1-Substituted 3-Dimethylaminoprop-2-en-1-ones as Building Blocks in Heterocyclic Synthesis: Routes to 6-Aryl- and 6-Heteroaryl-2*H*-pyran-2-ones and 6- and 4-Arylpyridin-2(1*H*)-ones

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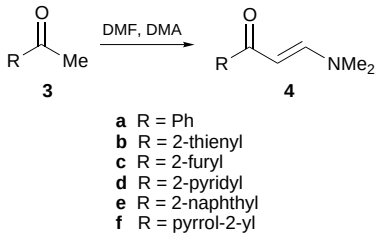
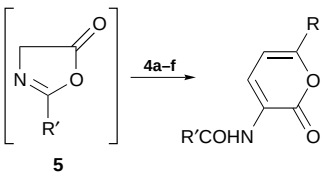
Several new 6-substituted-3-acylamino-2*H*-pyran-2-ones **6a–j** have been prepared from the reaction of enaminones **4a–f** with *N*-acyl- and *N*-benzoyl-glycines; the enaminones **4a–c** react with malononitrile in ethanol solution and in the presence of a base to yield amides **11a–c** which are converted into 6-aryl-1,2-dihydro-2-oxypyridine-3-carbonitriles **13a–c** on reflux in acetic acid.

In conjunction with our interest in the synthesis of functionally substituted heteroaromatic compounds as potential pharmaceuticals,[7–10] the development of an efficient route for the synthesis of 6-aryl- and 6-heteroaryl-2*H*-pyran-2-ones as potential anti-HIV agents seemed interesting. Recently Kocevar and co-workers[12–14] have described a one-pot synthesis of 3-acylaminopyranones by mixing 1,3-dicarbonyl compounds, triethyl orthoformate or dimethylformamide dimethyl acetal and *N*-acylglycines with a large excess of acetic anhydride. Since this method seemed the simplest way to synthesise our required compounds we investigated the reaction of hippuric acid, dimethylformamide dimethyl acetal and the methyl ketones **3a–f**. However, under these conditions only oily mixtures of products were obtained. We thus decided to modify this synthetic approach by first condensing **3a–f** with dimethylformamide dimethyl acetal, utilizing a literature procedure for the synthesis of **4a** from **3a**[15] and reacting the produced 1-substituted 3-dimethylaminoprop-2-en-1-ones **4a–c**,**e** with *N*-acylglycines. We found that **4a** reacts with hippuric acid in refluxing acetic anhydride to yield a product of molecular formula $C_{18}H_{13}NO_3$ which can be formulated as the oxazolone derivative **7a** or the pyranone **8a**. Structure **8a** was established for this product based on the ^{1}H NMR spectrum which revealed an absence of any signals for sp^3 carbons at δ 3.0–5.0 but showed two doublets at δ 7.16 and 8.22 for the pyranone 5-H and 4-H, respectively. Similarly the reaction of **4b–f** with hippuric acid afforded the pyranones **8b–f**. When **4a–c**,**e** were refluxed with glycine in the presence of acetic anhydride the pyranones **8g–j** were obtained in good yields. It is assumed that acetyl glycine generated *in situ* is cyclised into **5b** which then reacts with **4a–c**,**e** yielding the final isolable **8g–j**. The ^{1}H NMR spectra of all compounds **8a–j** revealed characteristic doublets for 4-H and 5-H with J = 8 Hz. The formation of **8a-j** from **4a–f** with either *N*-acylglycines or hippuric acid can thus be considered as an extension of the Kepe pyranone synthesis[12–14] to enable the synthesis of 6-aryl- and 6-heteroaryl-pyran-2-ones.

Compounds **4a–c** reacted with malononitrile in ethanol and in the presence of a base, affording 1:1 adducts. We first assigned the pyran structures **10a–c** for these products, by assuming initial formation of the Michael adducts **9a–c** and subsequent cyclization. However, the ^{1}H NMR spectrum for compound **11b**, for example, revealed a two-proton doublet at δ 5.77 and 7.23 with a J value of 13 Hz which can be only attributed to *trans* olefinic protons. We therefore considered structures **11a–c** for these reaction products. They are assumed to be formed *via* initial hydrolysis of malononitrile to cyanoacetamide by water present in the solvent. This was



a R = Ph
b R = 2-thienyl
c R = 2-furyl
d R = 2-pyridyl
e R = 2-naphthyl
f R = pyrrol-2-yl

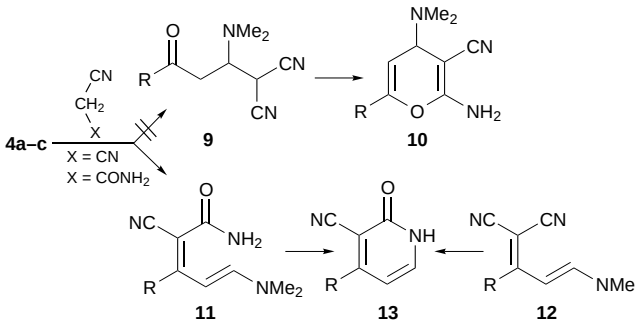


8a R = R′ = Ph
b R = 2-thienyl, R′ = Ph
c R = 2-furyl, R′ = Ph
d R = 2-pyridyl, R′ = Ph
e R = 2-naphthyl, R′ = Ph
f R = pyrrol-2-yl, R′ = Ph
g R = Ph, R′ = Me
h R = 2-thienyl, R′ = Me
i R = 2-furyl, R′ = Me
j R = 2-naphthyl, R′ = Me

followed by condensation of the active methylene group with the carbonyl of compounds **4a–c**. Water eliminated in the reaction then hydrolyses a further amount of malononitrile and the reaction can thus proceed to completion. This structure was confirmed by preparing the same reaction products *via* condensation of cyanoacetamide with **4a–c** under the same reaction conditions.

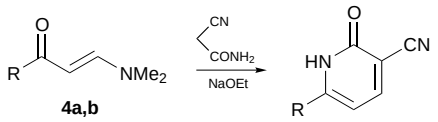
Furthermore, compounds **11a–c** were converted into the pyridinones **13a–c** which were also obtained by hydrolysis of 3-aryl-2-cyano-5-dimethylamino-2,4-penta-2,4-dienenitriles **12a–c** by the action of acetic acid–hydrochloric acid mixture.

Attempts to prepare **11a–c** by direct hydrolysis of **12a–c**, recently obtained in our laboratory,[21] in ethanol–piperidine for 24 h, failed, thus supporting the assumption that cyanoacetamide and not malononitrile is the reactive species in this reaction.



9–13a R = Ph
b R = 2-thienyl
c R = 2-furyl

*To receive any correspondence.



4a,b

14a R = Ph
b R = 2-thienyl

In contrast to the observed formation of the pyridinones **13a–c**, treatment of **4a**,**b** with cyanoacetamide in sodium ethoxide solution afforded the pyridinones **14a**,**b**.

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Techniques used: IR, ^{1}H and ^{13}C NMR, mass spectrometry

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