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A New Route for Manufacture of 3-Cyano-1-naphthalenecarboxylic Acid

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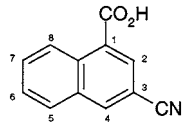
Abstract:

3-Cyano-1-naphthalenecarboxylic acid is an intermediate required for manufacture of tachykinin receptor antagonists. The 1,3-disubstitution pattern on the naphthalene skeleton complicates the synthesis of this cyano acid. Previous literature-based chemistry is unattractive for large-scale manufacture due to stoichiometric use of mercury salts, low yield, and other operational difficulties. An attractive new route has been developed by establishing the 1,3-substitution on the carbon atoms destined for only one-half of the naphthalene 2-ring system, via 3-bromocoumalate, and then building up the rest of the naphthalene ring system by Diels−Alder addition of 3-bromocoumalate to in situ-generated benzyne. The resulting 4-bromo-2-naphthoate was converted to the required cyanoacid by transformation of ester to nitrile followed by carbonylation of the bromo substituent. The new route has been scaled up successfully and offers significant advantages over previous literature chemistry in terms of improved process environmental implications, improved yield, lower cost, and improved robustness and ease of operation at larger scales of operation.

Introduction

3-Cyano-1-naphthalenecarboxylic acid (**1**) is an intermediate required for manufacture of tachykinin receptor antagonists such as ZD6021[1] under investigation for treatment of depression, asthma, urinary incontinence, and other disease conditions. The apparent structural simplicity of this target belies the synthetic complexity required for its preparation, which is exacerbated by the aromatic electrophilic substitution directing influence of the two naphthalene ring substituents.

Possible synthetic precursors might be considered, for example, having an electron-withdrawing meta-directing substituent in the 1-position of the naphthalene ring system in an attempt to direct electrophilic substitution to the 3-position; however, in practice such substituents tend to deactivate the substituted ring, directing reaction to the



(1)

8-position or the 5-position on the other ring, as can be seen with chlorination and also with nitration of 1-naphthalenecarboxylic acid (α-naphthoic acid)[2] (Schemes 1 and 2). Thus, this approach would give intermediates with inappropriate 1,8- or 1,5-disubstitution, not easily converted to cyanoacid (**1**).

Conversely, starting with an electron-donating substituent in the naphthalene 1-position, so as to activate the substituted ring to electrophilic attack, results in ortho/para direction, for example, nitration of 1-methylnaphthalene to give 1-methyl-4-nitronaphthalene[3] (Scheme 3). This again does not therefore give the 1,3-disubstitution required for easy conversion to cyanoacid (**1**).

The route used by research and early development chemists for the preparation of early samples of cyanoacid (**1**)[1,17] used naphthalic anhydride (**2**) as starting material for electrophilic bromination[4] (Scheme 4). This overcomes the

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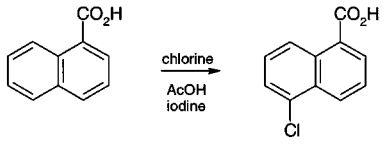
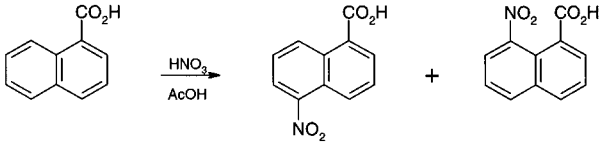
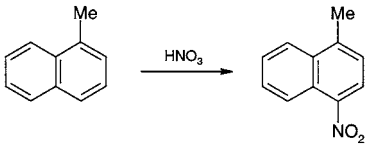
Scheme 1



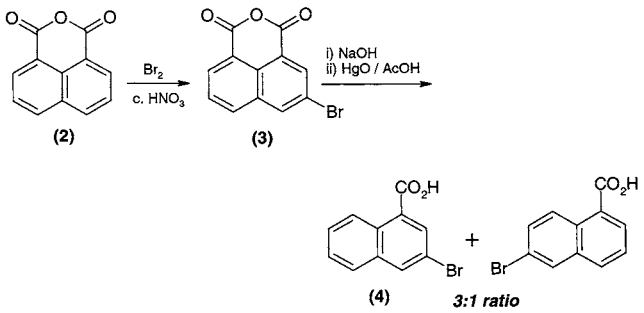
Scheme 2



Scheme 3



Scheme 4



problem of ring selectivity with meta-directing functionality, by symmetrical deactivation (to electrophilic substitution) of *both* naphthalene rings, to allow conversion to 3-bromonaphthalic anhydride (**3**), albeit with operational difficulties foreseen for future scale-up associated with bromination in concentrated nitric acid and with less than perfect chemoselectivity, for example versus nitration. This strategy, however, defers the problem of ring differentiation to the next stage, with the need to then selectively decarboxylate from the unbrominated side of the bromonaphthalic anhydride in converting bromoanhydride (**3**) to bromoacid (**4**). The decarboxylation was achieved via (environmentally unattractive) mercuration[5] to give 3-bromo-1-naphthalenecarboxylic acid (**4**), contaminated by the 6-bromo isomer with a 3:1 isomer ratio. The required 3-bromo isomer (**4**) was purified by recrystallisation from hot glacial acetic acid and was then converted to the target cyanoacid (**1**) by esterification, cyanation, and then ester hydrolysis (Scheme 5).[1,17]

Whilst suitable for materials preparation in support of early product development, this chemistry was deemed unsuitable for much larger scale of manufacture on account

