Synthesis of indoles via alkylidenation of acyl hydrazides

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Abstract

Indoles have been synthesised via alkylidenation of acyl phenylhydrazides using phosphoranes and the Petasis reagent, followed by in situ thermal rearrangement of the product enehydrazines. The Petasis reagent provides an essentially neutral equivalent of the [acid-catalysed] Fischer indole synthesis, but with acyl phenylhydrazides as starting substrates. Alkylidene triphenylphosphoranes convert aroyl phenylhydrazides to indoles, but acyl phenylhydrazides derived from aliphatic carboxylic acids undergo a Brunner reaction to form indolin-2-ones.

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The indole ring system is a crucial structure in drug discovery, and has become an essential component in many pharmacologically active compounds. The extensive number of synthetic routes to and applications of indoles emphasises the great interest in this area. While a wide range of methods exist, significant efforts have been made to provide syntheses under mild reaction conditions, which tolerate a wide range of functional groups and start from readily available substrates.1,2

The most commonly used method for the preparation of indoles remains the Fischer indole synthesis discovered in 1883.3,4 In spite of extensive studies, important efforts are still focussed on providing synthetic routes under mild conditions and with good regiocontrol on the outcome of the reaction.5,6

Our current approach to indoles arises from our recently reported alkylidenation of Weinreb amides 17,8 in non-classical Wittig reactions.5,9 The expected initial products, enamines 2, were not isolated, but instead underwent easy hydrolysis to ketones and aldehydes 3. These transformations make use of the enhanced reactivity of the Weinreb amide carbonyl group as an electrophile, due to the inductive effect of the methoxy oxygen atom.

This reaction extends the scope of the Wittig reaction, and provides alternative routes to ketones and aldehydes from Weinreb amides without the use of organometallic reagents.

Success in that study led us to investigate the reactivity of Wittig reagents with acyl hydrazides 4. While expected to be less reactive than the Weinreb amides, the hydrazides 4 still benefit from the activating inductive effect of an electronegative nitrogen atom attached to the amide nitrogen. If alkylidenation of acyl hydrazides could be established, then the expected initial products would be the enehydrazines 5, which are the normal intermediates in the Fischer indole synthesis (Scheme 1).

This approach to indoles could have significant benefits, since it would take advantage of the key property of the Wittig reaction in defining the position of the alkene in enehydrazine 5. As alluded to above, the major drawback of the normal acid-catalysed Fischer indole synthesis is the reversible tautomerism of the enehydrazine; where the enehydrazine is derived from a fully enolisable ketone, this tautomerism leads to mixtures of regioisomers at the enehydrazine stage, and therefore ultimately results in a regioisomeric pair of indoles.

To test the reactivity of acyl hydrazides towards phosphorus ylides, a range of hydrazides were prepared in straightforward manner as shown below (Scheme 2) from the corresponding acids...
or acid chlorides. The synthesis of the formyl derivative 22 used a different approach; hydrolysis of the N-propionyl hydrazide 9 afforded the dimethylphenylhydrazine 20—this was reacted with formic pivalic anhydride to afford the desired product 22 in 78% yield.

The reaction of methylenetriphenylphosphorane with the N-benzyldihydrazide 15 afforded 2-phenylindole 23 in good yield (78%). This was followed by equally successful reactions to form the 2-(2-furyl)indole 24 and the 2-(3-pyridyl)indole 25, thereby showing equal success with electron-rich and electron-poor aroyl hydrazides. Further studies were undertaken with the benzoyl hydrazide 15. Attempts to form 2-phenyl-3-alkylindoles were unsuccessful. Reaction of 15 with n-butylidenetriphenylphosphorane afforded the corresponding 3-alkylindoles 22 in high yield (70% and 96%, respectively).

The formyl hydrazide 22 provided opportunities to form 3-substituted indoles, and towards this end, this substrate was reacted with alkylidenetriphenylphosphoranes. Reaction with n-butylidenetriphenylphosphorane afforded 3-phenylpropylidenetriphenylphosphorane afforded the corresponding 3-alkylindoles 26 in high yield (70% and 96%, respectively).

Extending the reactions to the N-acetylhydrazide 8 produced an unexpected result (Scheme 4). Here, N-methylindolin-2-one 32 was isolated in 76% yield. The analogous product 33 was formed (92%) when the N-propionyl hydrazide 9 was reacted. In these cases, the phosphorane clearly shows its basic character and deprotonates 8/9 to form the enolate of the hydrazide 28/29. These undergo a Brunner indolin-2-one synthesis, in high yield, to afford 30/31 before condensation to the final products. Basicity of phosphoranes had been observed previously, but to our knowledge, this is the first report of indolin-2-one synthesis using a phosphorane. Our ultimate wish was to find a neutral equivalent of the Fischer indole synthesis, and these reactions clearly show that phosphoranes are deficient in this respect.

