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6-(Trifluoromethyl)pyrid-2-one: Development and Scale-Up of a Ring Synthesis Route Based on Trifluoroacetic Anhydride

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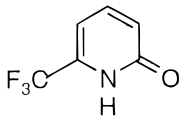
Abstract:

Three routes to 6-(trifluoromethyl)pyrid-2-one involving *de novo* synthesis of the pyridine ring have been investigated which would potentially allow rapid semi-technical scale manufacture. A route starting from ethyl 4,4,4-trifluoroacetoacetate (*β*-keto ester route) has been demonstrated. Development of the route was attempted; however, poor yields at a number of stages and scale-up difficulties made this route unattractive for commercial use. A four-stage route starting from trifluoroacetic anhydride and an alkyl vinyl ether (TFAA route) has been developed which gives good yields and productivity for all stages. The final stage of this route is a difficult decarboxylation of a nicotinic acid derivative, but an 80% yield of the required pyridone with a purity of >99.5% could be achieved without a separate purification stage. The route was scaled up to 2000 L, and several hundred kilograms of product was prepared.

Introduction

6-(Trifluoromethyl)pyrid-2-one (**1**) is a versatile intermediate of potential use in the preparation of pharmaceutical and agrochemical products. Although described in the



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literature,[1−3] existing syntheses of compound **1** are based on difficultly available starting materials or low-yielding processes. Thus 2-picoline can be converted to 2-chloro-6-(trifluoromethyl)pyridine (**3**), which can be hydrolysed using sodium hydroxide in DMSO[1] to give **1** in an overall yield of 35%. 2-(Trifluoromethyl)pyridine (**4**) can be N-oxidised and rearranged in refluxing acetic anhydride to give a 22% yield of the pyridone[4] **1** (Scheme 1). Starting materials for both of these routes are not readily available.

Recently, we were faced with an urgent requirement for hundreds of kilograms of pyridone **1** and no obvious route that could be used on this scale to make it. A route generation exercise (a brainstorming approach coupled to literature precedents) identified a total of 24 routes, and these were screened against several criteria, most notably chemical feasibility, raw material availability, product cost, and ease of scale-up, to leave routes in three areas (1a,b and 2).

1. Routes Based on (Trifluoromethyl)pyridines. *(a) Vapour Phase Chlorofluorination of 2-Picoline (Scheme 1).* The chlorofluorination chemistry is known[5] and involves vapour phase reaction of 2-picoline with hydrogen fluoride and chlorine over an aluminium fluoride catalyst at 300−600 °C. Establishment of a semi-technical facility to operate this type of continuous vapour phase process would have been an expensive and slow process, setting aside any possible patent obstacles. It was therefore not regarded as a viable approach for preparing hundreds of kilograms of pyridone **1** to the required time scale.

*(b) Fluorination of 2-Chloro-6-(trichloromethyl)pyridine (**2**) (Scheme 1).* 2-Chloro-6-(trichloromethyl)pyridine (**2**) is an existing commercial product (Nitrapyrin, DowElanco) and therefore an attractive substrate for pyridone **1**. Although not proven for this substrate, this approach did have very closely related precedents using either hydrogen fluoride[6,7] or potassium fluoride[8] and was operationally simpler than the chlorofluorination approach. Unfortunately, the temperatures required to effect the conversion using hydrogen fluoride would still have required the use of very specialised equipment, again setting aside any patent constraints. The conversion of 2-chloro-5-(trichloromethyl)pyridine to 2-fluoro-5-(trifluoromethyl)pyridine by treatment with potassium fluoride has been demonstrated.[9] Analogous chemistry might therefore have been an option with **2**, and this type of halex chemistry had the advantage of being operable in standard manufacturing assets.

2. *De Novo* Ring Synthesis. At the start of this work, no syntheses of the desired pyridone **1** had been reported which incorporated the trifluoromethyl group by pyridine ring synthesis from a fluorinated precursor. This approach, if successful, had a number of attractions for production of early quantities of a new fine chemical: (i) the fluorine would be introduced using raw materials that were readily available; (ii) because the fluorine was already present in a precursor, difficult and capital intensive fluorination technology would be avoided; (iii) the process steps in the ring synthesis might readily be carried out in a standard fine chemicals manufacturing plant; (iv) due to features i and ii above, scale-up

† Process Technology Department.
‡ Jealott's Hill Research Station.

(1) Torba, F. E. U.S. Patent 3682936, 1972 (Dow Chemical Company).
(2) Todeux, M.; Wakselman, C. European Patent 206951, 1986 (Rhone Poulenc).
(3) Bailey, T. D. U.S. Patent 4249009, 1981 (Reilly Tar).
(4) Kobayashi, Y.; Kumadaki, I. *Chem. Pharm. Bull.* **1969**, *17*, 510.
(5) Fujikawa, K.; Nishimura, S.; Tsujii, Y.; Yokomichi, I. European Patent 42696A1, 1981 (Ishihara Sanyo Kaishu).
(6) McBee, E. T.; Hass, H. B.; Hodinett, E. M. *Ind. Eng. Chem.* **1947**, *39*, 389.
(7) Fujloka, G. S.; Fung, A. P.; Werner, J. A.; Wilson, C. A. European Patent 110690, 1984 (Dow Chem. Co.).
(8) Japanese Patent 07304738, 1996 (Ihara Chem Ind. Co.).
(9) Scovell, E. G.; Watson, D. J. European Patent 63872, 1981 (ICI).

