Studies with 2H pyranones: Synthesis of new 3-substituted-4-hydroxy-2H-pyran-2-ones

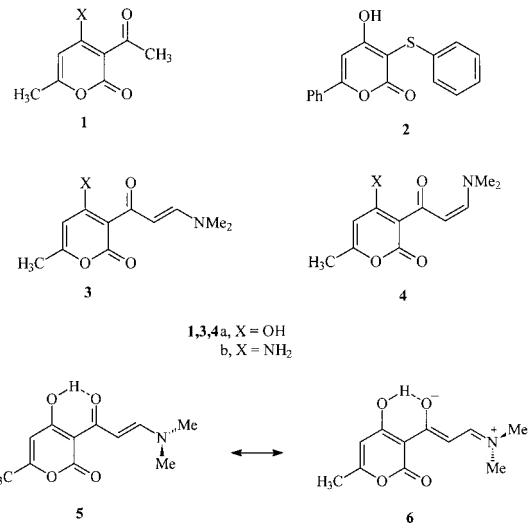
Balkis Al-Saleh[a], Nouria Al-Awadi[a], Halema Al-kandari[a], Mervat Mohammed Abdel-Khalik[a] and Mohamed Hilmy Elnagdi[a,b]*

[a]*Department of Chemistry, Faculty of Science, University of Kuwait, PO Box 5969, Safat, 13060 Kuwait,* [b]*Department of Chemistry, Faculty of Science, Cairo University, Giza, A.R. Egypt*

J. Chem. Research (S), 2000, 16–17
J. Chem. Research (M), 2000, 0201–0214

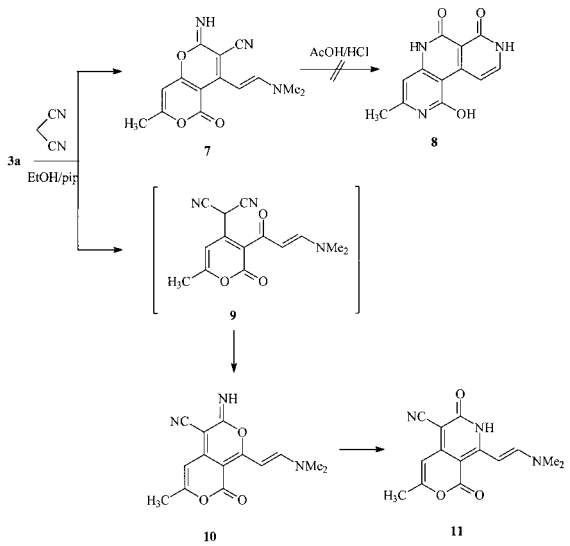
3-Acetyl-4-hydroxy-6-methyl-2H-pyran-2-one **1a** condensed with N,N-dimethylformamide dimethyl acetal yielding the enaminone **3a**. The latter reacted with a variety of reagents affording pyridine derivatives **11**, benzofuranoylpyranes **14** and **17**, pyranylpyranes **22**, pyranylpyrazole **29a,b** and pyranylisoxazole **33**.

In conjunction with our interest in exploring the synthetic potential of enaminones,[7] we report here on the synthesis of **3a,b** and their utilities for the synthesis of 3-heteraromatic 2H-pyran-2-one derivatives. Thus compound **3a** was prepared in 70% yield by reacting **1a** with N,N-dimethylformamide dimethyl acetal in refluxing dioxane. This procedure proved better than the literature procedure,[8] which produced some side products along with **3a**. The Z-form **4a** was not detected. The ^{1}H NMR spectra of the reaction product revealed only two mutually coupled trans olefinic protons at δ = 6.53 and δ = 8.17 ppm (J = 14Hz). IR spectrum of the reaction product revealed strong CO absorption at 1712 cm^{-1} for 2H-pyran-2-one carbonyl group while OH appeared as weak broad band at 3,500 – 3,300 cm^{-1} which indicates that **3a** exists in the hydrogen bonded form **5**.



The ^{13}C NMR spectra of the reaction product revealed enaminone carbonyl carbon at δ 186 ppm, which is in accordance with the proposed structure. The observed magnetic non-equivalence of the two methyl functions of the dimethyl amino moiety is believed to result from restricted rotation around CH = N bond in charge separated form **6**.

