Studies on Amine Oxide Rearrangements: Regioselective Synthesis of Pyrrolo[3,2-*f*]quinolin-7-ones

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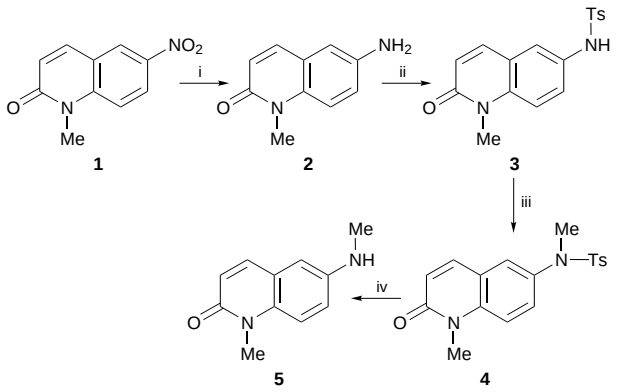
A number of derivatives of the hitherto unreported pyrrolo[3,2-*f*]quinolin-7-one tricyclic system have been synthesised from 6-nitroquinolone by successive reduction, tosylation, methylation, detosylation, prop-2-ynylation and treatment with *m*-chloroperoxybenzoic acid.

Earlier, Thyagarajan and co-workers reported a one-step process for the construction of the five-membered heterocyclic ring in benzo[*b*]thiophenes[1] and indoles.[2] The nitrogen heterocycles are obtained in almost quantitative yield by simply stirring a solution of the arylprop-2-ynylamine in dichloromethane at room temperature with 1 mol equiv. of *m*-chloroperoxybenzoic acid (*m*-CPBA). We subsequently reported[3] the synthesis of 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline *via* this amine oxide rearrangement and more recently decided to see whether the five-membered pyrrole ring of the pyrroloquinolone system with a 3,4-double bond in the quinolone portion could be constructed *via* the aforesaid amine oxide rearrangement route. Here we report the results of this latter investigation.

The 6-[*N*-(4-aryloxybut-2-ynyl)-*N*-methylamino]-1-methyl-2-quinolones **7a–g** required for this study were prepared in good yields from the reaction of 1-methyl-6-(*N*-methylamino)-2-quinolone **5** with 1-aryloxy-4-chlorobut-2-ynes **6** (Scheme 2). Substrates **7h** and **7i** were similarly prepared from compound **5** by its reaction with propargyl bromide and 4-chlorobut-2-yn-1-ol respectively. Compound **5** was in turn prepared from 6-nitroquinolone[4] through the sequence of reactions shown in Scheme 1.



Scheme 1 *Reagents and conditions:* i, Fe powder and NH_4Cl, heat; ii, toluene-4-sulfonyl chloride, pyridine, heat; iii, MeI, Me_2CO, K_2CO_3, reflux; iv, glacial acetic acid, conc. H_2SO_4, heat

Treatment of the tertiary amine **7a** with 1 mol equiv. of *m*-CPBA in dichloromethane at room temperature for 12 h afforded the pyrroloquinolone derivative **8a**. Similar subjection of the remaining substrates **7b–i** to the amine oxide rearrangement furnished the pyrroloquinolone derivatives **8b–g** (Scheme 3). We failed to obtain any tractable product from substrate **7h**. Substrate **7i** also did not provide any pure product.

The formation of the pyrroloquinolone derivatives **8** from the amines **7** is explicable[2] by the initial formation of an *N*-oxide **10** which undergoes a [2s,3s] sigmatropic rearrangement [similar to a Meisenheimer rearrangement in a tertiary allyl (aryl) amine][5] to give an intermediate **10a** (Scheme 4).

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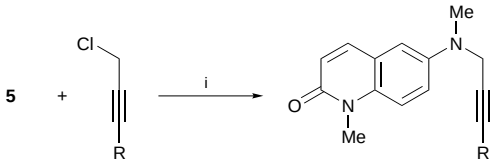
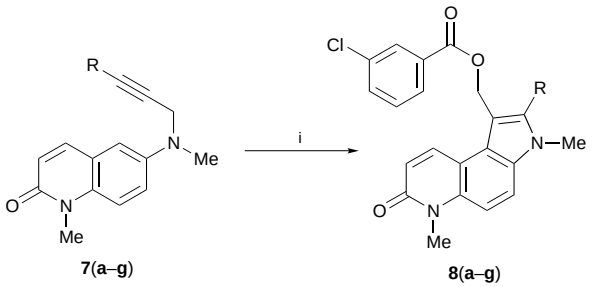
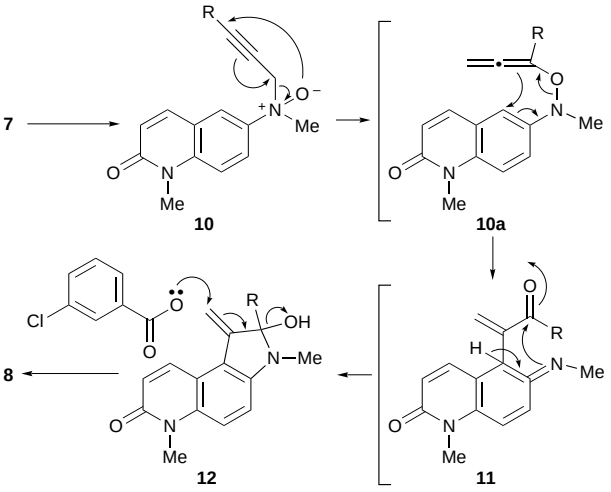