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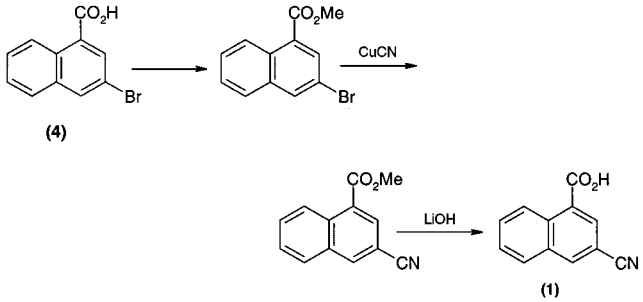
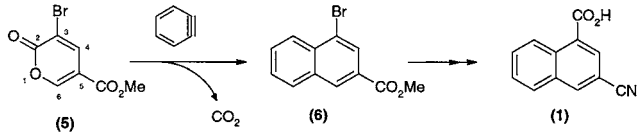
Scheme 5



Scheme 6



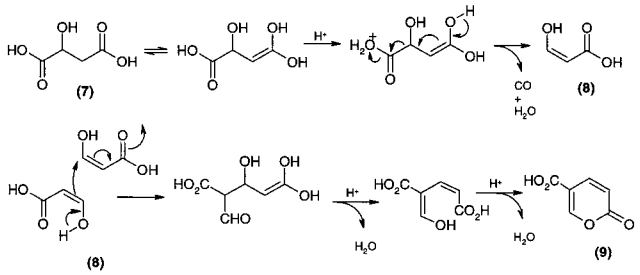
of poor selectivities and yields, unattractive process environmental implications of stoichiometric use of mercury reagent, operationally problematic bromination, and other scale-up difficulties. A variety of alternative synthetic strategies was accordingly evaluated with a view to scale-up for manufacture. One of these (forming the subject of this contribution) was based on Diels−Alder chemistry to construct the second naphthalene ring,[6] allowing the required 1,3-difunctionality to be established on the carbon atoms destined for one-half of the naphthalene 2-ring system [in bromocoumalate (**5**)], *before* assembly of the naphthalene double ring, thereby avoiding the problems of naphthalene ring selectivity. Thus, for example, bromocoumalate (**5**) (already bearing the required 1,3-disubstitution pattern in the form of bromo and carboxy substituents on atoms 3 and 5) is reacted with in situ generated benzyne to give, after decarboxylation, 1-bromo-3-naphthalenecarboxylate ester (**6**) which is then converted through a series of steps to required cyanoacid (**1**) (Scheme 6).

Results and Discussion of New Route Chemistry (Scheme 6)

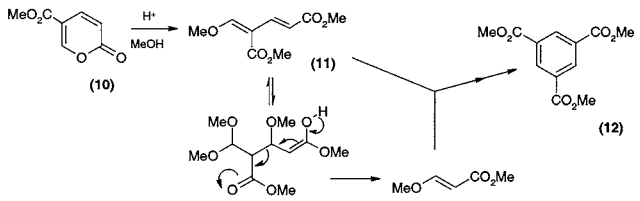
Coumalic Acid Synthesis. Malic acid (**7**) self-condenses to give coumalic acid (**9**) under strongly acidic dehydrating conditions in oleum.[7,8] Although it appears superficially as if decarboxylation occurs here, it is believed that this reaction actually proceeds via acid-catalyzed dehydration/decarbonylation of malic acid (**7**) to give aldehyde acid enol (**8**) which then condenses by Michael addition of enol to enone to give coumalic acid (**9**), after lactonisation and further dehydration (Scheme 7). Thus, the major gaseous reaction byproduct is actually carbon monoxide rather than carbon dioxide.

Carbon monoxide evolution and reaction exothermicity impose scale-up concerns associated with the need to accommodate gas disengagement (to avoid frothing), toxic carbon monoxide gas dispersion, and heat removal. These were addressed by carrying out the reaction at 75 °C, to avoid potentially hazardous accumulation of reaction intermediates, as well as by controlling the rate of oleum addition commensurate with heat and gas removal capabilities, to allow manufacture of crystallised coumalic acid in good purity and in ca. 65% yield from malic acid.

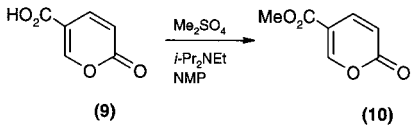
Scheme 7



Scheme 8



Scheme 9



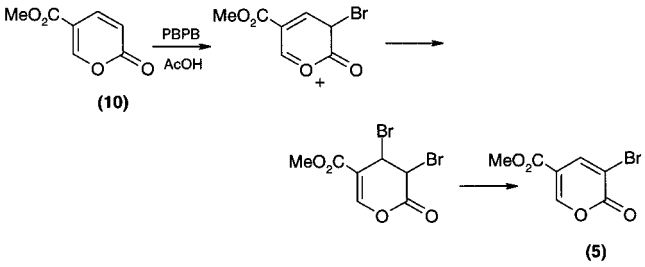
Coumalic Acid Esterification. Attempts to esterify coumalic acid (**9**) under acid conditions (e.g. formation of acid chloride and reaction with methanol, or formation of mixed anhydride with acetyl chloride followed by reaction with methanol) were thwarted due to instability of the methyl coumalate product (**10**) to give decomposition products (**11**) and (**12**), presumed to be a result of ring-opening and retro-Michael addition in the presence of methanol and acid (Scheme 8).

Whilst these problems were mitigated to some extent by buffering the increasing acidity through the course of reaction through addition of organic bases, better efficiency and process robustness were achieved by adopting instead milder esterification conditions provided by methylation of the coumalate anion (formed by use of non-nucleophilic Hünig's base *N*,*N*-diisopropylethylamine) using dimethyl sulphate (Scheme 9).

