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Phosphorus Mediated Cyclisation of a β-Arylaminoacrylamide to a Quinoline: A simple synthesis of SK&F 96067.

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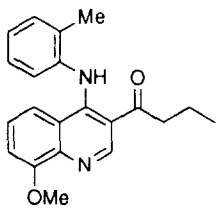
Abstract: The reversible (H^+/K^+)ATPase inhibitor SK&F 96067 **1** was prepared in two steps from Meldrum's Acid by cyclisation of the acrylamide **4** with $Ph_3P/C_2Cl_6/Et_3N$. Evidence for the formation of imidoylketene imine **3** was obtained by trapping with phenyl isocyanate. Thermal degradation of an amidine such as **12** also gave SK&F 96067 **1**.

The 4-arylaminoquinoline **1** (SK&F 96067) emerged from SB's gastrointestinal research programme as a reversible (H^+/K^+)ATPase inhibitor for the treatment of ulcers and related gastric disorders.[2] SK&F 96067 **1** can be prepared in five steps by the classical Conrad-Limpach cyclisation of a β-arylaminoacrylic ester at 255°C followed by further elaboration of the 4-quinolone obtained by treatment with $POCl_3$ followed by o-toluidine.[2] As part of our process research and development programme on SK&F 96067 we discovered two novel, short syntheses of **1**, and these are the subject of this letter.

There is now good evidence that the Conrad-Limpach cyclisation proceeds *via* a ketene derivative; for the 4-quinolone required in the case of **1**, this is the acyl ketene **2**. We reasoned that a more efficient approach to the synthesis of **1** might be by cyclisation of the corresponding imidoylketene imine **3**. An attractive approach to **3** appeared to be *via* dehydration of the acrylamide **4**, which was available in 71% isolated yield in a one-pot reaction from Meldrum's acid by an adaptation of the method reported by Pak.[3]



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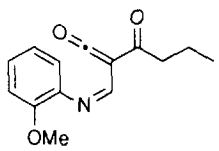

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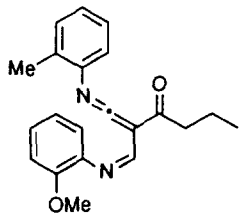
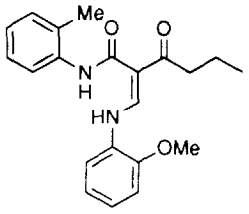


3

β-Arylaminoacrylamides have been converted to 4-arylaminoquinolines in the presence of dehydrating agents such as $SOCl_2$, $POCl_3$, PPA, PPE, and P_4O_{10}[4] and the intermediacy of imidoylketene imines has been invoked in some of these reactions,[4d] however the proposed

imidoylketene imines were not detected. In these cyclisations the 3-substituents in the 4-arylaminoquinolines formed are limited to Ph, COOMe, and CN. There is also evidence that phenyl imidoylketene imines generated from substrates other than β-aminoacrylamides cyclise efficiently to 4-arylaminoquinolines.[5] With acrylamide **4** acidic dehydrating agents gave poor yields (0-20%) of SK&F 96067 **1**. With $POCl_3$ the vinyl halide **5** was isolated in 50% yield together with 5% of **1**. Since **5** could not be produced from **1** under the reaction conditions, this highlights the reactivity of the ketone in the side chain of **4**.