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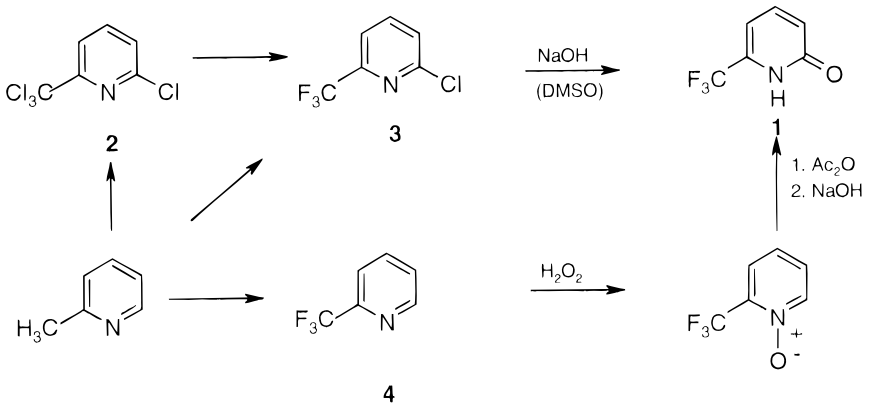
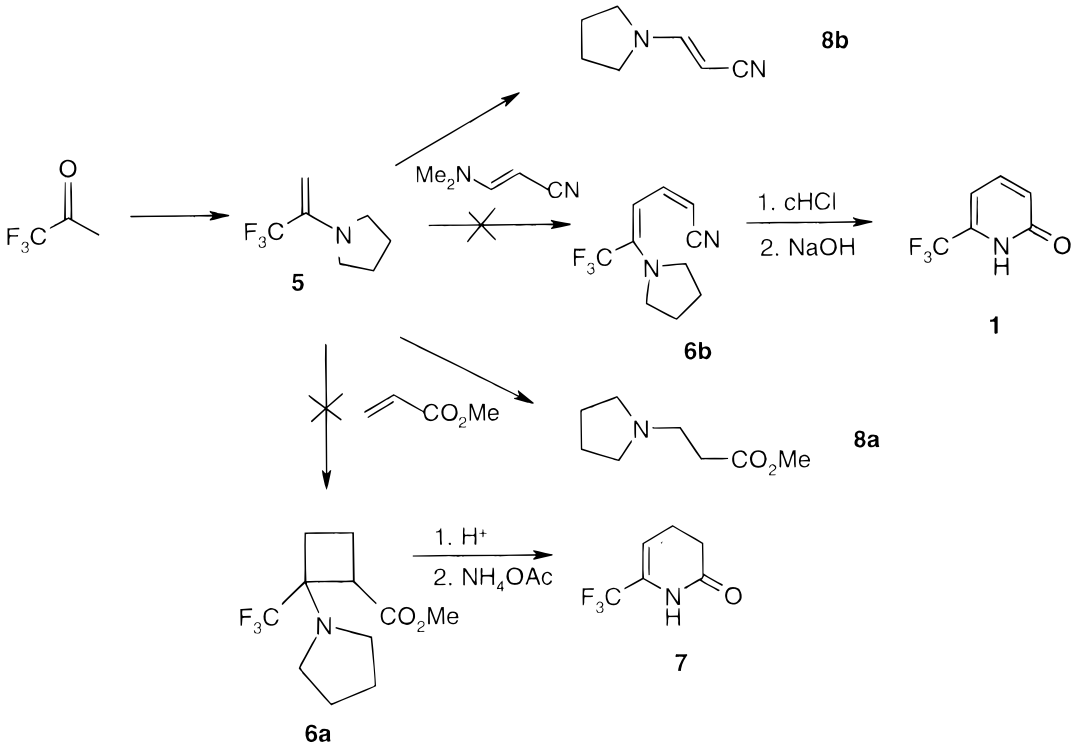
Scheme 1. **Chlorination and fluorination of 2-picoline**



Scheme 2. **The trifluoroacetone route**



to manufacture on the scale of hundreds of kilograms could be done quickly.

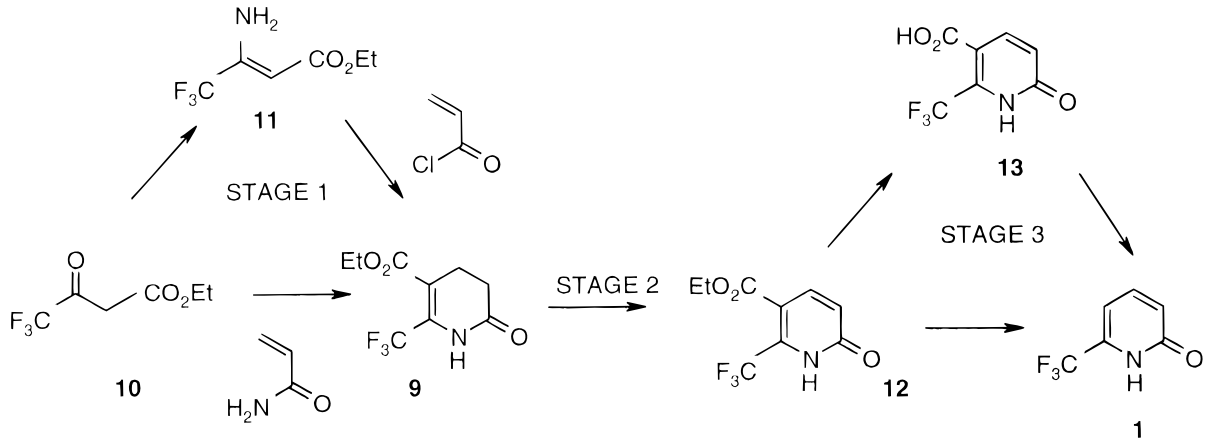
The only disadvantage of the approach was the relatively high cost of small precursor molecules containing fluorine. From the above analysis, it was clear that a *de novo* ring synthesis was a potentially very attractive option for manufacture of hundreds of kilograms of pyridone **1** in a relatively short time scale. This would also offer the prospect of a novel synthesis of a (trifluoromethyl)pyridine, although 5-methylpyrid-2-one has been prepared by a ring synthesis method.[10] The synthesis of 2-pyridones by cyclisation reactions is well documented in the literature,[11] and a variety of methods can be used; however, some are unsuitable for preparation of 6-(trifluoromethyl)pyridones. The route selection procedure considered a very wide range of options and identified three that seemed particularly appropriate: route 1, trifluoroacetone route; route 2, β-keto ester route; and route 3, trifluoroacetic anhydride route. In this paper we describe the selection and scale-up of a viable route.

(10) Hartman, L. A.; Stephen, J. F. European Patent 108483, 1984 (ICI).
(11) Klingsberg, E., Ed. *Pyridine and its Derivatives*; Interscience: New York, 1962; Part 3.

