A Facile Synthesis of 2-Pyridones by Nucleophilic Reaction on Pyran-2-thiones

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Pyridones constitute an important class of heterocyclic compounds. There are several methods available[1] for the preparation of pyridones. Among them we were interested in the synthesis of 2-pyridones from the corresponding 2-pyrones and ammonia or primary amines. In connection with our work on the construction of various heterocycles, we have prepared the pyrone **3** by acetylation[2] of the glutaconic acid **1**, followed by the hydrolytic rearrangement[3] of the acetylated compound **2**. We premised that **2** and **3** could be suitable precursors for 4,6-disubstituted-2-pyridones and accordingly we report here our work done on this field.

During our earlier work[2,3], it was noted that **2** was extremely sensitive towards amines while **3** was far less reactive. In some cases, though the products obtained from **2** and **3** were identical, yields of the products were very poor. Further, it was also noted that **3** reacted with amines only at high temperature and certain nitrogen nucleophiles like 1,2-diaminoethane **(4)** and 1,2-diaminobenzene **(6)** were incapable of reacting with **3** to provide the expected imidazopyridine **5** and pyridobenzimidazole **8** respectively. Reaction of **2** with **6** gave a totally different pyridobenzimidazole **7** through deacetylation[4] (Scheme **A**).

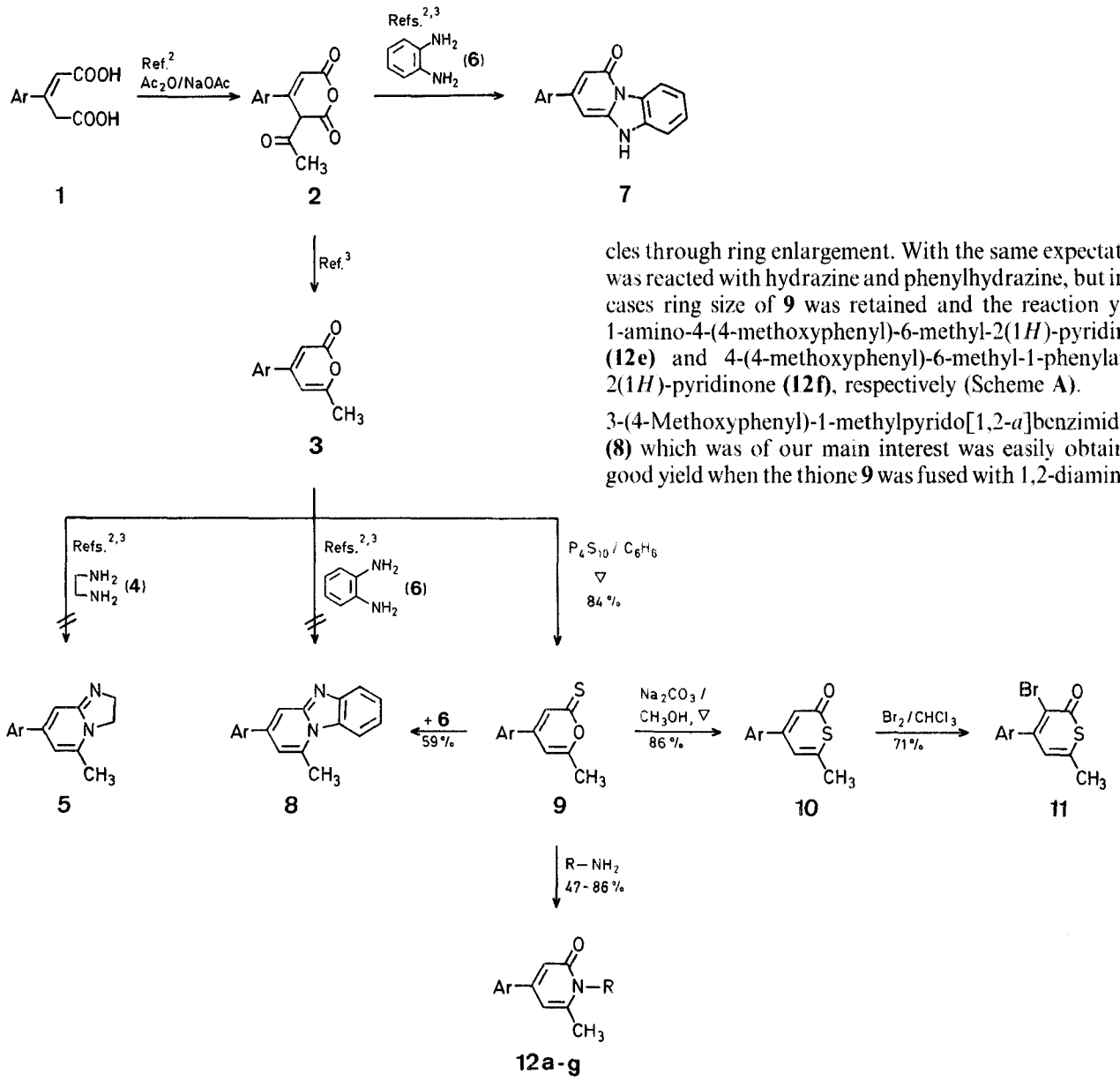
At this juncture, efforts were made to improve the yields of the products and to prepare **5** and **8**. To this end, we thought it imperative to activate the carbonyl group in **3** so as to make it more susceptible for nucleophilic attack. Hence, the carbonyl group in **3** was converted to thione, as thione is known to be more reactive for nucleophilic attack at the C-atom.