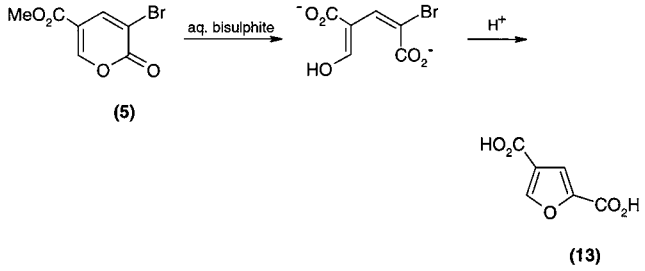
Although both methyl groups in dimethyl sulphate are capable of acting as methylating agents, in practice, the kinetics for the reaction of the second methyl group (i.e., for reaction of $MeSO_4^-$ with coumalate) were so slow as to necessitate use of approximately one equivalent of dimethylsulphate. A very slight undercharge of dimethylsulphate was used on scale-up so as to minimise toxic dimethylsulphate vapour pressure associated with the effluent before detox, to simplify effluent handling. Methylcoumalate (**10**) was isolated either by distillation under reduced pressure or by crystallisation to give high purity product in ca. 65% yield.

Methylcoumalate Bromination. Bromination of methylcoumalate (**10**) under mild conditions (using pyridinium bromide perbromide) gives methyl 3-bromocoumalate (**5**) with the required 1,3-functionality of bromine relative to the methyl ester substituent.[9] It is presumed that this occurs via bromine addition followed by HBr elimination (Scheme 10).

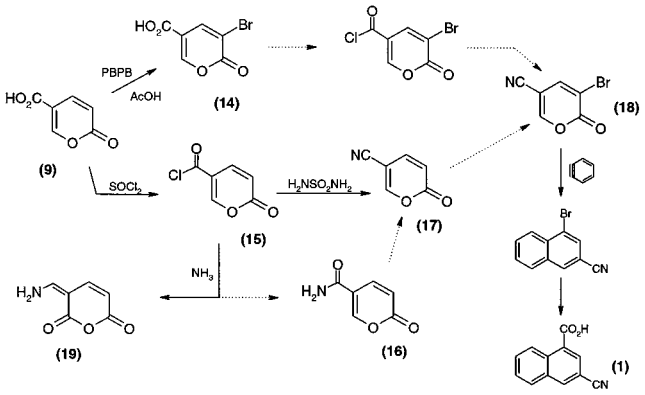
Scheme 10



Scheme 11



Scheme 12



Initial workup attempts using solvent extraction, followed by bisulphite washing to destroy excess bromine, gave varying yield loss, assumed to be due to hydrolysis and bromide elimination to give furan-2,4-dicarboxylic acid (**13**) (Scheme 11) (cf. ref 8).

Thus, workup was modified to isolate the product by precipitation and washing followed by recrystallisation giving high purity methyl 3-bromocoumalate (**5**) in ca. 82% yield.

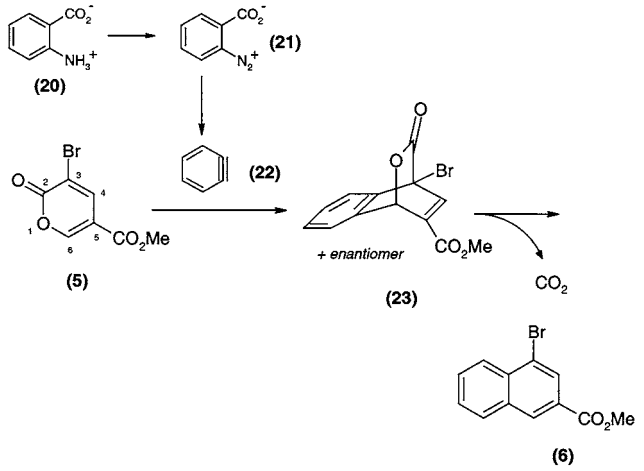
Alternative Route via Bromocoumalonitrile (18). In that the ester functionality on C-5 in coumalate (**5**) must at some stage thereafter be converted to nitrile for synthesis of cyanoacid (**1**), route variations based on earlier nitrile introduction (prior to Diels−Alder coupling with benzyne) were also investigated (Scheme 12). These route variations however proved less attractive for scale-up and manufacture due to inferior process efficiency and robustness associated with less stable intermediates.

Bromination of coumalic acid (**9**) by PBPB gave only around 50% yield of bromocoumalic acid (**14**) due to poor (slow) conversion and competing product decomposition.

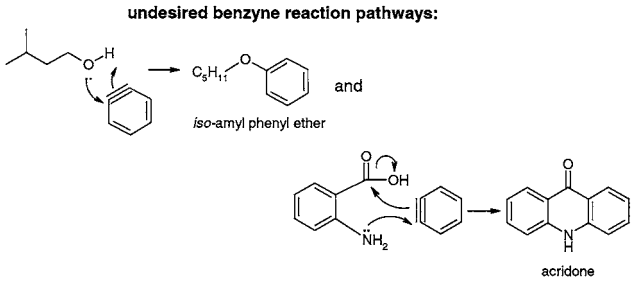
Coumalic acid (**9**) was, however, converted efficiently to coumalyl chloride (**15**) with thionyl chloride.

Reaction of acid chloride (**15**) with ammonia to give coumalamide (**16**)[10] [for subsequent dehydration to nitrile

Scheme 13



Scheme 14



(**17**)] is not feasible as this instead gives α-aminomethyleneglutaconic anhydride (**19**) due to attack by ammonia at C_6 competing with amide formation.[11]

Coumalyl chloride (**15**) was successfully converted to nitrile (**17**) by reaction with sulfamide[12] in sulfolane. Bromination of the coumalonitrile (**17**) was, however, problematic and only moderate-yielding due to competing decomposition of product (and possibly starting material, too), although subsequent Diels−Alder reaction of bromonitrile (**18**) with in situ generated benzyne did work efficiently (Scheme 12).