Discussion

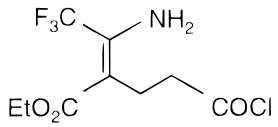
Route 1: The Trifluoroacetone Route (Scheme 2). Formation of the enamine **5** was readily achieved by reaction of 1,1,1-trifluoroacetone (TFA) with pyrrolidine in the presence of toluene-4-sulphonic acid (pTSA) as catalyst, initially at −5 °C but allowing the reaction mixture to warm to room temperature. A reaction period of 15 h in the absence of solvent and then a further reaction period after addition of dichloromethane as solvent gave the best yield (60% distilled). In those cases where poor yield was obtained, there was evidence of TFA undergoing self-condensation. Reaction of enamine **5** with methyl acrylate in dichloromethane at 0 °C gave none of the desired product **6a**. Instead, a 94% yield of the pyrrolidine/acrylate Michael adduct **8a** was obtained. Given that the reaction was conducted under carefully maintained anhydrous conditions, the formation of **8a** can only be associated with elimination

Scheme 3. **The β-keto ester route**



of the pyrrolidine from the enamine to give 1,1,1-trifluoropropyne followed by Michael addition of the liberated pyrrolidine to the acrylate. Altering the solvent to acetonitrile and conducting the reaction without solvent gave a performance similar to the dichloromethane reaction above. Related enamine chemistry had been patented by Bayer[12] as a route to 2-chloro-5-methylpyridine and its derivatives. In this case, the enamine is reacted with (dimethylamino)-acrylonitrile (instead of methyl acrylate) and thus a separate aromatisation step in the synthesis is avoided. However, treatment of stage 1 enamine **5** with 3-(dimethylamino)-acrylonitrile in dichloromethane or without solvent at from −50 °C to +40 °C again gave none of the desired product **6b**. Instead, a reaction analogous to that seen with methyl acrylate occurred to give the pyrrolidine/acrylonitrile Michael adduct **8b** in excellent conversion. Due to these adverse results, work on the trifluoroacetone route was abandoned.

Route 2: The β-Keto Ester Route (Scheme 3). Clearly, there are two approaches to the preparation of the dihydropyridone ethyl ester **9**. The first involves initial enamine formation between the β-keto ester and ammonia followed by reaction of the enamine with acryloyl chloride. Thus, ethyl trifluoroacetoacetate (**10**) was reacted with gaseous ammonia to give the corresponding enamine **11**[13] in 41% yield after distillation. Reaction of the enamine **11** with acryloyl chloride neat at 130 °C for 5 h then gave a low yield (27%) of the desired product **9**, with the initial carbon-alkylated but uncyclised compound **14** being the main impurity. Persistence of the intermediate enamine was probably due to either formation of the unreactive hydrochloride salt or the inherent low basicity of the enamine arising from α-trifluoromethyl and β-ethoxycarbonyl substituents.



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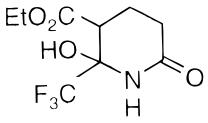
The second option involves the reaction of ethyl trifluoroacetoacetate with acrylamide and was preferred for large-scale use as it avoids handling gaseous ammonia and uses acrylamide rather than the more difficult to handle acryloyl chloride. Thus condensation under Dean and Stark conditions in toluene followed by removal of toluene solvent (atmospheric pressure) gave the crude product **9**, which after recrystallisation gave the desired stage 1 product in 41% yield. Removal of toluene under reduced pressure at a lower temperature gave a lower yield (32%), with the cyclised but undehydrated hydroxypyridone **15** as a substantial impurity.



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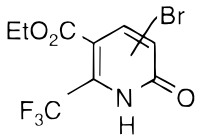
The use of higher temperatures was investigated by carrying out the reaction at 140 °C in the absence of both solvent and pTSA, but this gave only the hydroxypyridone **15** (61% yield). Use of mesitylene as solvent at 150 °C did generate the desired pyridone **9** but only in 11% conversion. The resistance of **15** to dehydration is perhaps not surprising given that an E1 elimination would involve formation of a carbenium ion α to a CF_3 group, a disfavoured process. The aromatisation step to **12** was found to be crucially dependent on the purity of the stage 1 product **9**. Use of ether-triturated **9** gave good yields of **12** (73%) with NBS in CCl_4 at reflux. Use of recrystallised (CCl_4) material, on the other hand, gave only 40% yield, with 14% unreacted dihydropyridone **9** and 9% of the ring-brominated product **16** (identified by GCMS).



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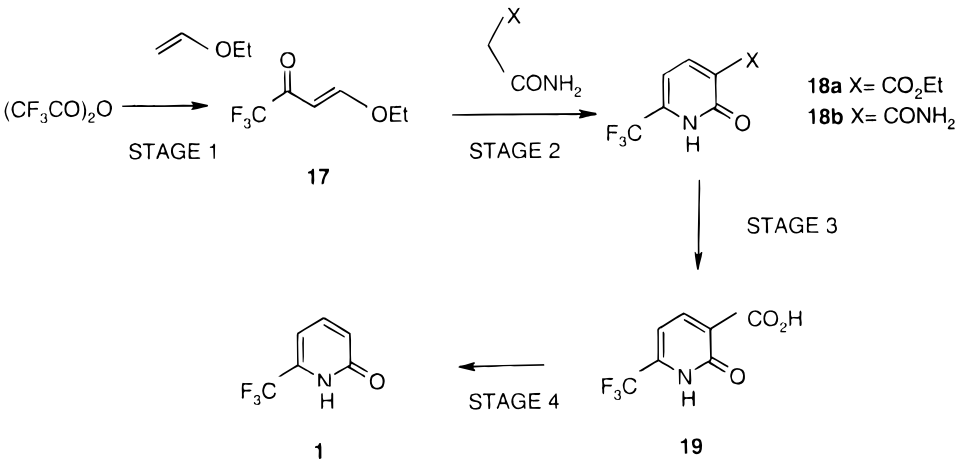
The detailed factors influencing this reaction are not well understood, but we have on a number of occasions observed that halogenosuccinimide reactions are sensitive to minor impurities in reactants.

Also, increasing the scale of the reaction from 2 g of substrate to 25 g resulted in a decline in yield from 73% to 33%. In most cases, when the yield was low, ring bromination to give compound **16** was a significant competing

(12) Kraus, H. European Patent 584491, 1992 (Bayer AG).
(13) Lutz, A. W.; Trotto, S. H. *J. Heterocycl. Chem.* **1972**, *9*, 513. Sato, J.; et al. Japanese Patent 06321877, 1994 (Nissan Chem. Ind.).

