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Substituent directed regioselective synthesis of 2-oxonicotonic acids and methyl nicotinates☆

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Abstract—An innovative synthesis of aryl tethered 1,2-dihydro-2-oxopyridine-3-carboxylic acids has been developed through nucleophile induced ring transformation of methyl 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carboxylates using either cyanamide or arylamidine in excellent yields. Further, the reaction of methyl 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carboxylates with formamidine acetate under analogous reaction conditions did not follow the same course of reaction and produced methyl nicotinate, regioselectively, in good yield. Decarboxylation of a 6-aryl-4-methylsulfanyl-1,2-dihydro-2-oxopyridine-3-carboxylic acid has been achieved by heating in PPA. The 4-methylsulfanyl substituent in **3** has also been oxidized to the corresponding methylsulfonyl group with *m*-chloroperbenzoic acid.

Pyridine and 1,2-dihydro-2-oxopyridine ring systems are present as substructures in a variety of naturally occurring alkaloids[1] and pharmacologically active molecules[2] with wide synthetic potential for generating molecular diversity by preparing quinolines,[3] isoquinolines,[4] indolizidines[5] and quinolizidines[5a] of therapeutic importance. The development of an efficient methodology for the regiocontrolled synthesis of congested 1,2-dihydro-2-oxopyridine-3-carboxylic acids and methyl nicotinates is a major challenge in medicinal and heterocyclic chemistry.

The synthetic strategy for the preparation[6] of 1,2-dihydro-2-oxopyridine-3-carboxylic acids involves oxidation, rearrangement and hydrolysis of various 3,5-diarylpyridines. These are also prepared by the hydrolysis of 3,5-diaryl-2-fluoropyridines[7] in 1,4-dioxane in excellent yields. The synthesis of 5-alkoxycarbonyl-1,2-dihydro-2-oxopyridine-3-carboxylic acids has been reported by nucleophilic addition of malonic esters to alkynyl imines,[8] and by coupling of a nitrile with a dienolate. A similar condensation of nitriles with dianions of β-ketoesters afforded 1,2-dihydro-4-hydroxy-2-oxopyridine-3-carboxylic acids.[9,10]

Acyl ketene dithioacetals have been found to be very useful synthons for the preparation of congested 1,2-dihydro-2-oxopyridine-3-carboxylic acids by base catalyzed substitution–cyclization reactions.[11] Recently, transition metal catalyzed synthesis of highly functionalized 2-oxopyridines has been reported[12] by reaction of azazircona cyclopentenones with alkynes in the presence of $NiCl_2(PPh_3)_2$.

The chemistry of 1,2-dihydro-2-oxopyridine-3-carboxylic acids is poorly explored and suitable synthetic procedures are lacking. They have been obtained directly by oxidation of quinoline[13] with dioxovanadium ions (VO_2^+) as well as by oxidation of 8-quinolinol and 8-quinolinamine using vanadium(V)[14] in 5 M sulfuric acid. Typically, this class of compounds has been synthesized[15] by the acid hydrolysis of 1,2-dihydro-2-oxopyridine-3-carbonitriles. Recently, Marcoux et al.[16] have reported their synthesis from the reaction of diethyl malonate with vinamidinium hexafluorophosphate salt and ammonium acetate in DMF.

Despite the numerous procedures for the construction of 1,2-dihydro-2-oxopyridine-3-carboxylic acids, most suffer from limitations such as lack of generality, harsh

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reaction conditions, poor yields and the formation of complex mixtures of side products. These difficulties necessitate the development of an efficient novel protocol for the synthesis of 1,2-dihydro-2-oxopyridine-3-carboxylic acids.

Methyl 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carboxylates have been employed as precursors for the construction of 6-aryl-4-methylsulfanyl-1,2-dihydro-2-oxopyridine-3-carboxylic acids and methyl nicotinates through base-catalyzed ring transformation using either cyanamide or arylamidine and formamidine acetate. The methyl 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carboxylates were prepared[17] from the reaction of an aryl methyl ketone with methyl 2-carbomethoxy-3,3-dimethylthioacrylate in the presence of KOH in DMSO.