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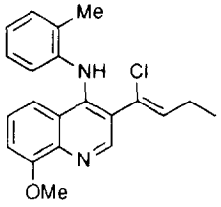

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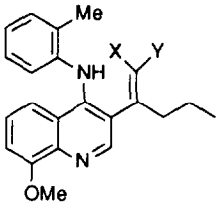
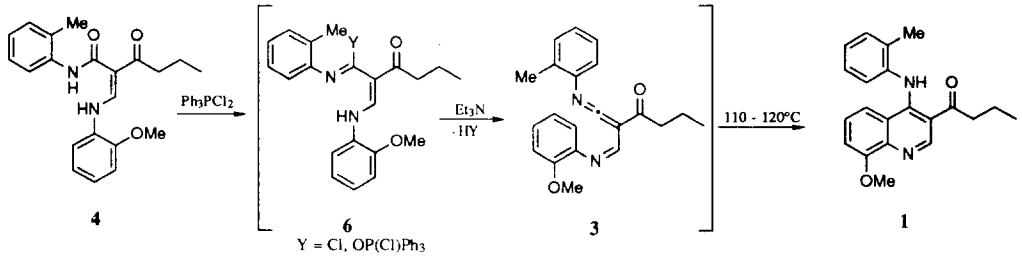


7 X=Y=Cl
8 X=H, Y=Cl

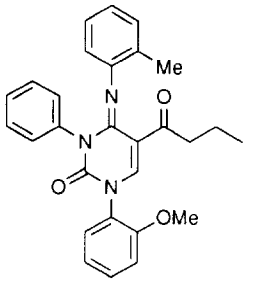
The preparation of imidoylketene imines from acrylamides using the $Ph_3P/CCl_4/Et_3N$ reagent system has been reported.[6] In some of these cases, although 4-aminoquinolines could in principle be formed, attempts to cyclise the imidoylketene imines were not reported. Treatment of the acrylamide **4** with $Ph_3P/CCl_4/Et_3N$ reagent mixture in chlorobenzene at 120°C gave SK&F 96067 **1** in 2-68% yield. The variable yield of **1** obtained was shown to be a result of the instability of the product to the reaction conditions. In order to optimise the preparation of **1**, mechanistic studies were undertaken. The Ph_3P/CCl_4 reagent combination has received much attention, and in the presence of a third component from which water can be eliminated, two pathways have been identified.[7] In these dehydration reactions triethylamine is added to remove HCl generated. Examination of reaction mixtures of acrylamide **4** and $Ph_3P/CCl_4/Et_3N$ by ^{31}P NMR showed that one third of the Ph_3P which reacted was converted to the phosphonium salt $(Ph_3PCH_2Cl)^+ Cl^-$ and the remaining two-thirds to Ph_3PO. These observations are in accord with a pathway elucidated by Appel for the reaction of amides with the $Ph_3P/CCl_4/Et_3N$ reagent system.[7b,c] Triphenylphosphine dichloride formed by reaction between Ph_3P and phosphonium salts in this pathway[7b,c] was identified by us as the agent responsible for cyclisation of the acrylamide **4**; addition of Ph_3PCl_2 to **4** and excess Et_3N in chlorobenzene at 120°C gave 50-60% solution yields of **1**. It is also important that non-polar solvents are used, so that the Ph_3PCl_2 exists in the covalent trigonal bipyramidal form. Addition of Lewis acids or use of polar solvents such as acetonitrile, where Ph_3PCl_2 exists in the tetrahedral ionic form,[8] does not lead to the formation of SK&F 96067 **1**. The reactivity of **1** towards the Ph_3PCl_2/Et_3N reagent mixture precluded the use of this reagent directly and the efficiency of the $Ph_3P/CCl_4/Et_3N$ reagent mixture is ascribed to the production of a standing, but low, concentration of Ph_3PCl_2. Mechanistically we envisage this cyclisation to proceed as shown in **Scheme 1**. Thus reaction of **4** with Ph_3PCl_2 leads to an activated amide such as **6**, where Y= Cl[7b] or $OP(Cl)Ph_3$. Reaction of **6** with the base present eliminates HCl or Ph_3PO respectively to give the imidoylketene imine **3** which undergoes a thermally induced electrocylic reaction to furnish **1**.