Scheme 4. **The trifluoroacetic anhydride (TFAA) route**



process. As with stage 1, the decarboxylation of pyridone **12** could be achieved via either a one-step or a two-step process. The one-step Krapcho decarboxylation of **12** (LiCl, wet DMSO, 180 °C) gave only a very a low conversion (5%) to the desired pyridone **1**. Extension of the reaction time from 6 to 18 h increased the conversion only to 9%.

In the alternative two-step procedure, pyridone ester **12** was readily hydrolysed to the acid **13** in 77% isolated yield by refluxing in concentrated hydrochloric acid. Subsequent decarboxylation of the acid **13** to pyridone **1** was effected in 100% conversion by refluxing in quinoline (250 °C) for 6 h. Workup by addition of toluene, extraction of the product into aqueous base, and acidification, however, gave only a low isolated yield of pyridone **1** (21%). Overall, although chemically feasible, this route did not look attractive for scale-up.

Route 3: The Trifluoroacetic Anhydride (TFAA) Route (Scheme 4). This route is attractive because it is short, uses readily available raw materials, and involves standard "wet" chemistry. The route has been reported for the synthesis of pyridones **18**,[14] but the onward conversion to the pyridone **1** has hitherto not been reported in the literature.

Stage 1. The preparation of the enone **17** has been reported several times in the literature,[15] using both trifluoroacetyl chloride and TFAA. Generally the yields quoted are high, but the reaction concentration employed, an important consideration for scale-up, has varied considerably. When we investigated the process in detail, we found that although it was possible to obtain high mass yields of enone **17**, the quality of the crude product varied greatly, as did its stability with respect to decomposition by polymerisation. The procedure most generally referred to[16] involves the addition of 1.43 equiv of TFAA to ethyl vinyl ether and pyridine in dichloromethane, although alternative nonhalogenated aprotic polar solvents would also probably be suitable. This process was run at 16% w/v and in our hands gave the desired product **17** in 95% isolated yield. **17** produced by this literature procedure gave good performance in stage 2. Increasing the reaction concentration from 16% to 20% w/v resulted in formation of material of low and inconsistent quality. Purification by distillation was possible, but given the tendency of the product to polymerise, it was more desirable for scale-up not to have to distil the product. Use of crude **17** from the more concentrated reactions in stage 2 gave poor yields, though the isolated stage 2 product quality was acceptable by GC analysis. Analysis of isolated **17** by NMR from a concentrated experiment revealed that product purity was very low (approximately 25%). Monitoring a concentrated reaction by NMR showed that complete vinyl ether consumption occurred after addition of only 1 equiv of TFAA. Further, the reaction was very clean at this point but product quality deteriorated as excess TFAA was added.

An experiment at 20% concentration using 1 equiv of TFAA together with a shorter reaction time (0.5 h compared with 4 h previously) gave the desired product in 85% isolated yield and high purity. This material was much more stable than previous concentrated-process product and also gave good performance in the subsequent stage 2 process. Given that the biggest contribution to the cost of the product was the cost of TFAA, the process using 1 equiv not only was much more robust but also gave a lower product cost.

Scale-Up of Stage 1. Study of the stage 1 reaction using calorimetry showed the heat of reaction was −286 kJ/mol. Addition of all of the anhydride at once under adiabatic reaction conditions was calculated to give a temperature rise of 277 K, which would be more than sufficient to cause overpressurisation of the reactor on scale-up. However, with a controlled addition of TFAA over 2−3 h, a smooth heat output was observed with only 3% of the total reaction heat being evolved after completion of the addition, thus indicating that no accumulation of reactants was taking place. Calorimetry also showed that decomposition of **17** started from about 46 °C. However, even at 55 °C the decomposition was slow to develop and, in the case of chloroform solutions, took nearly 5 h to reach the boiling point of the solvent but was more pronounced in the case of the neat product. For the above reasons, the maximum batch temperature during stage 1 processing was restricted to 45 °C and the heating medium was restricted to a maximum of 60

(14) Lang, R. W.; Wenk, P. F. *Helv. Chim. Acta* **1988**, *71*, 596.
(15) Gambaryan, N. P.; Simonyan, L. A.; Petrovskii, P. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1967**, No. 4, 918. Colla, A.; Martins, M. A. P.; Clar, G.; Krimmer, S.; Fischer, P. *Synthesis* **1991**, No. 6, 483. Moriguchi, T.; Endo, T.; Takata, T. *J. Org. Chem.* **1995**, *60*, 3523. Koyanagi, T.; Yoneda, T.; Kanamori, F.; Kanbayashi, S.; Tanimura, T.; Horiuchi, N. European Patent 744400, 1996 (Ishihara Sangyo Kaisha).
(16) Hojo, M.; Masuda, R.; Kokoryo, Y.; Shioda, H.; Matsuo, S. *Chem. Lett.* **1976**, 499.

°C. Stage 1 was carried out in a 2270 L glass-lined mild steel reactor on a 1.25 kg mol scale, and a total of 1300 kg of product was manufactured. The yield from the very first batch was 23.6%, and this was due to water contamination resulting in TFAA hydrolysis. For the rest of the manufacture, the yields were in the range 65−75%. Key parameters associated with scale-up to protect product yield and quality were as follows: (1) trifluoroacetic anhydride addition should not exceed 7 h; (2) the chloroform distillation should be done as quickly as possible; (3) pyridinium trifluoroacetate should be removed as efficiently as possible from the product during the aqueous workup as it catalysed product decomposition.

Even so, a slow deterioration in the purity of the product was observed on standing, and in practice stage 1 was consumed in stage 2 as soon as possible.

Stage 2. This reaction was first described by Errera[17] (albeit mainly directed towards the 4-isomer) and results exclusively in the formation of one pyridone isomer. The literature procedure for stage 2[14] involves reaction of **17** with ethyl malonate monoamide, malonamide, or cyanoacetamide and sodium ethoxide in ethanol. Distilled **17** or material prepared via the dilute reaction or via the modified concentrated process gave yields of up to 86% of pyridone **18a** upon reaction with ethyl malonate monoamide. In contrast, use of undistilled **17** produced by the unmodified concentrated process gave a much poorer yield (28%). Ethyl malonate monoamide, however, is not available on a large enough scale to support a multi-hundred kilogram manufacture of pyridone **1**. Therefore the much more readily available malonamide was used although this initially gave low yields (37%) of pyridone **18b**. However, with improvements to the stage 1 reaction resulting in better quality **17**, the yields increased to 58%.