Methyl 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carboxylate possesses three electrophilic centers at C-2, C-4 and C-6 in which the latter is highly prone to nucleophilic attack due to extended conjugation and the presence of an electron-withdrawing substituent at C-3 of the pyran ring. During ring transformation with cyanamide, the amino group attacks at C-6 of the pyran ring with ring closure and concomitant loss of carbon dioxide and hydrolysis of the imino and ester groups to produce 6-aryl-4-methylsulfanyl-1,2-dihydro-2-oxopyridine-3-carboxylic acid **3**. Intermediate **A**, formed during the reaction, may yield either product **3** or **4** or a mixture of both; however, only **3** was isolated. The possibility for the formation of product **4** was ruled out on the basis of intramolecular hydrogen bonding which made the ester carbonyl carbon more electrophilic and the imino nitrogen more nucleophilic in nature. This situation favored ester hydrolysis and restricted tautomerization leading to an amino group. A plausible mechanism is depicted in Scheme 1 and the compounds prepared are listed in Table 1.

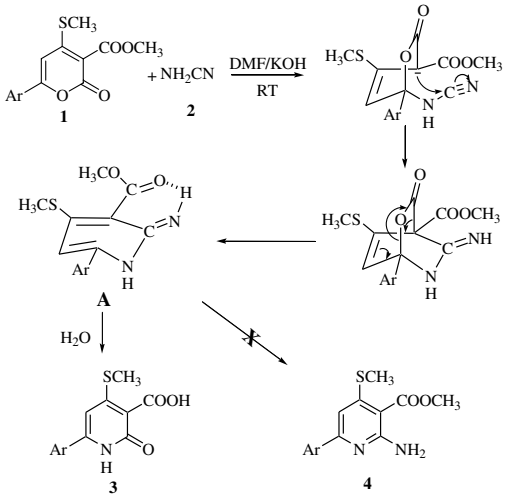
Ring transformation of **1** by arylamidinium chlorides **5** under analogous reaction conditions regioselectively provided 6-aryl-4-methylsulfanyl-1,2-dihydro-2-oxopyridine-3-carboxylic acids in excellent yields. The ring-transformed products were the same even though different reaction pathways followed. A plausible mechanism is depicted in Scheme 2.

Table 1. Comparative yields of the ring-transformed products using cyanamide and arylamidinium salts

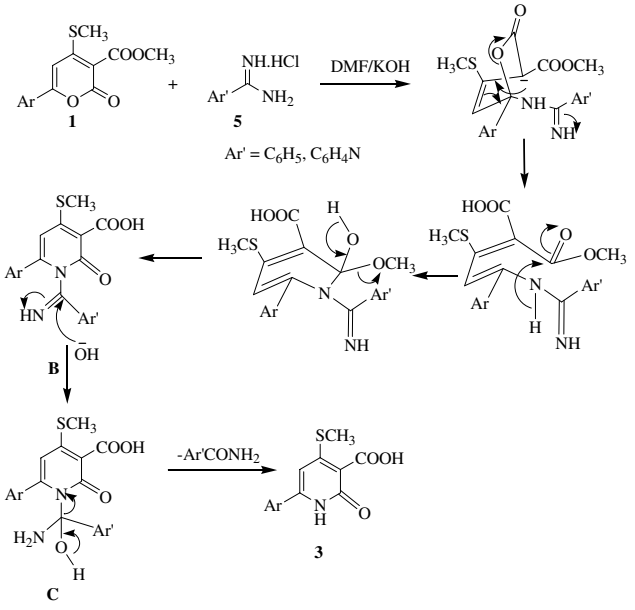
3	Ar	Yield (%) cyanamide	Yield (%) arylamidine
a	C_6H_5	73	87
b	$4F{\cdot}C_6H_4$	72	85
c	$4Cl{\cdot}C_6H_4$	76	90
d	$4Br{\cdot}C_6H_4$	79	94
e	$4CH_3{\cdot}C_6H_4$	80	89
f	$4CH_3O{\cdot}C_6H_4$	73	92
g	2-Thienyl	77	88
h	3-Pyridyl	75	79
i	1-Naphthyl	70	86
j	2-Naphthyl	76	80

The possible initial step in this reaction is attack of the nucleophile at position 6 of the 2*H*-pyran-2-one **1** with ring opening followed by ring closure involving the ester at C-3 and the amino group of the amidinium salt to form intermediate **B**, which in the presence of a base was transformed to **3** via intermediate **C** with elimination of arylamide as shown in Scheme 2.