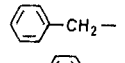
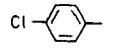
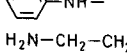
Amongst the various methods available for the conversion of a keto group to a thione group[5–10], the use of phosphorus pentasulphide was found to be more effective. Thus, when **3** was boiled in benzene with excess of phosphorus pentasulphide, 4-(4-methoxyphenyl)-6-methyl-2*H*-pyran-2-thione **(9)** was obtained in excellent yield.

When boiled in aqueous methanolic sodium carbonate solution **9** underwent rearrangement to give 4-(4-methoxyphenyl)-6-methyl-2*H*-thiopyran-2-one **(10)**. Compound **10** was subjected to bromination by reacting it with bromine in chloroform to form its 3-bromo-derivative **11**. Attempts were made to condense **11** with different primary and secondary amines, but, the bromine atom could not be replaced. When boiled with excess of aqueous ammonia, **9** yielded sulphur free products identified as 1,2-dihydro-4-(4-methoxyphenyl)-6-methyl-2-pyridinone **(12a)** which was identical with the one obtained[4] earlier in poor yields by the reaction of aqueous ammonia with **2** or **3**.

Reaction of **9** with other nitrogen nucleophiles like benzylamine, 4-chloroaniline, hydroxylamine, followed the same path to give 1-substituted-2-pyridinones **12b**, **12c**, and **12d**, respectively. Bidentate nitrogen nucleophiles like hydrazine, phenylhydrazine are known to condense with anhydrides or pyranones to furnish the corresponding 1,2-diazaheterocycles through ring enlargement. With the same expectation, **9** was reacted with hydrazine and phenylhydrazine, but in both cases ring size of **9** was retained and the reaction yielded 1-amino-4-(4-methoxyphenyl)-6-methyl-2(1*H*)-pyridinone **(12e)** and 4-(4-methoxyphenyl)-6-methyl-1-phenylamino-2(1*H*)-pyridinone **(12f)**, respectively (Scheme **A**).

3-(4-Methoxyphenyl)-1-methylpyrido[1,2-*a*]benzimidazole **(8)** which was of our main interest was easily obtained in good yield when the thione **9** was fused with 1,2-diaminobenzene **(6)** at 150 °C. Surprisingly, when the same reaction was carried out with 1,2-diaminoethane **(4)**, the reaction did not furnish the desired product **5**, but the open chain compound 1-(2-aminoethyl)-4-(4-methoxyphenyl)-6-methyl-2(1*H*)-pyridinone **(12g)** was obtained (Scheme **A**).



12	R	12	R
a	H	d	HO
b		e	H_2N
c		f	
		g	$H_2N-CH_2-CH_2-$

Scheme **A**

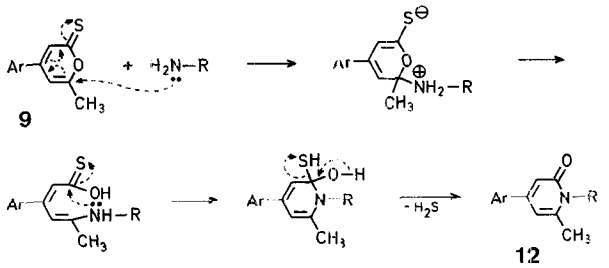
Examination of the results obtained revealed that during the reactions the ring size was not changed, further, in some cases the thione group was converted into keto group, necessarily through some rearrangement. The loss of sulphur and regeneration of the 2-carbonyl

