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An expeditious synthesis of imidazo[1,2-*a*]pyridines through nucleophile induced ring transformation reactions of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles†

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Abstract—An efficient and convenient synthesis of 2-(5-aryl-8-nitro-2,3-dihydroimidazo[1,2-*a*]pyridin-7(1*H*)-ylidene)acetonitriles (**3**) and 6-aryl-4-{2-[(*E*)-nitromethylidene]-1-imidazolidinyl}-2-oxo-2*H*-pyran-3-carbonitriles (**4**) through nucleophile induced ring transformation of suitably functionalized 2*H*-pyran-2-one (**1**) from imidazoliden-2-ylidene nitromethane is delineated.

Bridgehead nitrogen heterocycles[1,2] occupy an indispensable place in medicinal chemistry due to their diverse pharmacological activities. The therapeutic potential of imidazo[1,2-*a*]pyridines as antiviral,[3–6] antimalarial,[7] antiulcer,[8,9] antibacterial,[10] antifungal,[11,12] ionotropic,[13] herbicidal[14] compounds has been explored extensively. Recently, compounds with such ring systems were also reported as HIV-1 reverse transcriptase[15] (RT) and protease inhibitors,[16] and so we were prompted to seek expedient syntheses of highly functionalized imidazo[1,2-*a*]pyridines.

Tremendous efforts have been devoted to the synthesis of various imidazo[1,2-*a*]pyridines[17,18] to explore their therapeutic potential. Earlier, 3-nitro-5-substituted imidazo[1,2-*a*]pyridines were prepared[19] by reductive elimination of 3,5-disubstituted imidazo[1,2-*a*] pyridines with hydrazine hydrate in DMF and also by condensation[20] of aminopyridines with dibromoethane. Further, they have been obtained by cyclocondensation of 2-aminopyridines with substituted phenacylbromides of α-bromoacetophenones in poor yields.[21,22] 5,6,7,8-Tetrahydro-imidazo[1,2-*a*]pyridines were prepared[23] by condensation of lactams with 2-aminoacetaldehyde diethylacetal. They were also synthesized[24] by ruthenium complex-catalyzed *N*-heterocyclization of 2-aminopyridines with vicinal diols. Recently,[25] *gem*-difluoromethylated imidazo[1,2-*a*]pyridine derivatives were prepared from the corresponding α,α-difluoroacetyl anions and subsequent in situ nucleophilic addition to aryl and heteroaryl aldehydes. These reactions suffer from limitations on the introduction of substituents at specific positions and functional group intolerance of the conditions required. Thus, there is a need for an improved synthesis of imidazo[1,2-*a*]pyridines.

Our approach to the synthesis of imidazo[1,2-*a*]pyridines is very simple, convenient, economical and easy to work-up. The precursors used in this work are 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles (**1**) which may be considered as cyclic ketene hemimethylthioacetals with three electrophilic centers namely C-2, C-4 and C-6. Imidazoliden-2-ylidene nitromethane (**2**), a cyclic keteneaminal has been used as a source of an anion generated in situ by powdered KOH in DMF. The reaction is possibly initiated by attack of the nucleophile at C-6 followed by ring opening, decarboxylation and condensation–cyclization to yield 2-(5-aryl-8-nitro-2,3-dihydroimidazo[1,2-*a*]pyridin-7(1*H*)-ylidene)acetonitriles (**3**) together with 6-aryl-4-{2-[(*E*)-nitromethylidene]-1-imidazolidinyl}-2-oxo-2*H*-pyran-3-carbonitriles (**4**) in almost equal amounts, due to competitive reaction of the nucleophile at sites C-6 and C-4 of the lactone **1**, Scheme 1. The formation of product **4** is possibly initiated by Michael addition of **2** to the olefinic bond in **1** followed by elimination of methyl mercaptan.

