

ACTIVATED NITRILES IN HETEROCYCLIC SYNTHESIS: A NEW APPROACH FOR THE SYNTHESIS OF PYRAN DERIVATIVES

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Abstract.— The reaction of cinnamonnitriles with acetylacetone and ethyl acetoacetate is reported. Several new polyfunctional pyrans could be prepared. Spectral data of the synthesised products is reported.

Polyfunctional nitriles are highly reactive reagents that have been extensively used in heterocyclic synthesis.^{1,2} In continuation of our program directed towards the development of new procedures for the synthesis of polyfunctional heterocycles from simple laboratory available starting materials,³⁻⁵ we report here a new synthesis of substituted pyrans from polyfunctional nitriles. Although the reaction of cinnamonnitriles with active methylene heterocycles and with benzoylacetonitrile has recently been utilized as a source for polyfunctional pyrans,⁶⁻⁸ the utility of simple β -diketones and β -ketoesters in the same reaction has never been reported. As the pyrans, that may be formed, seems interesting for further chemical transformations, we have investigated the reaction of 1a,b with 2a-f.

Thus, it has been found that ethyl acetoacetate 1a reacted with benzylidene malononitrile 2a to yield a product of molecular formula $C_{16}H_{16}N_2O_3$ ($M^+ = 284$). The pyran structure 3a was assigned for this product based on spectral data. Thus, 1H NMR revealed a one proton singlet at δ 4.50 ppm for pyran H-4, a singlet at δ 2.22 ppm (CH_3) and at δ 6.88 ppm (NH_2) in addition to signals corresponding to ester and aromatic protons. Moreover, ^{13}C NMR can be only interpreted in terms of proposed structure (cf. chart 1). Other alternative possible isomeric forms would show completely different 1H NMR and ^{13}C NMR.

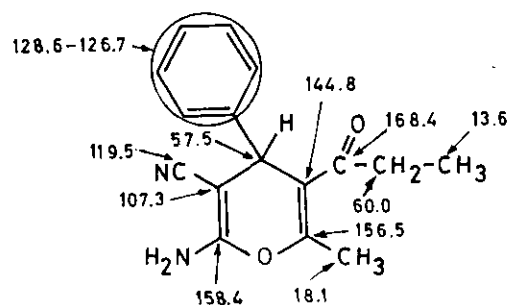
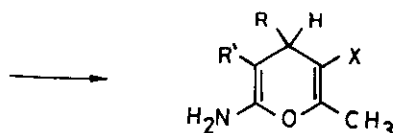
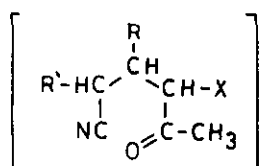
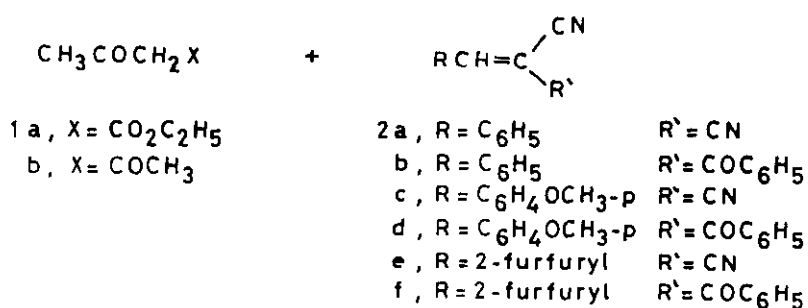


Chart 1

Similarly, 1a reacts with 2b-e yielding the corresponding pyrans 3b-e via Michael addition reaction.