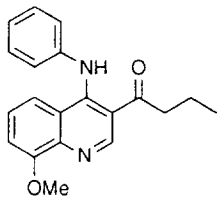
Scheme 1

From this mechanistic evaluation the optimum conditions for cyclisation of the acrylamide **4** were found to be the addition of CCl_4 (1 equiv) in chlorobenzene to a mixture of the acrylamide **4** (1 equiv), Ph_3P (1.6 equiv), and Et_3N (2 equiv) in chlorobenzene at 110-120°C. This procedure reproducibly gave 70-80% solution yields of **1**. One unattractive feature of this reaction was the formation of products **7** and **8** by Wittig reaction between the ketone side-chain of **1** and ylid by-products from the reagent mixture.[7b,c] These side reactions could be eliminated by replacing the CCl_4 by C_2Cl_6 as the chlorine source in the formation of Ph_3PCl_2, since ylid by-products are not formed. Cyclisation of the acrylamide **4** with $Ph_3P/C_2Cl_6/Et_3N$ was possible in refluxing toluene, giving a 70% solution yield (55% isolated) of **1.**

Evidence that the imidoylketene imine **3** is produced as an intermediate for the cyclisation reaction was obtained by reaction of acrylamide **4** with Ph_3PCl_2/Et_3N at ambient temperature in the presence of phenyl isocyanate.[6a] In this case the (4+2) cycloaddition product **9** was obtained in 55% isolated yield, and characterised by spectroscopic and single crystal X-ray analysis. Heating **9** at 250°C gave a mixture of **1** and **10** in 70% and 20% isolated yields respectively. Formation of **10** is rationalised by thermal degradation of **9** to the imidoylketene imine **3**, which cyclises to **1** or reacts with the aniline by-product to give the amidine **11**. This amidine can thermally eliminate either aniline to give **1,** or o-toluidine to give **10**. Thermal degradation of **12**, prepared by an unambiguous method,[9] gave **1** as the sole product in 70% solution yield. This result highlights that the intramolecular cyclisation leading to 4-aminoquinolines **1** and **10** operates efficiently only at elevated temperature and this is the reason why consistently high yields of **1** are obtained by the addition of CCl_4 or C_2Cl_6 to a hot mixture of the remaining reagents as described earlier.



9



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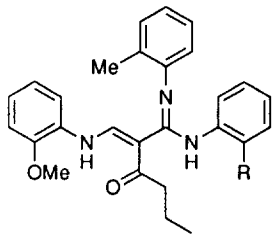
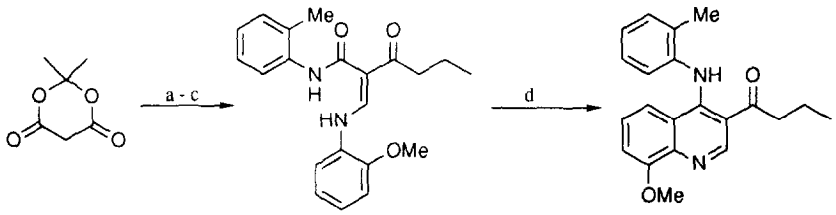


11 R = H
12 R = Me

In conclusion, a novel, two step synthesis of **1** from Meldrum's acid (**Scheme 2**) has been developed from a mechanistic evaluation of the key cyclisation reaction, and evidence for the intermediacy of an imidoylketene imine has been obtained. In addition, a novel approach to 4-arylaminoquinolines by thermal cyclisation of amidines of type **11** and **12** has been demonstrated; this is the subject of further evaluation in our laboratories.



4 **1**

Scheme 2 (a) ^{n}PrCOCl, pyridine, CH_2Cl_2; (b) o-toluidine; (c) DMF-DMA then o-anisidine - 71%; (d) Ph_3P(1.2 equiv)/C_2Cl_6(1.2 equiv)/Et_3N(3 equiv), toluene, 110°C - 55%.

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9. **12** was prepared by alkylation of 1-N-(2-methoxyphenylamino)-hex-1-ene-3-one with di-tolylcarbodiimide in the presence of sodium hydride.

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