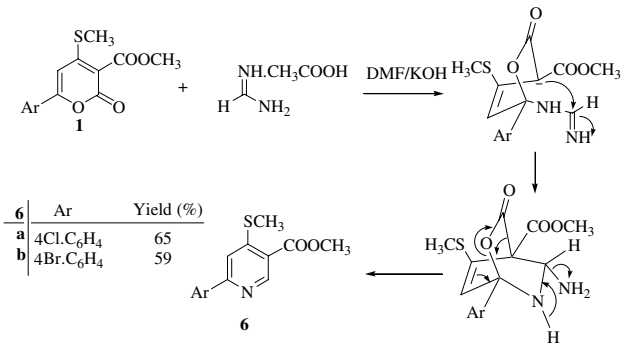
When ring transformation of **1** was carried out with formamidine acetate, the isolated product was characterized as methyl 6-aryl-4-methylsulfanylnicotinate **6**. This reaction followed a different pathway as depicted in Scheme 3. Possibly the reaction was initiated by attack of the nitrogen nucleophile at C-6 of the pyran ring followed by cyclization involving the amidine carbon and C-3 of the pyran ring with elimination of carbon dioxide and ammonia. The preference for the formation of product **6** could be due to lack of π-electron contribution from the aryl ring, which makes the formamidine carbon electrophilic and facilitates the intramolecular cyclization.



Scheme 1.



Scheme 2.



Scheme 3.

The structure of **3a** was confirmed by single crystal X-ray diffraction analysis and its ORTEP diagram is shown in Figure 1.[18]

The oxidation of 6-(naphthalen-2-yl)-4-methylsulfanyl-1,2-dihydro-2-oxopyridine-3-carboxylic acid with *m*-chloroperbenzoic acid at room temperature afforded 6-(naphthalen-2-yl)-4-methylsulfonyl-1,2-dihydro-2-oxopyridine-3-carboxylic acid **7** in very good yield. Compound **3** was decarboxylated in hot PPA at 90 °C for 8 h to yield 4-methylsulfanyl-6-phenyl-1,2-dihydro-2-oxopyridine **8** (Scheme 4).

All the compounds synthesized were characterized by spectroscopic analysis. Data of some representative compounds are given in the reference section.[19]

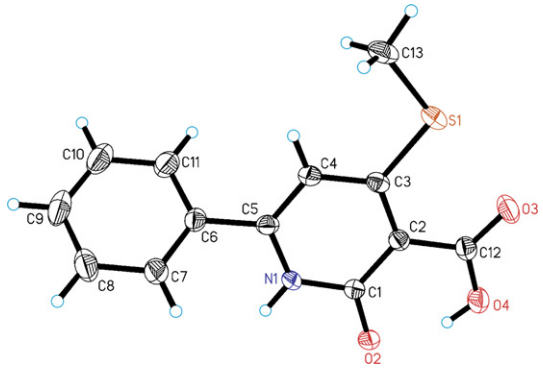
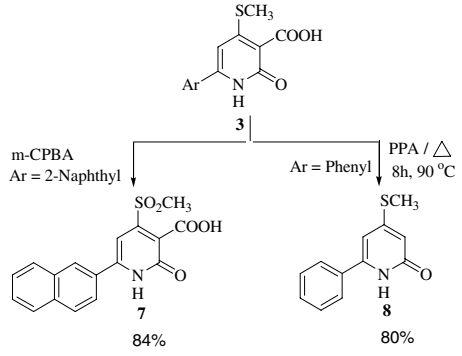


Figure 1. ORTEP diagram of **3a**.



Scheme 4.

The therapeutic importance and lack of efficient synthetic procedures for the construction of aryl tethered 1,2-dihydro-2-oxopyridine-3-carboxylic acids and methyl 6-aryl-4-methylsulfanylnicotinate inspired us to develop a simple and economical procedure for their preparation. This methodology provides an easy access to the regioselective synthesis of highly functionalized 6-aryl-4-methylsulfanyl-1,2-dihydro-2-oxopyridine-3-carboxylic acids and methyl 6-aryl-4-methylsulfanylnicotinate in excellent yields.