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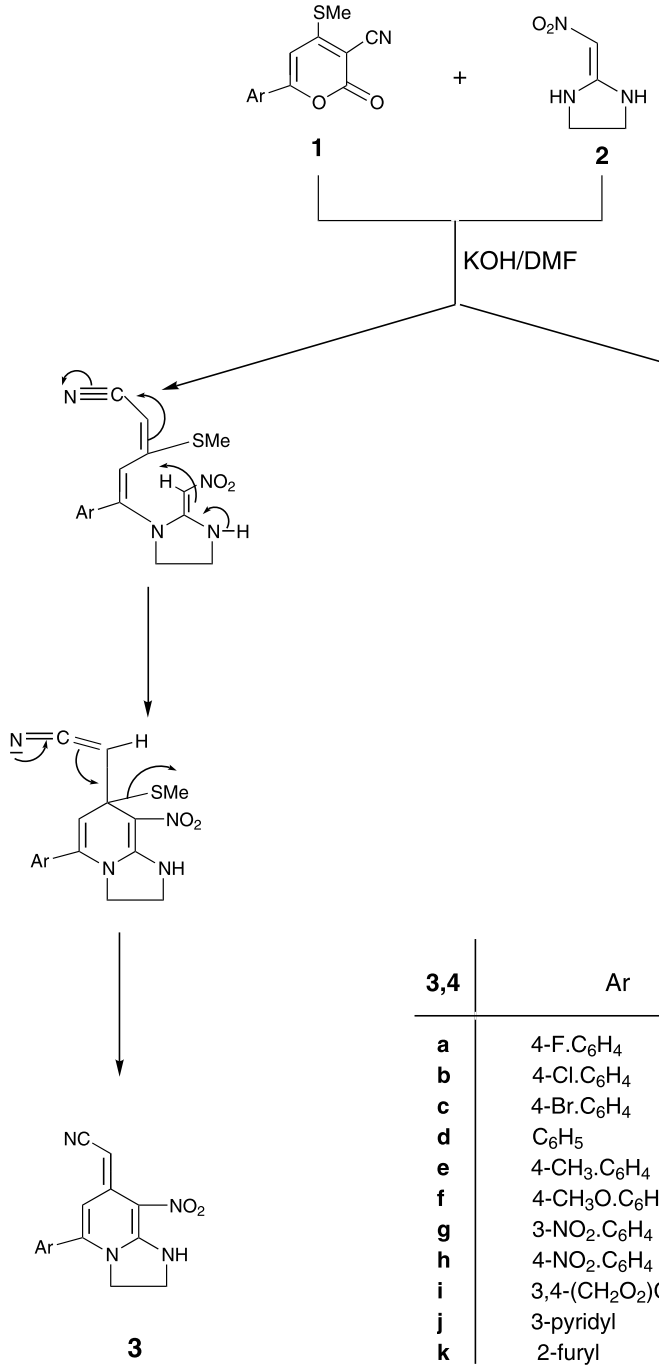

3,4	Ar	Yield (%) 3	4
a	4-F.C_6H_4	44	30
b	4-Cl.C_6H_4	42	35
c	4-Br.C_6H_4	39	32
d	C_6H_5	42	38
e	4-CH_3.C_6H_4	39	35
f	4-CH_3O.C_6H_4	41	36
g	3-NO_2.C_6H_4	30	32
h	4-NO_2.C_6H_4	33	30
i	3,4-(CH_2O_2)C_6H_3	39	40
j	3-pyridyl	55	-
k	2-furyl	38	30

Scheme 1.

This is a two-component reaction in which an equimolar mixture of pyran-2-one (**1**), imidazoliden-2-ylidene nitromethane (**2**) and powdered KOH in DMF was stirred at ambient temperature for 35–40 h under an inert atmosphere. The reaction mixture was poured into ice-water and neutralized to pH 7 by 10% HCl. The precipitate obtained was filtered, purified by column chromatography and characterized by elemental and spectroscopic analyses. The typical procedure and spectroscopic data for **3c** and **4c** are mentioned in the reference section.[26]

The structure of **3c** was further confirmed by single crystal X-ray diffraction.[27] The X-ray analysis reveals that there are two molecules in one asymmetric unit with similar conformations. Fig. 1 shows the crystal structure of one of the two molecules with the atomic numbering scheme. The molecule contains one potential hydrogen-bond donor (-NH group N1–H1 and N31–H31), which is involved in strong intermolecular hydrogen-bonding with one of the nitro group oxygens (N1–H1···O51: 2.812 Å and N31–H31···O21: 2.890 Å, respectively). This, together with Br···N≡C interactions