The reactivity of cyclohexyl hydrazide 19 mirrored that of the acetyl case 8, and produced the spiroindolin-2-one 34 (20%) as well as a low yield of indole 35 (3%). Clearly, the reactivity of amides with ‘enolisable' acyl hydrazides poses a problem for the Wittig reagents.

3-Methylbut-3-enoyl hydrazide 18 behaved differently, however, affording the homologated indolin-2-one 39 (Scheme 5). We propose that this results from conjugate addition of the phosphorane to the α,β-unsaturated hydrazide 18 to afford 36 followed by expulsion of triphenylphosphine. The resulting cyclopropane 37 then undergoes either base-induced deprotonation of one of the gem-dimethyl groups in tandem with ring-opening of the cyclopropane to form the enolate 38, or thermal prototropic formation of the enol that is equivalent to 38, followed by deprotonation. The enolate 38 then undergoes a Brunner reaction to the indolin-2-one product 39.

Our reason for proposing the cyclopropane intermediate 37 stems from isolation of an analogous cyclopropane 41 (42%) in the reaction of isopropylidenetriphenylphosphorane with Weinreb amide 40. Product 41 shows that gem-dimethylcyclopropanes can result from reaction between phosphoranes and α,β-unsaturated amides, although the gem-dimethyl group results from different reactants in each of the two cases.
reacted with the Petasis reagent. $^1$H NMR spectroscopic analysis of 45 revealed no diminution of the one-proton integral at C-3, and retention of 85% of deuterons on the methyl group at the 2-position in 45. Isotopomers (CH$_2$, CD$_2$ and CH$_3$) were observed, probably due to exchange caused by hydrochloric acid (2 M) during the work-up. $^2$D NMR spectroscopic analysis confirmed the absence of deuterium at C-3. A selectively deuterated product would not have been available from the conventional Fischer indole synthesis with labelled acetone. Consequently, our method can be used for regioselective labelling of indole products.

Typical procedure for the synthesis of indoles: A solution of tritiated methylthiolium in diethyl ether (1.58 M, 2.4 mL, 6.95 mmol, 4.8 equiv) was added slowly to a suspension of bis(cyclopentadienyl)titanium dichloride (770 mg, 3.09 mmol, 2.2 equiv) in toluene (5 mL) at −5 °C over 15 min. The mixture was stirred for 1 h at −5 °C, then for 1 h at rt. The mixture was cooled to 0 °C, and quenched carefully by addition of an ice-cold 6% aqueous ammonium chloride solution (10 mL). The phases were separated, and the organic phase was washed with water (10 mL), brine (10 mL), dried over sodium sulfate, filtered, and the solvent was removed in vacuo, until the solution had been reduced to one-third of the original volume, and then toluene (5 mL) was added. The solution of dimethyltitanocene in toluene was transferred via cannula to a solution of N-(3,3-dimethylacryloyl)-N,N-dimethyl-N-phenylhydrazine 18 (256 mg, 1.44 mmol, 1.0 equiv) in toluene (5 mL). The mixture was then heated at reflux for 72 h. The solvent was removed in vacuo and diethyl ether (25 mL) was added. The mixture was then filtered through Celite®, which was washed with additional diethyl ether (25 mL). The organic phase was washed with hydrochloric acid (2 M, 3 × 25 mL). The combined aqueous layers were washed with diethyl ether (2 × 25 mL), and the combined organic phase was dried over sodium sulfate, filtered, and the solvent was removed in vacuo. The crude mixture was finally purified by column chromatography (hexanes–diethyl ether, 98:2) to afford 1,2-dimethylindole 42 (110 mg, 53%). M.p 53–54 °C; [lit. $^{18}$ 54–55 °C]; [Found: [M]$^+$ (El$^+$) 145.0866, C$_{10}$H$_{11}$N requires [M]$^+$, 145.0868]; $^{1}$H NMR (400 MHz, DMSO-d$_6$) 2.40 (3H, d, J = 7.3 Hz, NCH$_3$), 4.29 (1H, s, CH$_2$), 6.20 (1H, br s, C=CH$_2$), 6.94–6.98 (1H, m, Ar–H), 7.03–7.08 (1H, m, Ar–H), 7.34–7.36 (1H, m, Ar–H), 7.41–7.42 (1H, m, Ar–H); $^{13}$C NMR (100 MHz, DMSO-d$_6$) 32.3, 39.4, 39.8, 120.5, 123.1, 128.4, 131.9, 137.9, 139.0; m/z (El$^+$) 145 ([M]$^+$, 100%), 144 ([M−H]$^+$, 100%).

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Supplementary data

Supplementary data (preparation of acyl hydrazides, synthesis of indoles using the Petasis reagent and its reactions with alkylidene triphenylphosphoranes) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.060.

References and notes