Typically, condensation reactions that lead to a salt of the pyridone product are run at low concentration to avoid excessive thickening of the reaction mass. Carrying out the literature procedure at 20% w/v concentration resulted in severe thickening of the reaction mass part way through the reflux stage. Operating the reaction at 10% w/v concentration reduced thickening to an acceptable level, giving an isolated yield of 80%. This yield was composed of 70% product precipitated directly from the reaction mixture after acidification and a further 10% obtained by aqueous/ethyl acetate extraction of the filtrates. A concentration of 10% w/v, however, is still unsatisfactory for a manufacturing process.

Addition of DMF as a cosolvent did reduce reaction thickening to an acceptable extent. Use of 1:4 DMF/ethanol at 20% concentration gave a 72% precipitated yield of stage 2 amide **18b**. In this case, simple solvent extraction to realise the additional yield was not possible due to the presence of DMF. Instead, most of the DMF had to be removed under vacuum, water added, and then an aqueous/organic extraction carried out. The most significant improvement, however, was the use of methanol as solvent and sodium methoxide as base, and this allowed a 20% w/v concentration to be used with perfectly acceptable physical form for scale-up. The reaction was carried out in two stages, firstly the addition of stage 1 to a solution of the malonamide anion (prepared from malonamide and sodium methoxide in methanol) to give the uncyclised intermediate. The mixture was then heated to reflux to accomplish the cyclisation to give the anion of the desired product **18b**. Acidification followed by distillation of the methanol to a batch temperature of 80 °C gave a slurry of the stage 2 product, which could then be isolated by filtration. In the laboratory, this process gave a yield of 85−90%, and the product was analytically pure by HPLC.

Scale-Up of Stage 2. This stage was carried out on a 0.94 kg mol scale in a 2270 L glass-lined mild steel reactor. A total of 1200 kg of product was manufactured in an average yield of 79%. There were no significant scale-up problems, and the product was >99% purity by HPLC.

Stage 3. Hydrolysis of the stage 2 ester **18a** by refluxing in hydrochloric acid afforded the stage 3 acid **19** in 68% isolated yield. Application of this method to the preferred intermediate, the stage 2 amide **18b**, also gave the desired acid in high yield. The research process for ester hydrolysis involved complete removal of aqueous HCl by distillation after reaction. However, this procedure was less suitable for amide hydrolysis since it left the product contaminated with ammonium chloride. Operating such a process at 20% w/v concentration gave **19** in 40% isolated yield, with a substantial amount of product remaining in the aqueous filtrates. Increasing the concentration still further to 100% increased the isolated yield to 62%, with a corresponding reduction in liquor losses. When process concentration was increased to 150%, however, two problems became apparent. Firstly, the amide **18b** had a relatively low bulk density, and so dissolving large quantities in a small volume of aqueous HCl was problematic. Secondly, the low aqueous volume relative to solid product generated meant that filtration left significant amounts of mother liquor behind, resulting in contamination of the product with ammonium chloride. The product could, however, be further purified by dissolution in acetone and then removal of the insoluble ammonium chloride by filtration.

Given these factors, a preferred stage 3 process was defined which incorporated moderate concentration (30% w/v) and distillative removal of aqueous HCl, followed by acetone precipitation of inorganic salts. Operation of this preferred process gave the stage 3 acid **19** in 96% isolated yield.

Although the work focused on acid-catalysed processes, it is likely that base-mediated hydrolyses could also be employed. Use of methanol as solvent would introduce the possibility of telescoping stages 2 and 3, although this possibility was not investigated.

Scale-Up of Stage 3. A even more convenient process was developed for scale-up in which stage 3 was refluxed with 20% sulphuric acid. The process was run at 16% concentration, and although a 6 h reflux period at 110 °C was necessary to obtain complete conversion in the laboratory, an 8 h period was found to be necessary on scale-up. The reaction is only mildly exothermic (−50 kJ/mol), and even with an "all in" process, a temperature rise of only 10 °C is calculated from this figure. A total of 1100 kg of stage

(17) Errera, G. *Chem. Ber.* **1898**, *31*, 1682.

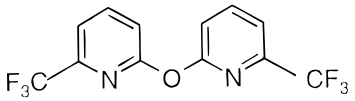
Table 1. **Decarboxylation of pyridone acid 19**

scale (g)	concn (%)	conditns	results
2	85	concd HCl, 18 h at reflux	no reactn
2	13	NMP, 6 h at 206 °C	9% conversn
5	na[a]	melt, 2.5 h at 250°C	79% yield, no solvent, 2% dipyridyl ether **20**
2	50	diethylaniline, 4 h at 217 °C	3.5% conversn (HPLC)
2	50	diphenyl ether, 4 h at 259 °C	20% conversn
2	50	DMI,[b] 10 h at 225 °C	90% conversn, drown-out and extraction of product failed
2	50	diethylene glycol, 2 h at 215 °C	by-product accounts for 53% by area (HPLC)
2	50	propylene carbonate, 4 h at 240 °C	by-product accounts for 80% by area (HPLC)
2	20	quinoline, 4 h at 190 °C; copper catalyst	no reactn
1	50	quinoline, 4 h at 235 °C; copper catalyst	100% by HPLC
1	50	quinoline, 4 h at 235 °C	100% by HPLC, poor separation between aqueous and organic layers on workup
2558	90	quinoline, 4 h at 230 °C	79% yield, toluene added to facilitate workup

[a] Not applicable. [b] DMI = 1,3-dimethylimidazolidinone.

3 was made in an average yield of 88% (laboratory figure was 95%).

Stage 4. The ease of decarboxylation of pyridinecarboxylic acid isomers decreases in the order 2-isomer > 4-isomer > 3-isomer.[11,18] The pyridonecarboxylic acid **19** has a melting point of about 200 °C, and a melt decarboxylation at 220 °C for 2 h followed by 4 h at 250 °C afforded the desired stage 4 pyridone **1** in 50% yield. The dipyridyl ether **20** was the only detectable impurity (15% yield)



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Reaction monitoring indicated that decarboxylation became more favoured relative to dipyridyl ether formation with high reaction temperature and short reaction time. The reaction was therefore carried out at 250 °C but for only 2.5 h. This resulted in a substantial yield increase (to 79%) and dramatically reduced dipyridyl ether **20** formation (2%), to give excellent purity of **1** (95% by HPLC area).