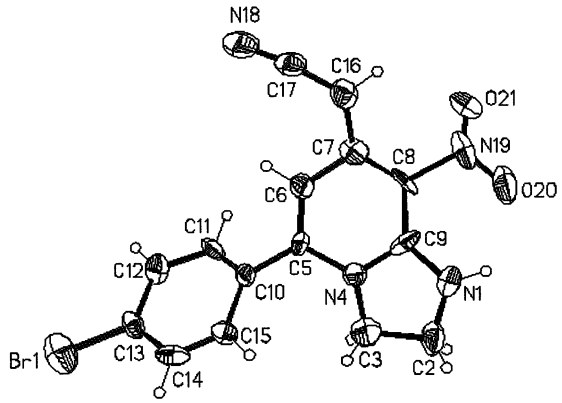

Figure 1. ORTEP diagram showing the molecular structure of **3c**.

(Br1···N48: 3.397 Å and Br2···N18: 3.257 Å, respectively), mainly stabilizes the crystal packing in the solid state.

This procedure provides an efficient and convenient synthesis of highly functionalized imidazo[1,2-*a*]-pyridines, difficult to obtain by other routes.

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26. Typical procedure: A mixture of 6-(4-methylphenylethyl-sulfanyl-2*H*-pyran-2-one-3-carbonitrile (0.32 g, 1 mmol), imidazoliden-2-ylidene nitromethane (0.13 g, 1 mmol) and KOH (85 mg, 1.5 mmol) in 15 ml of dry DMF was stirred at room temperature under a nitrogen blanket for 40 h. After this time, the reaction mixture was poured into ice water and neutralized with 10% HCl. The crude product obtained was filtered and purified on Si gel column, using $CHCl_3$:hexane (2:1) as eluent. Two products isolated from the column were characterized spectro-

scopically as **3c** and **4c**, respectively. Compound **3c**: mp> 260°C, yield 39%, NMR ($CDCl_3$) 4.01–4.05 (m, 2H, CH_2), 4.12–4.17 (m, 2H, CH_2), 6.19 (s, 1H, ArH), 6.38 (s, 1H, CHCN), 7.14 (d, 2H, $J=8.4$ Hz, ArH), 7.49 (d, 2H, $J=8.4$ Hz, ArH), 8.95 (sb, 1H, NH); IR (KBr) ν 2205 cm^{-1} (CN); MS (m/z) 359 (M^+). Compound **4c**: mp> 260°C, yield 29%. NMR ($CDCl_3$) δ 3.81 (t, 2H, CH_2), 3.92 (t, 2H, CH_2), 6.01(s, 1H, CH), 6.27 (s, 1H, CH), 7.29 (d, 2H, $J=8.3$ Hz, ArH), 7.46 (d, 2H, $J=8.3$ Hz, ArH), 8.98 (s, 1H, NH); IR (KBr) ν 2205 cm^{-1}(CN); MS (m/z) 403(M^+).

27. Crystal data for **3c**: $C_{15}H_{11}BrN_4O_2$, $M=359$, monoclinic, Pc, $a=17.700(1)$, $b=10.636(1)$, $c=7.603(1)$ Å, $\beta=93.50(1)°$, $V=1428.6(2)$ $Å^3$, $Z=4$, $D_c=1.670$ g cm^{-1}, λ (Mo Kα) $=0.71073$ Å, $F(000)=720$, brown rectangular crystal, size 0.40×0.30×0.15 mm, 4419 reflections measured (3803 unique), $R_w=0.11$ for all data, conventional $R=0.082$ on F values of 2685 reflections with $I>2\sigma(I)$, $S=1.281$ for all data. Unit cell determination and intensity data collection ($2\theta=54°$) was performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: XSCANS [Siemens Analytical X-ray Instruments Inc.: Madision, Wisconsin, USA 1996], SHELXTL-NT [Bruker AXS Inc.: Madision, Wisconsin, USA 1997]. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC deposition No: 171295).