Acknowledgements

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18. The ORTEP diagram, Figure 1, shows the crystal structure of **3a** and its conformation. The molecule contains a planar pyridone ring (X1A) that consists of a phenyl ring (X1B) substituted at C5, a carboxylic acid at C2 and a methylsulfanyl group at C3. The twisting angle between the least-square mean plane of the phenyl and pyridone ring is 46.3°. The structural analysis shows the presence of an intermolecular $\pi\cdots\pi$ interaction (centroid separation X1A$\cdots$X1A = 3.932, X1B$\cdots$X1B = 3.748 Å); (symmetry codes: $2-x$, $1-y$, $1-z$; $2-x$, $1-y$, $-z$). The crystal packing further reveals the formation of intermolecular C–H$\cdots$O [H13B$\cdots$O3 = 2.48 Å, ∠C13–H13B–O3 = 171°, C13–O3 = 3.4326 Å] and N–H$\cdots$O interactions [H1$\cdots$O2 = 1.98 Å, ∠N1–H1–O2 = 175°, N1–O2 = 2.8385 Å], (symmetry codes: $1-x$, $2-y$, $1-z$; $2-x$, $-y$, $1-z$) and intramolecular O–H$\cdots$O interaction [H4$\cdots$O2 = 1.74 Å, ∠O4–H4–O2 = 154°, O4–O2 = 2.5038 Å]. Crystal data of **3a**: $C_{13}H_{11}NO_3S$, $M = 261.29$, triclinic, $P(-1)$, $a = 6.995(1)$ Å, $b = 7.655(1)$ Å, $c = 11.964(1)$ Å, $\alpha = 75.82(1)°$, $\beta = 83.63(1)°$, $\gamma = 76.64(1)°$, $V = 603.3(13)$ Å^3, $Z = 2$, $D_c = 1.438$ g cm^{-3}, μ(Mo-Kα) = 0.267 mm^{-1}, $F(000) = 272$, rectangular block, colourless, size = $0.3 \times 0.25 \times 0.075$ mm, 2672 reflections measured ($R_{int} = 0.0232$), 2109 unique, $wR_2 = 0.0994$ for all data, conventional $R = 0.0376$ [$(\Delta/\sigma)_{max} = 000$)] on F-values of 1642 reflections with $I > 2\sigma(I)$, $S = 1.032$ for all data and 165 parameters. Unit cell determination and intensity data collection ($2\theta = 50°$) were performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions were performed by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: XSCANS [Siemens Analytical X-ray Instrument Inc.: Madison, Wisconsin, USA 1996], SHELXTL-NT [Bruker AXS Inc.: Madison, Wisconsin, USA 1997]. CCDC (deposit No: 618376) contains the supplementary crystallographic data. These data can be obtained free of charge from www.ccdc.cam.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK. Fax: (internat.) +44 1223/336 033. E-mail: deposit@ccdc.cam.ac.uk.
19. General procedure for the synthesis of 6-aryl-4-methylsulfanyl-1,2-dihydro-2-oxopyridine-3-carboxylic acid **3**: *Procedure* **A** (Scheme 1): an equimolar mixture of methyl 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carboxylate (1 mmol) and cyanamide (50 mg, 1.2 mmol) in the presence of KOH (84 mg, 1.5 mmol) in DMF (5.0 mL) was stirred under a nitrogen atmosphere for 8 h. Consumption of starting material was monitored by TLC. Excess DMF was removed under reduced pressure, and the reaction mixture poured onto crushed ice with vigorous stirring and finally neutralized with 10% HCl (5.0 mL). The precipitate obtained was filtered, washed with water, dried and purified by column chromatography using 1% methanol in chloroform as eluent. *Procedure* **B** (Scheme 2): the product was obtained by stirring an equimolar mixture of methyl 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carboxylate (1 mmol), arylamidininium salt (1.2 mmol) and KOH (1.5 mmol) in DMF (3.0 mL) for 2–3 h. After usual work-up, the crude product was purified through column chromatography using 1% methanol in chloroform as eluent. Compound **3e**: Cream coloured solid; yield: 