Table. 2-Pyridones **12a–g** prepared

Product No.	Reaction conditions: Amine (mol)	Solvent (ml)	Temp. [°C]	Time [h]	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
12a	NH_3[b]	H_2O[b]	reflux	3	70	222–223°	$C_{13}H_{13}NO_2$ (215.3)	1645, 1440, 1240, 800	2.50 (s, 3H, CH_3); 3.93 (s, 3H, OCH_3); 6.45 (s, 1H, 5-H); 6.76 (s, 1H, 3-H); 7.10–7.70 (AA'BB', $4H_{arom}$, J = 8 Hz); 13.80 (br. s, 1H, NH, exchangeable with D_2O)
12b	C_6H_5—CH_2—NH_2 (0.029)	xylene (20 ml)	reflux	3	75	156–157°	$C_{20}H_{19}NO_2$ (305.4)	1650, 1600, 1590, 1300, 1250, 830	2.33 (s, 3H, CH_3); 3.83 (s, 3H, OCH_3); 5.37 (s, 2H, CH_2); 6.28 (s, 1H, 5-H); 6.65 (s, 1H, 3-H); 6.85–7.60 (m, $9H_{arom}$)
12c	4-Cl—C_6H_4—NH_2 (0.01)	none	140°	3	86	232–233°	$C_{19}H_{16}ClNO_2$ (325.8)	1665, 1615, 1590, 1500, 1300, 1250, 820	2.02 (s, 3H, CH_3); 3.87 (s, 3H, OCH_3); 6.37 (s, 1H, 5-H); 6.70 (s, 1H, 3-H); 6.88–7.63 (m, $8H_{arom}$)
12d	HO—$H_2N \cdot HCl$ (0.05)	pyridine (30 ml)	reflux	4	82	188–189°	$C_{13}H_{13}NO_3$ (231.3)	3150–2800, 1650, 1590, 1450, 1230, 1190, 810	2.50 (s, 3H, CH_3); 3.83 (s, 3H, OCH_3); 6.33 (s, 1H, 5-H); 6.70 (s, 1H, 3-H); 6.90–7.43 (AA'BB', $4H_{arom}$, J = 8 Hz); 8.25 (br. s, 1H, OH, exchangeable with D_2O)
12e	H_2N—$NH_2 \cdot H_2O$[c]	ethanol (20 ml)	reflux	2	78	170–171°	$C_{13}H_{14}N_2O_2$ (230.3)	3250–3140 1625, 1590, 1555, 1280, 1220, 1165, 995	2.50 (s, 3H, CH_3); 3.80 (s, 3H, OCH_3); 5.13 (br. s, 2H, NH_2); 6.30 (s, 1H, 5-H); 6.70 (s, 1H, 3-H); 6.83–7.56 (AA'BB', $4H_{arom}$, J = 8 Hz)
12f	C_6H_5—NH—NH_2 (0.03)	ethanol (20 ml)	reflux	1.5	69	207–208°	$C_{19}H_{18}N_2O_2$ (306.4)	3230, 1630, 1590, 1550, 1230, 810	2.46 (s, 3H, CH_3); 3.80 (s, 3H, OCH_3); 6.50 (s, 1H, 5-H); 6.72 (s, 1H, 5-H); 6.80–7.86 (m, $10H_{arom}$ + NH)
12g	H_2N—$(CH_2)_2$—NH_2 (0.02)	none	100°	1	47	270–271°	$C_{15}H_{18}N_2O_2$ (258.3)	1640, 1560	2.57 (s, 3H, CH_3); 2.87 (s, 4H, CH_2—NH_2, NH_2, exchangeable with D_2O); 3.83 (s, 3H, OCH_3); 4.31 (s, 2H, N—CH_2); 6.32 (s, 1H, 5-H); 6.71 (s, 1H, 3-H); 6.86–7.68 (AA'BB', $4H_{arom}$, J = 8 Hz)

[a] Satisfactory microanalyses obtained: C ±0.05, H ±0.11, N ±0.08.
[b] 40 ml of aqueous ammonia was used.
[c] 3 ml of hydrazine hydrate was used.

group were intriguing. The endocyclic conjugation might be responsible for the rearrangement and instead of the normal nucleophilic 1,2-addition, 1,6-addition could be possible. Based on these assumptions, a plausible mechanism has been suggested in Scheme **B**. During the recyclization, nitrogen may take precedence and hydrogen sulphide may be lost to form the 2-pyridone structure. The conversion of the carbonyl group of **3** to thione has thus proved its merit in the reactions and provided excellent yields of the products.



Scheme **B**

4-(4-Methoxyphenyl)-6-methyl-2*H*-pyran-2-thione (9):
A mixture of **3** (2.16 g, 0.01 mol) and phosphorus(V) sulphide (5 g, 0.011 mol) in dry benzene (30 ml) is heated under reflux for 4 h. The benzene is decanted and the residue is extracted with more boiling benzene (90 ml), the combined extract is washed with water (50 × 3 ml). The benzene layer is dried with anhydrous sodium sulphate, and evaporated to give crude **9** which is recrystallized from benzene/petroleum ether; yield: 1.95 g (84%); m.p. 140–141 °C.