Diels−Alder Reaction of Bromocoumalate (5) with in situ Generated Benzyne. The reaction of bromocoumalate (**5**) with benzyne (**22**) to give bromoester (**6**) is precedented[6] whereby benzyne is generated in situ by nitrosation of anthranilic acid (**20**)[13] (Scheme 13). This literature chemistry, however, involves stoichiometric preparation, isolation, and controlled addition of highly unstable benzenediazonium-2-carboxylate (**21**) to Diels−Alder reactions, which would be unsuitably hazardous for large-scale operation. Work was accordingly carried out to explore the scope for generating and consuming this intermediate in situ within the Diels−Alder reaction to make bromoester (**6**) (Scheme 13).

Aqueous diazotisation of anthranilic acid using sodium nitrite and hydrochloric acid in aqueous methanol[14] proved unsuitable for synthesis of bromoester (**6**); this was presumed to be due to competing diazonium salt hydrolysis in the separate aqueous phase. Use of homogeneous nonaqueous conditions in DME (ethylene glycol dimethyl ether) as solvent, with *iso*-amyl nitrite as nitrosating agent,[13,15] however, gave very efficient (93%) conversion of bromocoumalate (**5**) to bromoester (**6**), albeit with a large (1 equiv) excess of benzyne precursors required to compensate for benzyne consumption due to competing addition of *iso*-amyl alcohol (byproduct of nitrosation by *iso*-amyl nitrite) to benzyne to give *iso*-amylphenyl ether (Scheme 14).

Significant potential scale-up concerns were anticipated with the chemistry at this stage, associated with the thermal instability[16] of the benzenediazonium 2-carboxylate intermediate (**21**), the reactivity of the benzyne intermediate (**22**) and the thermal instability of the strained bridged lactone intermediate (**23**). It was critical therefore that large-scale manufacturing process conditions were designed to ensure no build up of any of these reaction intermediates. A combination of reaction tracking techniques, comprising isothermal power compensation reaction calorimetry along with evolved gas (nitrogen and carbon dioxide) monitoring plus chemical analysis of reaction mixture composition, confirmed that safe concentrations of reaction intermediates could be achieved by controlled portionwise co-addition of isoamyl nitrite and anthranilic acid (solution in DME) to bromocoumalate (**5**) in DME under reflux at not less than 85 °C. Under these conditions it was confirmed (i) that projected full-scale heat and gas evolution for specified anthranilic/nitrite feed rate could be accommodated by the manufacturing plant and (ii) that heat and gas evolution were approximately commensurate with anthranilic and nitrite addition with little subsequent lag (of heat or gas evolution) and hence no intermediate accumulation.

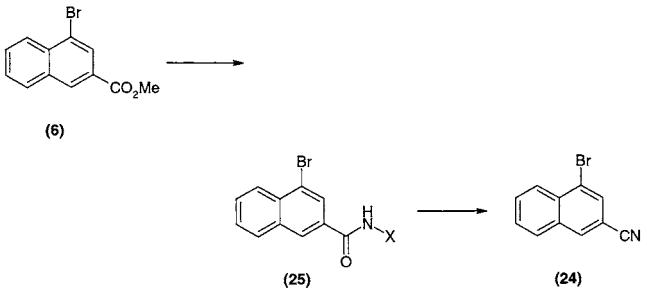
Whilst slow addition of nitrite was important to control the rate of generation of benzenediazonium 2-carboxylate, it was also found to be important to control the rate of addition of anthranilic acid so as to minimise unwanted addition of anthranilic acid to benzyne, giving acridone (Scheme 14), hence the controlled co-addition regime adopted for manufacturing process technology.

Conversion of Bromoester (6) into Bromonitrile (24). Nitriles are generally readily prepared from carboxylate esters by amination to the corresponding amide, followed by amide dehydration. Attempts to convert bromoester (**6**) to amide (**25**, X = H) were, however, disappointing with either very low conversion (e.g. on reaction with aqueous ammonia at ambient) or with poor selectivity under more extreme conditions (e.g. with a high degree of competing hydrolysis on reaction with 0.880 SG aqueous ammonia and catalytic KI in methanol at 130 °C under 4.25 bar pressure for 60 h, or with low conversion and poor selectivity on reaction with anhydrous 7 N methanolic ammonia and catalytic KI at 130 °C under 5 bar pressure for 48 h). Better results were achieved using hydroxylamine in place of ammonia, reacting bromoester (**6**) with hydroxylamine (liberated from hydroxylamine hydrochloride by methanolic KOH) in methanol at ambient temperature to give hydroxamic amide (**25**, X = OH) (Scheme 15).

Amide (**25**, X = H) was dehydrated by refluxing in thionyl chloride whilst hydroxamic amide (**25**, X = OH) was dehydrated by refluxing with PBr_3 in fluorobenzene giving, in both cases, bromonitrile (**24**) in good yields (over 90%).

More direct conversion of bromoester (**6**) to bromonitrile (**24**) was achieved by reaction with dimethylaluminium

Scheme 15

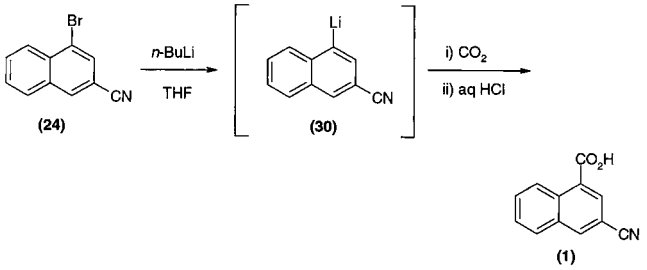


amide. This reagent was prepared by condensing excess anhydrous ammonia into 2 equiv of trimethylaluminium in toluene at −60 °C, warming to boil out excess ammonia, and then adding slowly to 1 equiv of the bromoester (**6**) in *m*-xylene at 110 °C, thereby avoiding potentially hazardous buildup of starting materials or bromoamide intermediate (**25**, X = H). Care was also taken to avoid adding excess dimethylaluminium amide as this otherwise reacts further with the required nitrile product. The reaction mixture was worked up by slow drown-out into excess 2 M hydrochloric acid at such a rate as to accommodate significant heat and gas generation. The bromonitrile product (**24**) was isolated in good yield by crystallisation.