80% (NH_2CN), 89% (ArC·NH·NH_2); mp >250 °C; IR (KBr) 3424, 3119, 3044, 2979, 2919, 2369, 1702, 1611, 1519, 1469, 1382, 1334, 1314, 1268, 1200, 1170, 1131, 1069, 980, 918, 876, 845, 815, 716 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): 2.38 (s, 3H, CH_3), 2.54 (s, 3H, SCH_3), 6.74 (s, 1H, ArH), 7.36 (d, $J = 7.44$ Hz, 2H, ArH), 7.77 (d, $J = 7.44$ Hz, 2H, ArH), 13.08 (br s, 1H, NH), 15.66 (s, 1H, COOH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.53, 21.15, 103.97, 107.30, 127.96, 128.81, 129.56, 141.55, 147.66, 165.20, 165.91 and 166.12; MS (ESI): 276 (M^++1); $C_{14}H_{13}NO_3S$ (275.32) calcd: C, 61.07; H, 4.76; N, 5.09. Found: C, 61.23; H, 4.92; N, 4.91.
General procedure for the synthesis of methyl 6-aryl-4-methylsulfanylnicotinates (**6a**): An equimolar mixture of methyl 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carboxylate (1 mmol), formamidine acetate (1.2 mmol) and KOH (1.5 mmol) in DMF (3.0 mL) was stirred for 2–3 h. After usual work-up and column chromatography purification using 40% hexane in chloroform as eluent, the desired compound was isolated as a white amorphous solid; yield: 191 mg (65%); mp 158–160 °C; IR (KBr): 2996, 2922, 2849, 2364, 1706, 1584, 1510, 1464, 1437, 1344, 1293, 1228, 1183, 1131, 1089, 1068, 1009, 963, 830, 784, 720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.53 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 7.45 (d, $J = 8.44$ Hz, 2H, ArH), 7.48 (s, 1H, ArH), 7.95 (d, $J = 8.44$ Hz, 2H, ArH), 9.09 (s, 1H, ArH); MS m/z 294 (M^++1); HRMS: (EI, 70 eV) calcd for $C_{14}H_{12}ClNO_2S$ 293.02773 (M^+), found m/z 293.02719. *Synthesis of 4-methanesulfonyl-6-naphthalen-2-yl-2-oxo-1,2-dihydropyridine-3-carboxylic acid* (**7**): The product was obtained by stirring a mixture of 4-methylsulfanyl-6-naphthalen-2-yl-2-oxo-1,2-dihydro-pyridine-3-carboxylic acid and *m*-chloroperbenzoic acid in dichloromethane at room temperature for 10 h. The solvent was removed under reduced pressure and the crude product obtained was purified by silica gel column chromatography to afford a yellow powder using chloroform/methanol (19:1) as eluent; yield: 84%; mp >250 °C; IR (KBr): 3430, 2928, 2862, 2367, 2340, 1700, 1621, 1586, 1533, 1452, 1353, 1266, 1089, 1020, 971, 823, 764 cm^{-1}; ^{1}H NMR (DMSO-d_6/$CDCl_3$, 200 MHz): δ 2.89 (s, 3H, SCH_3), 7.59 (s, 1H, ArH), 7.64–7.68 (m, 2H, ArH), 7.94–8.13 (m, 4H, ArH), 8.53 (s, 1H, ArH), 13.40 (br s, 1H, NH), 15.82 (s, 1H, COOH); MS (ESI): 344 (M^++1); $C_{17}H_{13}NO_5S$ (343.35) calcd: C, 59.47; H, 3.82; N, 4.08. Found: C, 59.55; H, 3.76; N, 4.14. *Synthesis of 4-methylsulfanyl-6-phenyl-2-oxo-1,2-dihydropyridine* (**8**): The product was obtained by heating 4-methylsulfanyl-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carboxylic acid in polyphosphoric acid (PPA) at 90 °C for 8 h. The reaction mixture was diluted with distilled water and the precipitate obtained was filtered and purified by silica gel column chromatography to afford a white solid using hexane/ethyl acetate (4:1) as eluent; yield: 80%; mp >250 °C; IR (KBr): 3435, 2928, 2862, 2367, 2340, 1658, 1630, 1586, 1533, 1452, 1353, 1266, 1089, 1020, 971, 823, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.46 (s, 3H, SCH_3), 6.22 (s, 1H, ArH), 6.32 (s, 1H, ArH), 7.48–7.54 (m, 3H, ArH), 7.61–7.64 (m, 2H, ArH), 10.34 (br s, 1H, NH); MS (ESI): 218 (M^++1); $C_{12}H_{11}NOS$ (217.28) calcd: C, 66.33; H, 5.10; N, 6.45. Found: C, 66.25; H, 5.16; N, 6.51.