Although operationally straightforward in the laboratory, scale-up of a melt process would have been difficult. **1** has a boiling point of about 220 °C and thus distils over at the reaction temperature. However, with a melting point of 124−126 °C and a tendency to sublime, operating such a process on a plant scale would be difficult, though not impossible. This potential problem could be overcome either by conducting the reaction below the boiling point of the stage 4 pyridone **1** or by carrying out the reaction in a solvent. A range of solvents were investigated for the reaction, and representative results are given in Table 1.

This work showed that quinoline as solvent and a 4 h reaction period at 235 °C gave good conversion. Isolation of the product was accomplished by base extraction followed by acidification and filtration to give initially an isolated yield of 38%. The modest size of the isolated yield compared to the excellent chemical conversion was due to the relative inefficiency of the isolation procedure. Quantitative conversion was still achieved at higher concentrations, but the aqueous base extraction of the product resulted in very poor organic/aqueous separations. However, this problem could be overcome by addition of toluene as cosolvent after completion of the reaction and before starting the work-up, and this resulted in an isolated yield of up to 80% and with excellent product purity.

Scale-Up of Stage 4. The Stage 4 reaction had a number of features that made it unattractive for scale-up. Firstly, some of the product sublimes as it forms and this sublimate can easily block the reactor vents. Evolution of carbon dioxide increases the vaporisation of the product and also means that there is a serious risk of overpressurisation of the reactor if the vent system becomes obstructed. Partial sublimation of the product cannot be avoided, and in addition to the need for prevention of vent blockages, steps must also be taken to capture product that sublimes; otherwise yield losses will occur. To overcome these potential problems, the reactor was configured as follows:

(1) The vent system was designed to ensure that the maximum gas evolution rate of 560 L/min could be accommodated. (2) All parts of the vent, air condenser, and emergency pressure relief system were heated to at least 135 °C during the reaction to prevent buildup of product. (3) The air condenser outlet was directed to a spray condenser containing an excess of 6% sodium hydroxide solution.

Significant amounts of tarry by-products are formed in the stage 4 reaction, and these must be removed before product isolation. In addition, the quality target for stage 4 was >99% strength and with all impurities (quinoline, stage 3, and unknowns) each to be <0.1%. The tarry by-products were removed by carbon screening of the reaction mass after dilution with toluene. The pyridone product was extracted into sodium hydroxide solution, and the quinoline was removed by back-extraction with toluene. Finally, the product was isolated by addition of hydrochloric acid to pH 6−7 at 30 °C. At this isolation pH, any un-decarboxylated materials remain as their sodium salts and are lost in the filtrates. Washing the product with water removed any inorganic salts and gave the product as a water wet paste of approximately 75% strength but with >99.5% organic purity.

(18) Elderfield, R. C., Ed. *Heterocyclic Compounds*; John Wiley and Sons: New York, 1950; Vol. 1.

The process was operated on a 0.5 kg mol scale in a 450 L reactor, and a total of 600 kg of product was manufactured with an average yield of 71%.

Overall, the TFAA route to pyridone **1**[19] was fairly easy to operate and few modifications were required to a standard fine chemicals manufacturing plant to be able to operate the processes. Above all, it enabled the required product to be manufactured in a fraction of the time that would have been required for the syntheses described in the literature.

Conclusions

At the start of this work, there was no practical synthesis of pyridone **1** that could be used to make hundreds of kilograms of material quickly. Three possible ring synthesis routes were investigated, and one route based on TFAA, ethyl vinyl ether, and malonamide was developed and used to make 600 kg of pyridone **1**. A study of the reaction of TFAA with ethyl vinyl ether and of factors that affect the thermal stability of the product led to a considerably more robust process that was operable on the 2000 L scale. The use of readily available malonamide was proved in place of the difficultly available malonate monoamide, and along with improvements in stage 1, this gave significant cost savings (ca. £40/kg). The decarboxylation of pyridone **19** proved the most difficult stage to operate due to product sublimation problems and formation of substantial amounts of tar under the high-temperature conditions. These problems were overcome by inclusion of solvent washes and carbon treatment, and overall the route delivered pyridone **1** of >99.5% purity without a separate purification stage. The route selection and process development was carried out against a tight timetable, and the first quantities of pyridone **1** were manufactured after a total of 9 months from the initial route generation exercise, and 5 months from initiating work on the TFAA route.

Experimental Section

Solvents and reagents were obtained from commercial suppliers and were not further purified.

^{1}H NMR were recorded on a Bruker AC200, 200 MHz instrument. Gas chromatography was performed using a Hewlett-Packard 5890 gas chromatograph using a CPsil5CB column (25 m × 0.25 mm × 0.25 μm).

Yields quoted are of isolated products and are based on product weight times the GC area % except for the pyridone **1**, which was determined by quantitative HPLC against a pure reference sample. The HPLC method used a Hichrom HiRPB column, 70:30 H_2O/CH_3CN with H_3PO_4 buffer. Concentration of reactions (%) refers to the weight of substrate divided by the volume of solvent. All moisture sensitive reactions were carried out using used dried solvents (usually molecular sieves) and under an atmosphere of nitrogen. Sodium alkoxides were handled in a dry nitrogen atmosphere.

Enamine 5 (*N*-(1,1,1-Trifluoro-2-propen-2-yl)pyrrolidine). A 250 mL round bottom flask was equipped with an overhead stirrer and thermometer. To this flask was added pyrrolidine (16.1 g, 0.22 mol) under nitrogen, and then the mixture was cooled to −5 °C (acetone/ice bath). 1,1,1-Trifluoroacetone (25 g, 0.22 mol) was added portionwise followed by pTSA (1.0 g, 5.8 mmol), and the reaction mixture was stirred at room temperature for 15 h. Dichloromethane (100 mL) was added, and the reaction mixture was stirred for a further 57 h. The reaction mass was concentrated *in vacuo*, and then the crude product was purified by distillation (50 °C, 34 mmHg) to give the desired product **5** (21.9 g, 60% yield): ^{1}H NMR ($CDCl_3$) δ 5.25 (br s, 2H, CH_2), 2.85 (m, 4H, NCH_2), 1.75 (m, 4H, CH_2); MS (*m*/*z*) 165 (84, M^+), 164 (100), 137 (37), 122 (35), 68 (34).

