125.9 (CH), 128.3 (CH), 128.5 (CH), 135.1 (CH), 141.6 (C), 146.1 (C), 147.2 (C), 155.6 (C), 159.5 (C); HRMS: M^+ requires $\text{C}_{18}\text{H}_{15}\text{NO}_2$, 277.1103, found 277.1102. 2-(4'-Fluorophenyl)-6,7-methylenedioxy-quinoline **14cc'** (yellow solid); Mp: 139–142 $^{\circ}\text{C}$;

ν_{\max} (Golden Gate)/ cm^{-1} : 2962–2784, 1617, 1600, 1498;
 δ_{H} (400 MHz, CDCl_3): 6.11 (2H, s), 6.77 (1H, s), 7.17–7.20
(2H, m), 7.43 (1H, s), 7.66 (1H, d, J 8.5), 8.01 (1H, d, J
8.5), 8.09–8.11 (2H, m); δ_{C} (100 MHz, CDCl_3): 101.7
(CH_2), 102.5 (CH), 106.0 (CH), 115.7 (d, J 21.4, CH),
116.9 (CH), 124.0 (C), 129.0 (d, J 8.6, CH), 135.6 (CH),
146.4 (C), 147.8 (C), 150.9 (C), 154.2 (C), 162.5 (d, J 249,
CF); HRMS: M^+ requires $\text{C}_{16}\text{H}_{10}\text{FNO}_2$, 267.0696, found
267.0695. 2-(3'-Furyl)-6,7-methylenedioxy-quinoline **14cd'**

(yellow solid); Mp: 124–127°C; ν_{\max} (Golden Gate)/ cm^{-1} :
2914–2848, 1618, 1577, 1513, 1494; δ_{H} (400 MHz, CDCl_3):
6.09 (2H, s), 7.02 (1H, s), 7.04 (1H, d, J 1.6), 7.37 (1H, s),
7.44 (1H, d, J 8.4), 7.52 (1H, d, J 1.6), 7.93 (1H, d, J 8.4),
8.08 (1H, s); δ_{C} (100 MHz, CDCl_3): 101.8 (CH_2), 102.7
(CH), 105.8 (CH), 109.0 (CH), 117.1 (CH), 123.9 (C),
127.5 (C), 135.3 (CH), 141.4 (CH), 143.8 (CH), 146.5 (C),
147.5 (C), 149.6 (C), 150.8 (C); HRMS: M^+ requires
 $\text{C}_{14}\text{H}_9\text{NO}_3$, 239.0582, found 239.0581.