$C_{13}H_{12}SO_2$ (232.3) calc. C 67.24 H 5.17 S 13.79
found 67.17 5.21 13.71

I.R. (KBr): ν = 1625, 1590, 1490, 1170, 1160, 1093, 810 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 2.40 (s, 3H, CH_3); 3.87 (s, 3H, OCH_3); 6.57 (s, 1H, 5-H); 7.30 (s, 1H, 3-H); 6.50–7.60 ppm (AA'BB', $4H_{arom}$, J = 8 Hz).

4-(4-Methoxyphenyl)-6-methyl-2*H*-thiopyran-2-one (10):
A solution of **9** (2.32 g, 0.01 mol) in methanol (40 ml) is heated under reflux in aqueous 10% sodium carbonate (10 ml) for 1 h. The mixture is diluted with water (75 ml), the precipitate formed is filtered, and recrystallized from benzene/petroleum ether; yield: 2.0 g (86%); m.p. 80–81 °C.

$C_{13}H_{12}SO_2$	calc.	C 67.24	H 5.17	S 13.79	
(232.3)	found	67.18	5.19	13.82	

I.R. (KBr): ν = 1620, 1590, 1550, 1500, 1280, 1240, 1028, 810 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 2.40 (s, 3H, CH_3); 3.80 (s, 3H, OCH_3); 6.43 (s, 1H, 5-H); 6.80–7.43 ppm (m, 5H, H_{arom} + 3-H).

3-Bromo-4-(4-methoxyphenyl)-6-methyl-2*H*-thiopyran-2-one (11):
A mixture of **10** (1.16 g, 0.005 mol) and bromine (0.6 g, 0.0075 mol) in chloroform (25 ml) is heated under reflux for 1.5 h. Evaporation of chloroform gives the residue which on treatment with cold methanol gives crude **11** which is recrystallized from ethanol; yield: 1.1 g (71%); m.p. 134–135°C.

$C_{13}H_{11}BrSO_2$	calc.	C 50.16	H 3.53	Br 25.72	S 10.28
(311.2)	found	50.07	H 3.50	25.62	10.28

I.R. (KBr): ν = 1620, 1600, 1580, 1475, 1240, 835, 750 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 2.36 (s, 3H, CH_3); 3.83 (s, 3H, OCH_3); 6.60 (s, 1H, 5-H), 6.86–7.36 ppm (AA'BB', $4H_{arom}$, J = 8 Hz).

6-Methyl-2(1*H*)-pyridones 12a–g; General Procedure:
A mixture of 4-(4-methoxyphenyl)-6-methyl-2*H*-pyran-2-thione (**9**; 2.32 g, 0.01 mol) and the appropriate amine component, either pure or in a solvent is heated between 1–4 h (see Table for the amount of amine used and exact experimental conditions), cooled and worked up as given below.

12a: The reaction mixture is cooled, the product separated is filtered, washed with water and recrystallized from ethanol.

12b: The solvent is removed in vacuum and the residue is triturated with petroleum ether. The crude product is recrystallized from benzene/petroleum ether.

12c: The mixture is acidified with 2 normal hydrochloric acid (10 ml), the precipitate formed is filtered, washed with water and recrystallized from ethanol.

12d: The mixture is poured into water (75 ml), the precipitate is filtered, washed with water and recrystallized from ethanol.

12e and **12f:** The separated product (yellow needles in the case of **12e**) is filtered and recrystallized from benzene/ethanol and ethanol respectively.

12g: The mixture is diluted with water and recrystallized from ethanol/dimethylformamide.

3-(4-Methoxyphenyl)-1-methylpyrido[1,2-*a*]benzimidazole (8):
A mixture of **9** (2.32 g, 0.01 mol) and 1,2-diaminobenzene (**6**; 2.16 g, 0.02 mol) is fused in an oil bath at 150°C for 1.5 h. The reaction mixture is cooled and triturated with benzene when **8** separates. It is filtered and recrystallized from benzene/petroleum ether; yield: 1.8 g (59%); m.p. 204–205°C).

$C_{19}H_{16}N_2O$	calc.	C 79.16	H 5.55	N 9.72	
(304.4)	found	79.10	5.50	9.70	

I.R. (KBr): ν = 1660, 1570, 1263, 840 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 2.06 (s, 3H, CH_3); 3.83 (s, 3H, OCH_3); 6.40 (s, 1H, 5-H); 6.70–7.60 ppm (m, 9H, 3-H + H_{arom}).

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