Treatment of **3a** with malonoitrile in refluxing ethanolic piperidine afforded a product of condensation with water elimination. The ^{13}C NMR spectra indicated the presence of only one CN signal. The isometric structures **7** and **11** seemed reasonable. Structure **11** was tentatively proposed, on the basis of the stability of the product, in acetic acid under reflux in the presence of aqueous hydrochloric acid. These conditions are expected to convert **7** to **8**. It is thus believed that **11** is formed by initial condensation of the ring carbonyl with the active methylene moiety in malononitrile yielding **9** which cyclizes into **11** via the intermediate **10** (Scheme 1). The ^{1}H NMR spectra of compound **11** showed the characteristic pattern corresponding to an AB system at δ 7.95 and 8.03 ppm and J 13 Hz for vinylic *trans* protons.



Scheme 1

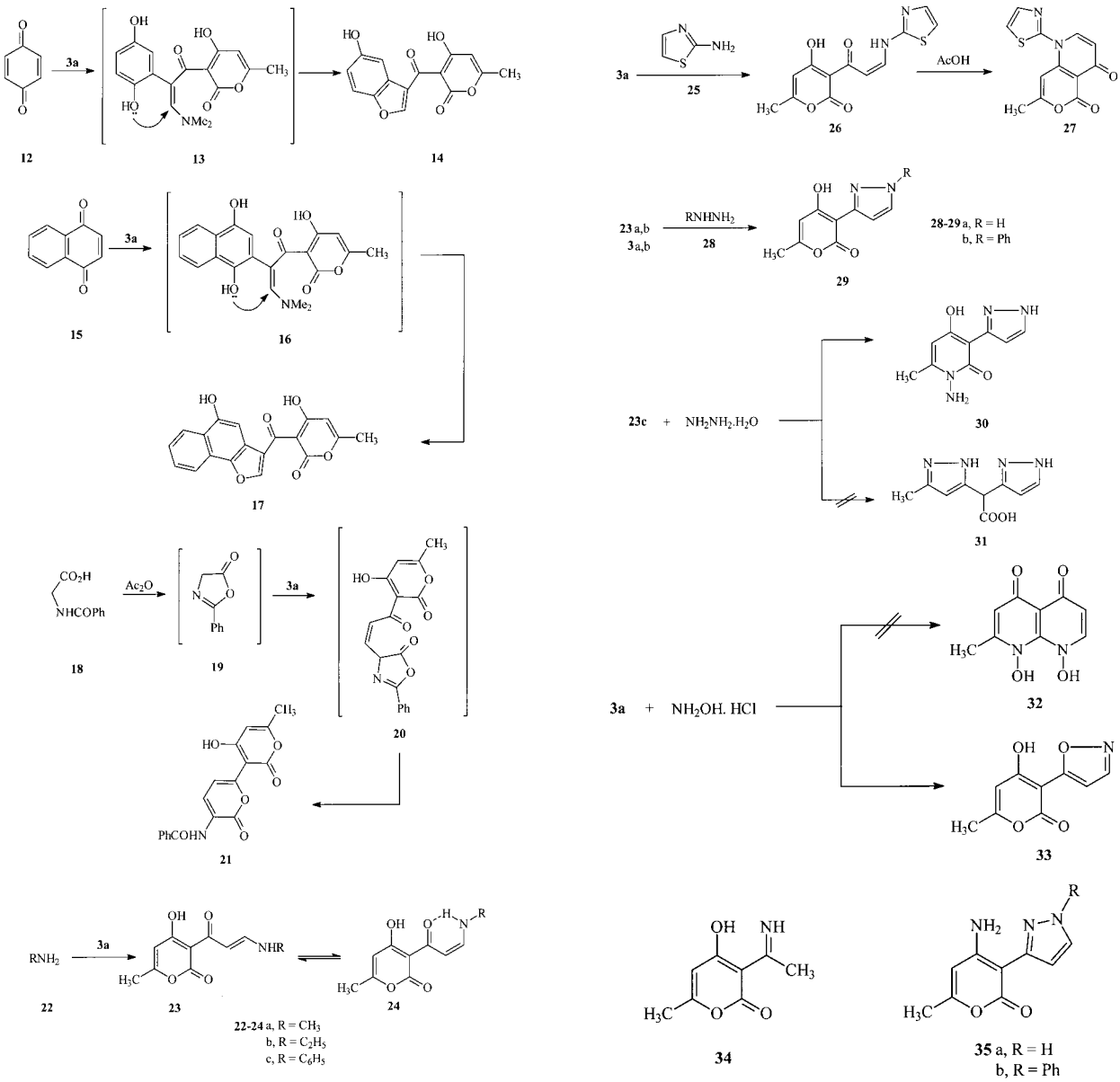
Reacting **3a** with 1,4-benzoquinone **12** resulted in the formation of **14**. Similarly, reacting **3a** with 1,4-naphthoquinone **15** afforded **17**. The formation of **14** and **17** from **12** and **15**, is assumed to occur via initial addition of the enaminone of, electron rich C-2, to the active double bond in **12** and **15** yielding the adducts **13** and **16**, that cyclize into the final products.