	R
a	$PhOCH_2$
b	$4\text{-}ClC_6H_4OCH_2$
c	$4\text{-}MeC_6H_4OCH_2$
d	$2,4\text{-}Cl_2C_6H_3OCH_2$
e	$2,4\text{-}Me_2C_6H_3OCH_2$
f	$3,5\text{-}Me_2C_6H_3OCH_2$
g	$4\text{-}NO_2C_6H_4OCH_2$
h	H
i	$HOCH_2$

Scheme 2 *Reagents and conditions:* i, Me_2CO, K_2CO_3, NaI, reflux, 12 h



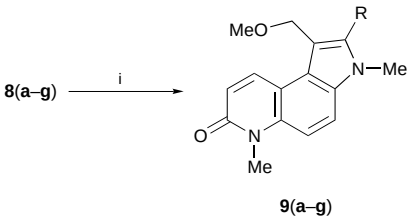
Scheme 3 *Reagents and conditions:* i, *m*-CPBA, CH_2Cl_2, room temp., 12 h



Scheme 4

This undergoes a [3s,3s] sigmatropic rearrangement followed by ketol formation to give the ketol **12**, acid-catalysed allylic rearrangement of which gives the final product **8**.

The *m*-chlorobenzoate group of the pyrroloquinolone derivatives **8a–g** is easily replaced by a methoxy group (S_N2 displacement) when compounds **8a–g** are refluxed in absolute methanol for 2 h, providing a series of methoxy derivatives **9a–g** (Scheme 5).

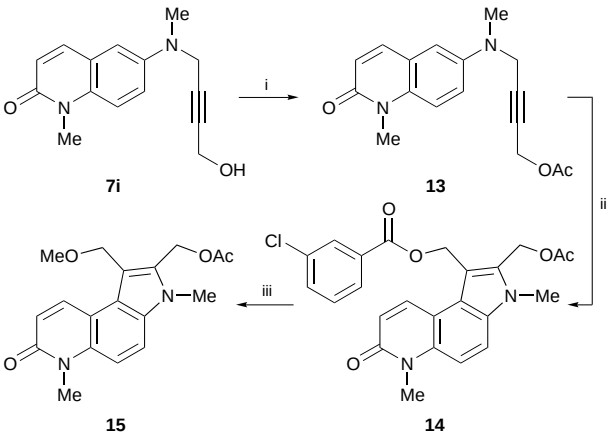


Scheme 5 *Reagents and conditions:* i, MeOH, reflux

Only a single product was obtained from the amine oxide rearrangement of each of the substrates studied, and in some cases it was possible to conclude from the ^{1}H NMR spectra that this was the expected angularly fused product. However, in other cases the structures were difficult to confirm as the aromatic protons were not well separated. All the substrates except **7h** and **7i** studied so far contained an aryloxybut-2-ynyl group and consequently the rearranged product **8** as well as the methanolysis product **9** contained aryloxy aromatic protons. Substrates **7h** and **7i** did not give any isolable pyrroloquinolone. Thus in an attempt to synthesise a pyrroloquinolone devoid of any aryloxy appendage, compound **7i** was converted into the methoxy derivative **15** by the route shown in Scheme 6.

The ^{1}H NMR spectrum of **15** exhibited two well separated *ortho*-coupled aromatic 1 H doublets (*J* 9.5 Hz) centred at δ 7.32 asnd 7.55 as well as two 1 H doublets (*J* 10 Hz) at δ 6.82 and 8.44 due to the quinolone π-bond protons. The presence of the two *ortho*-coupled aromatic protons at δ 7.32 and 7.55 conclusively shows this product to be the angularly fused pyrroloquinolone.

To our knowledge this is the first report of the synthesis of the pyrrolo[3,2-*f*]quinolin-7-one ring system. The method described is extremely facile and mild, and its generality has been tested by the successful conversion of eight substrates (**7a–g** and **13**) into the corresponding derivatives **8a–g** and **14** regioselectively and in excellent yields. It is notable that the 3,4-double bond of the quinolone is totally unaffected by the peracid. The quinolone nitrigen is also unaffected, as the lone-pair availability is lowered by the adjacent carbonyl function. The present report is also an example of the application of an amine oxide rearrangement in heterocyclic substrates leading to polyheterocycles.



Scheme 6 *Reagents and conditions:* i, Ac_2O, NaOAc, heat; ii, *m*-CPBA, CH_2Cl_2, room temp., 12 h; iii, MeOH, reflux

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Techniques used: UV, IR, ^{1}H NMR, mass spectrometry, elemental analysis

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