The efficiency of this more direct conversion led to its adoption for larger-scale manufacture.

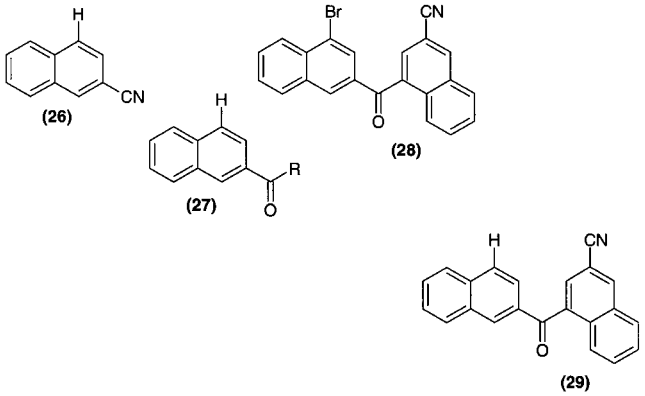
Conversion of Bromonitrile (24) into Cyanoacid (1). Two approaches were investigated: lithiation/carboxylation (Scheme 16) and also Pd-catalysed carbonylation/solvolysis (Scheme 17). These are described in turn.

Scheme 16



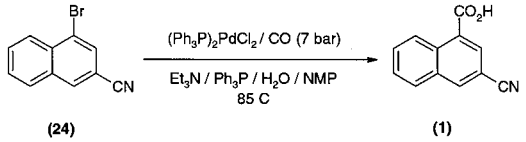
For the lithiation/carboxylation approach (Scheme 16), addition of *n*-butyllithium to the bromonitrile (**24**) at −78 °C, followed by addition of carbon dioxide and then acid workup gave a small amount of cyanoacid (**1**) but with competing protodehalogenation to give nitrile (**26**) as the major reaction product, along with ketone (**27**, R = *n*-butyl) and small amounts of coupled products (**28** and **29**). This suggests poor stability of the lithiated intermediate (**30**) in the reaction mixture, as well as poor selectivity between metallo-dehalogenation and butyl anion addition to the nitrile and some addition of the lithiated intermediate (**30**) to nitriles (**24**) and (**26**). *sec*-Butyllithium was tried in place of *n*-butyllithium in an attempt to discourage nucleophilic attack on nitrile; this did improve reaction selectivity but still gave only 29% yield of cyanoacid (**1**), with ketone (**27**, *R*-*sec*-butyl) as the major reaction product.

The poor selectivity and reaction intermediate instability of this approach, likely to worsen on scale-up as a result of



poorer mixing, increasing localised butyllithium concentration, and increasing hold times at larger scales of operation, meant that lithiation/carboxylation was dropped in favour of carbonylation for conversion of bromonitrile (**24**) to cyanoacid (**1**) (Scheme 17).

Scheme 17



Best results for carbonylation of bromonitrile (**24**) were achieved using bis(triphenylphosphine) palladium (II) chloride (2.5 mol %, unoptimised) as catalyst (presumably reduced to Pd(0) active catalytic species in situ) with added triphenylphosphine ligand. Carbonylation gives the acid bromide, which reacts with cosolvent (water or methanol) to give acid or ester product, with triethylamine used to neutralise HBr generated during the solvolysis step. Initial carbonylation experiments were carried out using methanol as cosolvent; this gave the cyano acid (**1**) as its methyl ester in good yield (ca. 80%) but required an additional step of selective hydrolysis of ester to acid (**1**) (as per Discovery Research route above: Scheme 5). Carrying out the carbonylation with water in place of methanol gave the required cyanoacid (**1**) directly in ca. 60% yield, obviating the need for the additional stage, and allowed more effective removal of palladium residues from the product by product extraction into aqueous base followed by acidification and re-extraction of product into solvent. The product was purified by recrystallisation from toluene/isohexane.

The new route chemistry was scaled up successfully (through 20−100-L scales of operation) for most of the stages before the project was terminated.

Conclusions

The described new route to cyanoacid (**1**) (Scheme 6) offers a number of advantages for manufacturing scale-up, as compared with the literature route used for early discovery and development (Schemes 4 and 5),[1,17] in terms of the following:

(i) avoiding the process environmental implications of handling stoichiometric mercuric waste

(ii) improved yield: 11% achieved and >20% achievable with further development cf. ca. 5% for previous route[17]

(iii) lower-cost starting materials

(iv) increased scale-up robustness and ease of operation: all stages well-controlled and operationally straightforward, in contrast to the previous route's poorly scaleable highly exothermic bromination step, difficult purification imposed by 3:1 decarboxylation regioselectivity, variable heterogeneous cyanation step, and chemoselectivity sensitivity of the final hydrolysis step.[17]

These advantages were proven with scale-up and operation at around 100-L-scale of reaction for most of the stages, with the exception of the final carbonylation stage.

Experimental Section

Conversion of Malic Acid (7) to Coumalic Acid (9). Oleum (20% in sulphuric acid, 287 g) was added dropwise over 2 h to a suspension of malic acid (200 g) in concentrated H_2SO_4 (313 g) at 75 °C and the resulting solution stirred for a further 4 h, maintaining the temperature at 75 °C throughout. The mixture was cooled and then drowned-out into ice-cold water (800 mL) over 1 h. After stirring for 15 min and standing overnight, the mixture was cooled to below 10 °C and the product isolated by filtration to give **9**[18] (71 g, 95% purity, 65% yield) after washing and drying.