Compound **3a**, also reacted with hippuric acid **18** in refluxing acetic anhydride to yield the pyranone **21**. It is assumed that hippuric acid, first cyclizes into the oxazolone **19**, which then reacts with the enaminone **3a**, yielding **20**, that further rearranges into the pyranone **21**. A similar reaction sequence has recently been proposed by us to account for the formation of pyranones from the reaction of enaminones with hippuric acid[9].

Compound **3a** reacted with methylamine, ethylamine and aniline in acetic acid at room temperature to yield enaminones, which were found to exist, as mixture of the E and Z-forms **23a,c** and **24a–c**. The existence of Z-form for these compounds is in contrast to the observed predominance of E-form for **3a** and **4a**. This is attributed to the stabilization of Z-form for these compounds through hydrogen bonding.

Treatment of compound **3a** with 2-aminothiazole **25** at room temperature afforded **26** which cyclized into **27** upon reflux in acetic acid. Note that the mass spectra of **26** showed no molecular ion peak, as it cyclized into **27** prior to ionization by E1. Compound **23,ab** or **3a,b** also reacted with

* To receive any correspondence: Fax: 00 202 2953940



hydrazine hydrate and with phenylhydrazine, in acetic acid on cold or refluxing ethanol for 2 h, to yield the pyranylpyrazole **29a,b**. However, when compound **23c** was treated with excess hydrazine hydrate, pyrazoly-N-aminopyridine **30** was formed. The pyrazolylpyrazole structure **31**, formed via a mechanism similar to that reported in literature[10] for the reaction of **1a** with hydrazine hydrate, was excluded, based on IR and ^{1}H NMR spectrum which revealed the existence of N-amino function.

Although reaction of **3a** with hydroxylamine in ethanol and ammonium acetate has been reported[11] earlier to yield, **32**, we found that the reaction of **3a** with hydroxylamine hydrochloride in refluxing ethanolic ammonium acetate affords the pyranylisoxazole **33**.

Replacement of the hydroxyl group at C-4 in **1a** with ammonia or amines has been reported[12] to yield **1b**. In contrast ring opening and recrystallization into 4-pyridone was claimed in literature[13] to be effected by action of ammonia.

In fact, our results show that under a variety of conditions, a product that may be formulated as **1b** or **34** was formed. Structure **1b** was confirmed, as the ^{13}C NMR spectra indicated in acyl carbonyl carbon at δ 183 ppm. Moreover, compound **1b**, was well illustrated as it affords **3b** on treatment with N, N-dimethylformamide dimethyl acetal. This product when reacted with hydrazine hydrate or phenyl hydrazine afforded compounds **29a,b** which are formed most likely through the non-isolable intermediate **35a,b**.

University of Kuwait Research Grant Sc091 and Sc089 finance this work. We are grateful to the University of Kuwait General Facility projects in the Chemistry Department for the Analytical and Spectral Measurements. Techniques used: ^{1}H NMR, ^{13}C NMR, IR, Mass spectra and elemental analysis.

Received 3 August 1999; accepted after revision
30 December 1999
Paper 06293I

References

7. F. Al-Omran, M. M. Abdel-Khalik, *et al*. *Synthesis* 1997, 91–94.
8. K. Roth and W. Lowe. *Z. Naturforsch* 1977, **32b**:1175–1178.
9. F. Al-Omran, N. Al-Awadhi, *et al*. *J. Chem. Res.*, (S), 1997, 84–85 (M) 1997, 0601–0615.
10. P. Cantos, M. De March, *et al*. *Bull. Chem. Soc. Jpn.*, 1987, **60**, 4425.
11. W Lowe. *Arch Pharm (Weinheim, Ger.)* 1978; **311**, 414.
12. A. Akhrem A. M., Moiseenkov, *et al*. *Izv. Akad. Nauk SSSR, Ser. Khim.* 1972, 917 [CA 1972, **77**, 114175].
13. H. Takalo, P. Pasanen and J. Kankare. *Acta. Chem. Scand., Ser. B* 1988, **B42**, 373.