Michael Adduct 8a (*N*-(2-(Methoxycarbonyl)ethyl)-pyrrolidine). A round bottom flask was equipped with a stirrer bar, a thermometer, and an inert atmosphere. To this flask were added enamine **5** (1.6 g, 8.7 mmol) and dichloromethane, and then the mixture was cooled to 0 °C (ice bath). Methyl acrylate (0.84 g, 9.8 mmol) was added, and then the reaction mixture was stirred for 15 h (allowing it to warm slowly to ambient temperature). Concentration in vacuo gave the title compound **8a** in 94% yield: ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3H, CO_2CH_3), 2.82 (m, 2H, NCH_2), 2.60 (m, 4H, NCH_2; 2H, CH_2CO_2 overlapping), 1.82 (m, 4H, NCH_2CH_2); MS (*m*/*z*) 157 (6, M^+), 84 (100), 42 (20).

Michael Adduct 8b ((*E*)-1-Cyano-2-pyrrolidinoethene). A 10 mL round bottom flask was equipped with a stirrer bar, a thermometer, and an inert atmosphere. To this flask were added enamine **5** (1.0 g, 6.1 mmol) and dichloromethane (5 mL), before cooling of the mixture to −50 °C (dry ice/acetone bath).

3-(Dimethylamino)acrylonitrile (0.58 g, 6.1 mmol) was added, and then the reaction mixture was allowed to warm slowly to room temperature and then stirred for a further 72 h at room temperature before being heated to 40 °C with agitation for a further 15 h. A 100% conversion to the title compound **8b** resulted (by GC): ^{1}H NMR ($CDCl_3$) δ 7.15 (d, 1H, CHCN, J = 12.8 Hz), 3.65 (d,1H, NCH, J = 12.8 Hz), 2.90 (br m, 4H, NCH_2), 2.02 (br m, 4H, NCH_2CH_2); MS (*m*/*z*) 122 (100, M^+), 94 (47), 79 (17), 67 (15), 52 (22), 41 (31).

Dihydropyridone 9 ((3,4-Dihydro-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyrid-2-one)). A 1 L round bottom flask was equipped with an overhead stirrer, a temperature controller, and a Dean and Stark apparatus. To this flask were charged the β-keto ester **10** (92 g, 0.495 mol), acrylamide (28 g, 0.390 mol), pTSA (1.0 g, 5.2 mmol), and toluene (400 mL). The reaction mixture was stirred at room temperature for 0.5 h, then heated to 110 °C, and held for 48 h. Toluene was removed by distillation at atmospheric pressure to give the desired product **9** (55.0g, 41% yield). Recrystallisation from CCl_4 gave the purified product **9** (30 g, 32% yield): ^{1}H NMR ($CDCl_3$) δ 8.18 (br s, 1H, NH), 4.28 (q, 2H, OCH_2CH_3, J = 7.4 Hz), 2.78 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 1.32 (t, 3H, OCH_2CH_3 , J = 7.4 Hz); MS (*m*/*z*) 237 (33, M^+), 217 (13), 192 (100), 152 (31), 116 (26).

Pyridone Ester 12 ((5-(Ethoxycarbonyl)-6-(trifluoromethyl)pyrid-2-one)). A round bottom flask was equipped with a reflux condenser, a thermometer, and a stirrer bar. To this flask were added the dihydropyridone ester **9** (2.09

(19) de Fraine, P. J.; Bowden, M. C.; McNeilly, P. UK Patent Application GB2305174A, 1997 (Zeneca Limited).

g, 8.65 mmol), NBS (1.6 g, 8.61 mmol), and CCl_4 (17 mL). The reaction mass was heated to 80 °C for 20 h, and then cooled to 0 °C.

The resultant solid (succinimide) was removed by filtration, and the filtrate was concentrated *in vacuo* to give the desired product **12** (1.8 g, 73% yield): ^{1}H NMR ($CDCl_3$) δ 10.15 (br s, 1H, NH), 8.05 (d, 1H, CH, J = 8.2 Hz), 6.95 (d, 1H, CH, J = 8.2 Hz), 4.40 (q, 2H, OCH_2CH_3, J = 7.4 Hz), 1.40 (t, 3H, OCH_2CH_3 , J = 7.4 Hz); MS (*m*/*z*) 235 (10, M^+), 207 (43), 190 (100), 162 (12), 134 (13).

Pyridone 1 (6-(Trifluoromethyl)pyrid-2-one). A 500 mL round bottom flask was equipped with a reflux condenser, a thermometer, and a stirrer bar. To this flask were added pyridone ester **12** (4.0 g, 16.2 mmol) and concd HCl (200 mL). The reaction mixture was heated to reflux for 6 h before cooling and addition of water (1 L). The product was extracted into ethyl acetate (3 × 250 mL), and then the organic layer was washed with water. Drying ($MgSO_4$) and concentration *in vacuo* gave the desired product **13** as a pale green solid (3.6 g, 77% yield): ^{1}H NMR ($CDCl_3$) δ 9.75 (br s, 1H, CO_2H), 7.78 (d, 1H, CH, J = 8.6 Hz), 6.57 (d, 1H, CH J = 8.6 Hz); MS (*m*/*z*) 207 (100, M^+), 190 (35), 162 (61), 135 (52). A 25 mL round bottom flask was equipped with a reflux condenser, a thermometer, and a stirrer bar. To this flask were added pyridone acid **13** (3.4 g, 11.7 mmol) and quinoline (3.15 g, 23.4 mmol). The reaction mixture was heated with agitation to 250 °C for 6 h before being cooled to room temperature. Toluene (24 mL) was added and the product extracted into 30% sodium hydroxide solution (2 × 7.5 mL). Acidification of the caustic solution gave the desired product **1** (0.2 g, 10.5% yield). Extraction of the aqueous layer with ethyl acetate (3 × 100 mL) gave a further 0.2 g of the desired product **1**. Total isolated product = 0.4 g, 21% yield. Further product was evident in the aqueous layer by HPLC: ^{1}H NMR ($CDCl_3$) δ 7.68 (m,1H, CH), 6.98 (m, 2H, CH); MS (*m*/*z*) 163 (100, M^+), 135 (78), 115 (76), 66 (67), 39 (85).