Conversion of Coumalic Acid (9) to Coumalic Acid, Methyl Ester (10). Diisopropylethylamine (104.4 g) was added to a suspension of coumalic acid (115.5 g) in *N*-methylpyrrolidone (600 mL) at 25 °C, dimethylsulphate (100.9 g) was added over 1 h and the reaction stirred at 25 °C for 2 h. The reaction mass was diluted with 1 L of toluene, the mixture was poured into water (1 L) at 20−30 °C over 15 min. The organic layer was separated, the aqueous layer was extracted with toluene (500 mL), and the combined organic layers were washed with aqueous sodium bicarbonate solution (1 L of 10% w/w solution) and then water (1 L). Solvent was removed by evaporation in vacuo and the crude product pyrone ester purified, either by short-path distillation or by crystallisation and trituration, to give (after removal of residual solvent by evaporation in vacuo) the coumalic acid methyl ester[19] (78.8 g, 99% purity, 64% yield).

Conversion of Coumalic Acid, Methyl Ester (10) to 3-Bromocoumalic Acid, Methyl Ester (5). A solution of pyrone ester (39 g, 95% purity) in acetic acid (117 g) was added over 3.5 h to a refluxing solution of pyridinium tribromide (105 g) in glacial acetic acid (105 g). The mixture was held at reflux for 3 h and then cooled to ambient. Water (1 L) was added, and the crude product was isolated by filtration and then washed with water (2 × 200 mL). The crude product was purified by recrystallisation from toluene and isohexane to give 3-bromocoumalic acid, methyl ester[6] (46 g, 82% yield).

Conversion of 3-Bromocoumalic Acid, Methyl Ester (5) to Methyl 4-Bromo-2-naphthoate (6). Isoamyl nitrite (24.2 g) and a solution of anthranilic acid (28.0 g) in ethylene glycol dimethyl ether (90 g) were both added in separate streams at matching rate over 3 h to a refluxing solution of 3-bromo coumalic acid, methyl ester (23.3 g) in ethylene glycol dimethyl ether (135.8 g) in the presence of catalytic trichloroacetic acid (0.165 g). The reaction mixture was heated under reflux for a further 1 h after the end of addition to ensure complete reaction. The reaction mass was cooled to 50 °C, toluene (279 g) was added, and the mixture was then cooled to ambient. The toluene solution was washed with sodium hydroxide solution (75 mL, 2M), sodium bisulphite solution (75 mL, 5%), water (75 mL), hydrochloric acid (75 mL, 2 M), and water (75 mL). Solvent was removed by evaporation under reduced pressure to give methyl 4-bromo-2-naphthoate[6] (30 g, 85% purity, 93% yield). ^{1}H NMR ($CDCl_3$): 3.98 (s, 1 H, OCH_3), 7.60 (t, 1 H, J = 7.4 Hz, ArH), 7.71 (t, 1 H, J = 7.4 Hz, ArH), 7.96 (d, 1 H, J = 7.4 Hz, ArH), 8.25 (d, 1 H, J = 7.4 Hz, ArH), 8.38 (s, 1 H, ArH), 8.58 (s, 1 H, ArH). MS: 266 (M^+), 264 (M^+), 235, 233, 207, 205, 126, 74, 63.

Conversion of Methyl 4-bromo-2-naphthoate (6) to 4-Bromo-2-naphthonitrile (24). Dimethylaluminium amide was prepared by the reaction of a solution of trimethylaluminium in toluene (150 mL, 2 M) with excess anhydrous ammonia (25.5 g) at −60 °C. The mixture was allowed to warm to ambient temperature, and excess ammonia was then removed by evaporation by heating slowly up to 110 °C. The resulting dimethylaluminium amide solution in toluene was then added over 1 h to a stirred solution of the bromonaphthoate (39.8 g) in *m*-xylene (321.7 g) at 110 °C. The reaction was held at 110 °C for a further hour and then rapidly cooled to room temperature. The reaction mass was drowned-out into aqueous HCl (750 mL, 2 M) over 1.5 h at 5−10 °C. The resulting mixture was filtered and the filter cake washed with toluene (2 × 138 g). The aqueous phase from the filtrates was separated, and solvent was removed from the combined organic filtrates by evaporation under reduced pressure to leave the crude product which was recrystallised from toluene/isohexane to give 4-bromo-2-naphthonitrile (18.9 g, 54% yield). ^{1}H NMR ($CDCl_3$): 7.7 (m, 2 H, ArH), 7.9 (dd + d, 2 H, ArH), 8.20 (s, 1 H, ArH), 8.28 (d, 1 H, J = 8.4 Hz, ArH). MS: 233 (M^+), 231 (M^+), 152, 125, 76.

Conversion of Methyl 4-bromo-2-naphthoate (6) to 4-Bromo-2-naphthonitrile (24) via 4-Bromo-2-naphthamide (25, X = H). To a Carius tube equipped with small magnetic flea and protective outer metal casing were charged methyl 4-bromo-2-naphthoate (1.18 g), aqueous ammonia (9 mL), potassium iodide (0.075 g), and methanol (2 mL). The apparatus was sealed and lowered into an oil bath at 130 °C. The mixture was heated with stirring at 130 °C under 4.25 bar autogenic pressure for 66 h and was then allowed to cool to ambient temperature/pressure. The mixture was further cooled to 0 °C to complete crystallisation and filtered to collect the product. The product was dissolved in EtOAc (50 mL) and the resulting solution washed with 10% w/v aqueous Na_2CO_3 (2 × 10 mL). The organic layer was separated and dried ($MgSO_4$), and the solvent was removed by evaporation under reduced pressure to give the product 4-bromo-2-naphthamide as colourless prisms (0.38 g, 94% purity by GC area, 33% yield).

(18) Bailey, T. D. U.S. Patent 4,230,864, 1980

(19) Marko, I. E.; Evans, G. R. *Tetrahedron Lett.* **1993**, *34*, 7309.

To a 10-mL one-necked round-bottomed flask equipped with magnetic stirrer, condenser, and inert atmosphere was charged 4-bromo-2-naphthamide (0.093 g) and thionyl chloride (2 mL). The mixture was heated under reflux for 18 h and the excess thionyl chloride removed by evaporation under reduced pressure to afford the crude product 4-bromo-2-naphthonitrile as a yellow solid. ^{1}H NMR ($CDCl_3$): 8.15 (s, 1H, ArH), 8.24 (d, 1H, J = 7.4 Hz, ArH), 7.90−7.62 (m, 4H, ArH). MS: 233 (M^+), 231 (M^+), 152, 125, 76.

Conversion of Methyl 4-bromo-2-naphthoate (6) to 4-Bromo-2-naphthonitrile (24) via 4-Bromo-*N*-hydroxy-2-naphthamide (25, X = OH). To a 100-mL two-necked round-bottomed flask equipped with magnetic stirrer, graduated pressure-equalised dropping funnel, and inert atmosphere were charged methyl 4-bromo-2-naphthoate (2.69 g), hydroxylamine hydrochloride (2.78 g), and methanol (16 mL). Methanolic KOH (5 M, 10 mL) was added dropwise over 40 min to the vigorously stirred suspension at room temperature. The reaction mixture was then stirred at room temperature for 17 h after addition of base and was concentrated to ca. half volume by evaporation under reduced pressure (water bath < 45 °C). A 1:1 mixture of water/glacial acetic acid (50 mL) was added with vigorous stirring; stirring was continued for 40 min, and a further portion of 1:1 water/glacial acetic acid (20 mL) was added when the suspension became too thick to stir. Stirring was continued for 1 h, and the product was filtered off under reduced pressure and washed with cold water (3 × 15 mL). The product hydroxamic acid was dried in the vacuum oven at 70 °C to give 4-bromo-*N*-hydroxy-2-naphthamide as a beige powder (2.2 g, 76% purity by LC area, 76% yield).

To an oven-dried 250 mL two-necked round-bottomed flask equipped with magnetic stirrer, condenser, septum, and inert atmosphere was charged 4-bromo-*N*-hydroxy-2-naphthamide (2.0 g) and fluorobenzene (80 mL). Phosphorus tribromide (1.8 mL) was added dropwise over 10 min to the stirred suspension at room temperature, and the mixture was heated to reflux (85 °C), whereupon a clear orange solution was obtained. Reflux was continued for 18 h, and the solution was allowed to cool. The crude reaction mixture was poured into saturated aqueous $NaHCO_3$ solution (50 mL) and the product extracted with toluene (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), and the solvent was removed by evaporation under reduced pressure. The residue was crystallised from methanol to give the product 4-bromo-2-naphthonitrile as pale yellow prisms (0.73 g).

Conversion of Coumalic Acid (9) to 3-Bromo-2-oxo-2*H*-pyran-5-carbonitrile (3-Bromocoumalonitrile) (18) via 2-Oxo-2*H*-pyran-5-carbonitrile (Coumalonitrile) (17). Coumalic acid (3.91 g) and thionyl chloride (31 mL) were charged to a 100-mL two-neck round-bottomed flask equipped with condenser, magnetic stirrer, and inert atmosphere, and the suspension was heated to reflux for 1 h. The clear yellow solution was allowed to cool, and the excess thionyl chloride was removed in vacuo. Sulfamide (3.22 g) was added, and the solid mixture was heated to 120 °C (bath temp) for 1 h. The acid chloride melted after a few seconds, and HCl was vigorously evolved. After ca. 15 min, a red foam was obtained, which on further heating collapsed to a dark red viscous oil. After 1 h, the reaction mixture had solidified. The reaction mixture was allowed to cool and was transferred to a separating funnel with 10% w/v aqueous $NaHCO_3$ solution (150 mL) (heating with the latter being necessary to remove the crude product from the flask). The product was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were washed with saturated NaCl solution (100 mL). The extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was purified by crystallisation from MeOH (2 mL) at 0 °C. The product 2-oxo-2*H*-pyran-5-carbonitrile was obtained as dark orange prisms (1.7 g).

2-Oxo-2*H*-pyran-5-carbonitrile (2.0 g), pyridinum bromide perbromide (5.28 g), dimethoxy ethane (13 g), and toluene (12,98) were charged to a 100-mL two-neck round-bottomed flask equipped with condenser, magnetic stirrer, and inert atmosphere and was heated under reflux for 4 h. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The extracts were dried ($MgSO_4$), and the solvent was removed by evaporation under reduced pressure. The residue was swirled with ether (20 mL), and the extracts were decanted off. The residue was purified by crystallisation from acetone to give the 3-bromo-2-oxo-*2H*-pyran-5-carbonitrile as an orange powder (1.25 g, 81% purity by LC area, 31% yield). ^{1}H NMR ($CDCl_3$): 7.74 (d, 1H, J 2.5 Hz, H_a), 8.04 (d, 1H, J = 2.2 Hz, H_b). MS: 201 (M^+), 199 (M^+), 173, 171, 144, 142, 120, 64, 29.