Ketone 17 (1,1,1-Trifluoro-4-ethoxybut-3-en-2-one). A dry nitrogen purged 500 mL round bottom flask was equipped with an overhead stirrer, a dropping funnel, and a thermometer. To this flask were added ethyl vinyl ether (30.0 g, 0.417 mol), pyridine (36 mL, 0.417 mol), and chloroform (100 mL).

The mixture was cooled in a water bath, and trifluoroacetic anhydride (87.6 g, 0.417 mol) in chloroform (50 mL) was added dropwise over 0.5 h, the reaction temperature being maintained at ca. 25 °C. Upon completion of addition, the reaction mixture was stirred for a further 5 min, before quenching by the addition of water. The aqueous layer was extracted with dichloromethane (100 mL), and the combined organics were water washed (100 mL). The material was dried ($MgSO_4$) and concentrated under reduced pressure to give the stage 1 product **17** (59.7 g, 85% yield) as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 7.90 (d, 1H, CH, J = 13.0 Hz), 5.85 (d, 1H, CH, J = 13.0 Hz), 4.10 (q, 2H, OCH_2CH_3, J = 7.4 Hz), 1.40 (t, 3H, OCH_2CH_3, J = 7.4 Hz); MS (*m*/*z*) 168 (7, M^+), 99 (62), 71 (100), 69 (35).

Pyridone Amide 18b (2-Hydroxy-6-(trifluoromethyl)-nicotinamide). A dry nitrogen purged 20 L round bottom flask was equipped with an overhead stirrer, a reflux condenser, and a thermometer. To this flask were added methanol (6.28 kg) and sodium methoxide in MeOH (1.92 kg, 10.6 mol). After stirring to dissolve the solid, malonamide (772 g, 7.41 mol) was added in one portion. Enone **17** (1.98 kg, 7.59 mol) was then added over 30 min at <25 °C, and the mixture was stirred at 25 °C for 2 h. The reaction mass was heated to reflux (65 °C) for 2 h, before cooling to 45 °C and quenching by the addition of 1 M HCl (until the pH value fell between 1 and 3). Methanol was removed by distillation at atmospheric pressure before addition of water (9.4 L) to the residue. This was stirred for 1 h at room temperature and filtered to give the desired product **18b** (1.29 kg, 81% yield): ^{1}H NMR (D6 acetone) δ 8.60 (br d, 2H), 7.55 (br s, 1H), 7.35 (d, 1H); MS (*m*/*z*) 206 (100, M^+), 190 (67), 163 (40), 142 (16), 114 (21), 69 (21).

Pyridone Acid 19 (3-Carboxy-6-(trifluoromethyl)pyrid-2-one). A 20 L round bottom flask was equipped with an overhead stirrer, a reflux condenser, and a thermometer. To this flask were added amide **18b** (2.73 kg, 12.2 mol), water (10.5 kg), and H_2SO_4 (3.65 kg, 36.5 mol) (**cautiously**).

The mixture was heated to reflux and held for 6 h at this temperature before being allowed to cool to room temperature. The desired product **19** was filtered off as a pale brown solid (2.57 kg, 88% yield): ^{1}H NMR (DMSO) δ 12.35 (br s, 1H, OH), 8.60 (d, 1H, CH, J = 7.4 Hz), 7.43 (d, 1H, CH, J = 7.4 Hz).

Pyridone 1 (6-(Trifluoromethyl)pyrid-2-one) (Quinoline Process). A 5 L round bottom flask was equipped with an anchor stirrer, a temperature controller, and a Dean and Stark distillation receiver. To this flask was added quinoline (2864 g, 19.2 mol), which was then heated to 60 °C. 3-Carboxy-6-(trifluoromethyl)pyrid-2-one (**19**) (2558 g, 10.62 mol) was added before slow heating to 230 °C (reflux), distilling off any water present. A milky white liquid was collected at 118 °C (223.8 g). Once on reflux, the reaction was stirred for 4 h before being allowed to cool. Toluene (10.48 kg), 47% sodium hydroxide solution (1.65 kg), and water (22 kg) were charged to the reaction mass, and the mixture was agitated for 0.25 h. Solids (brown/black tar) were removed by filtration (Whatman No. 1 filter paper) before the layers were separated. The toluene layer was extracted with 6.4% sodium hydroxide solution (6 kg), and then all of the aqueous extracts were combined. Toluene (7 kg) was charged to the combined aqueous extracts and the mixture stirred for 0.25 h, before the toluene was separated off. To the aqueous layer was added Norit CN4 carbon (88 g), and the mixture was stirred overnight. The carbon was screened off (via Whatman No. 1 filter paper), and then concentrated HCl was added to the filtrate (with cooling to control the resultant exotherm) to adjust the pH to 6−7, before stirring for 2 h. The desired product **1** was filtered off and water washed (2 × 1 kg). The final product **1** was a water wet solid (65% water) (1371 g, 79.3% yield): ^{1}H NMR ($CDCl_3$) δ 7.68 (m, 1H, CH), 6.98 (m, 2H, CH); MS (*m*/*z*) 163 (100, M^+), 135 (78), 115 (76), 66 (67), 39 (85).

Pyridone 1 (6-(Trifluomethyl)pyrid-2-one) (Neat Process). A 25 mL 3-necked round bottom flask was fitted with a magnetic stirrer bar, a thermometer, a still head, a receiver adapter, and a flask.

The stage 3 acid **19** (5.11 g, 0.02 mol) was charged to the reaction flask and heated to 250 °C with an isomantle. After 2 h at 250 °C, the reaction mixture was allowed to cool to room temperature overnight. The reaction mixture was reheated to 250 °C and held at this temperature for a further 40 min, after which time the reaction temperature fell to 203 °C. Analysis by HPLC showed only product and no unreacted starting material. The reaction mass was dissolved in acetone (to facilitate removal from the reaction flask), and the solvent was then removed by rotary evaporation to give the product **1** as a black solid (3.5 g). GC area % of product = 94.5%. NMR indicated the presence of 4% acetone. Yield of product = 3.17 g (79%): ^{1}H NMR ($CDCl_3$) δ 7.68 (m, 1H, CH), 6.98 (m, 2H, CH); MS (*m*/*z*) 163 (100, M^+), 135 (78), 115 (76), 66 (67), 39 (85).

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