Conversion of 3-Bromo-2-oxo-2*H*-pyran-5-carbonitrile (3-Bromocoumalonitrile) (18) to 4-Bromo-2-naphthonitrile (24). Solutions of anthranilic acid (1.8 g, 12.8 mmol) in ethylene glycol dimethyl ether (DME) (10 mL, 8.7 g) and isoamyl nitrite (1.54 g, 12.8 mmol) in DME (10 mL, 8.7 g) were added dropwise over 20 min to a stirred solution of 3-bromocoumalonitrile (1.15 g, 4.6 mmol) and trichloroacetic acid (0.047 g, 0.29 mmol) in DME (40 mL, 34.7 g) under reflux. The mixture was heated under reflux for a further 10 min, allowed to cool, and poured into water (100 mL). The product was extracted with CH_2Cl_2 (2 × 50 mL), and the volatiles were removed by evaporation under reduced pressure. The product was crystallised from the residual amyl alcohol at −20 °C, and the dirty orange solid was collected by filtration in vacuo and dried in the oven at 40 °C to give 4-bromo-2-naphthonitrile (0.81 g, 49% yield).

Conversion of 4-Bromo-2-naphthonitrile (24) to 3-Cyano-1-naphthoic acid (1) via Metallo-Dehalogenation and Carboxylation. To a 50-mL four-neck round-bottomed flask equipped with a magnetic stirrer, thermometer, septum, CO_2 inlet, N_2 inlet/bubbler, and external dry ice/acetone cooling bath were charged 4-bromo-2-naphthonitrile (0.35 g, 1.25 mmol), anhydrous hexane (2 mL), and anhydrous THF (8 mL). The suspension was cooled to −75 °C, and *n*-butyllithium (0.6 mL of 2.5 M solution in hexane, 1.5 mmol) was added dropwise over 20 min to the vigorously stirred suspension. The resulting bright red solution is stirred for a further 5 min, and then carbon dioxide (0.11 g, 2.5 mmol) was bubbled very slowly through the reaction mixture

with external cooling that maintained the reaction mixture temperature between −60 and −75 °C. Reaction was judged complete when no further temperature increase was observed upon addition of carbon dioxide. The mixture was stirred at −65 °C for a further 10 min and was then added cautiously to 2 M HCl. The product was extracted with ethyl acetate (3 × 50 mL), the combined extracts were dried ($MgSO_4$), and the solvent was removed by evaporation under reduced pressure to give 3-cyano-1-naphthoic acid[1,17] (ca. 20% yield by LC and GC−MS analysis, contaminated by approximately equimolar 2-cyanonaphthalene as seen by LC area and GC−MS). ^{1}H NMR (d_6 DMSO) 200 MHz: δ 7.73 (ddd, 1 H, J = 8.4, 7 and 1 Hz, C_7−H), 7.84 (ddd, 1 H, J = 7.5, 7, 1.5 Hz, C_6−H), 8.14 (d, 1 H, J = 7.5 Hz, C_5−H), 8.28 (d, 1 H, J = 1.5 Hz, C_2−H), 8.79 (broad s, 1 H, C_4−H), 8.85 (d, 1 H, J = 8.4 Hz, C_8−H). MS: 197 (M^+), 180, 152, 125, 29, 18.

Conversion of 4-Bromo-2-naphthonitrile (24) to 3-Cyano-1-naphthoic Acid (1) via Carbonylation. Bis-(triphenylphosphine)palladium (II) chloride (0.77 g), *N*-methyl-2-pyrrolidinone (171 g), 4-bromo-2-naphthonitrile (10 g), triphenyl phosphine (0.57 g), and triethylamine (11 g) were mixed in a nitrogen-inerted pressure vessel (Parr reactor) at ambient temperature. Water (15.5 g) was added and the reactor repeatedly purged with argon to remove residual air or oxygen. The reactor was then vented and re-pressurised with carbon monoxide to 7 bar absolute pressure (6 bar gauge pressure) and the mixture stirred at 85 °C for 10 h, maintaining carbon monoxide pressure within the reactor at 6 barg. The mixture was cooled to 50 °C and vented to atmospheric pressure, and the reaction mixture was then filtered through a bed of Celite to remove solids. The filter cake was washed with toluene (160.5 g) and then with water (124 g). The combined filtrates and washes were allowed to settle, and the lower aqueous layer was separated. The toluene layer was extracted with water (2 × 124 g). The combined aqueous phase and aqueous extracts were washed with toluene (120 g), and 2 M hydrochloric acid (64.5 mL) was then added to the aqueous solution over 30 min with stirring at 25−30 °C. The organic layer was separated off and retained, and the aqueous layer was extracted with toluene (2 × 120 g). The combined organic layer and toluene extracts were mixed with water (62 g) and 2 M sodium hydroxide solution (16.2 mL) to extract the product into the aqueous phase. The organic phase was extracted further with a mixture of water (62 g) plus 2 M sodium hydroxide solution (16.2 mL). The combined aqueous extracts were mixed with dichloromethane (350 g), and the mixture was acidified by addition of 2 M hydrochloric acid (43 mL) over 30 min at 25−30 °C. The lower organic phase was separated and retained, and the aqueous phase was extracted with further dichloromethane (100 g). The combined dichloromethane solution and extract were washed with 2 M hydrochloric acid (21.5 mL); toluene (120 g) was added, and dichloromethane was removed by evaporation under reduced pressure to leave a toluene solution of the product. This solution was heated to 60 °C, isohexane (300 g) was added over 30 min at 60 °C, and the mixture was cooled over 3 h to 5 °C so as to crystallise the product which was isolated by filtration. The product was washed with pre-cooled isohexane at 0−5 °C, and it was then dried overnight in a vacuum oven at 40 °C to give 3-cyano-1-naphthoic acid[1,17] (5.66 g, 65% yield). Spectroscopic data as above (previous experimental description).

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