	R	R'	X
3 a,	C ₆ H ₅	CN	CO ₂ C ₂ H ₅
b,	C ₆ H ₅	COC ₆ H ₅	CO ₂ C ₂ H ₅
c,	C ₆ H ₄ OCH ₃ -p	CN	CO ₂ C ₂ H ₅
d,	C ₆ H ₄ OCH ₃ -p	COC ₆ H ₅	CO ₂ C ₂ H ₅
e,	2-furfuryl	CN	CO ₂ C ₂ H ₅
f,	C ₆ H ₅	CN	COCH ₃
g,	C ₆ H ₅	COC ₆ H ₅	COCH ₃
h,	C ₆ H ₄ OCH ₃ -p	CN	COCH ₃
i,	2-furfuryl	CN	COCH ₃

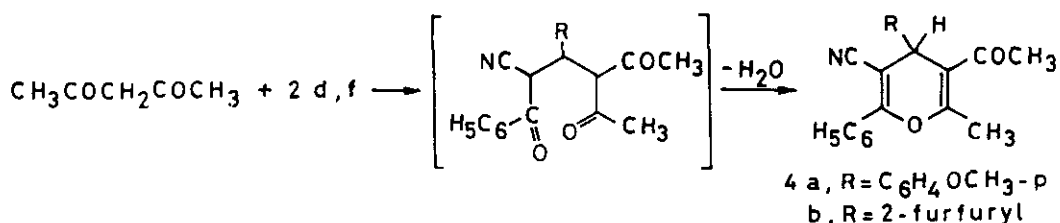


Chart 2

Acetylacetone 1b reacts also with 2a,b,c,e to yield the corresponding pyrans 3f-i. In case of 2d,f acetylacetone underwent condensation reaction yielding 5a,b via loss of water molecule.

As a general procedure, equimolecular amounts of either 1a or 1b were reacted with 2a-f in refluxing ethanol (30 ml) with catalytic amount of triethylamine for 3h. The solvent was then reduced to half its volume and the reaction mixture was left to cool. The products, so formed, were collected by filtration and crystallized from the proper solvent.

Table 1: List of compounds 3a-i; 4a-b.

Compound*	Solvent of Crystallization	Colour	Mp. (°C)	Yield %	Mol. Formula
3a	acetic acid	colourless	176	80	C ₁₆ H ₁₆ N ₂ O ₃
3b	DMF/H ₂ O	colourless	245	85	C ₂₂ H ₂₁ NO ₄
3c	ethanol	yellow	110	70	C ₁₇ H ₁₈ N ₂ O ₄
3d	DMF/H ₂ O	colourless	234	80	C ₂₃ H ₂₃ NO ₅
3e	ethanol	colourless	195	80	C ₁₄ H ₁₄ N ₂ O ₄
3f	DMF/H ₂ O	colourless	210	70	C ₁₅ H ₁₄ N ₂ O ₂
3g	ethanol	yellow	190	75	C ₂₁ H ₁₉ NO ₃
3h	ethanol	yellow	205	60	C ₁₆ H ₁₆ N ₂ O ₃
3i	ethanol	buff	220	75	C ₁₃ H ₁₂ N ₂ O ₃
4a	ethanol	yellow	195	65	C ₂₂ H ₁₉ NO ₃
4b	acetic acid	buff	140	70	C ₁₉ H ₁₅ NO ₃

* Satisfactory elemental analyses for all the newly synthesized compounds were obtained.

Table 2: IR and ¹HNMR data of compounds 3a-i; 4a-b.

Compound	IR, cm ⁻¹	¹ HNMR ppm
3a*	3420, 3340, 3280 (NH ₂); 2200 (CN); 1700 (CO).	1.18 (t, 3H, CH ₃); 2.22 (s, 3H, CH ₃); 3.95 (q, 2H, CH ₂); 4.50 (s, 1H, H-4); 6.88 (s, 2H, NH ₂), 7.12-7.37 (m, 5H, aromatic protons).
3b	3360, 3100(NH ₂); 1750, 1720 (CO)	1.18 (t, 3H, CH ₃); 2.4 (s, 3H, CH ₃), 3.3 (s, 2H, NH ₂); 4.2 (q, 2H, CH ₂); 4.6 (s, 1H, H-4); 7.2 - 7.6 (m, 10H, aromatic protons).
3c	3400, 3320, 3200 (NH ₂); 2200 (CN); 1710 (CO)	1.2 (t, 3H, CH ₃); 2.5 (s, 3H, CH ₃); 3.8 (s, 3H, OCH ₃); 4.2 (q, 2H, CH ₂); 4.6 (s, 1H, H-4); 6.2 (s, 2H, NH ₂); 7.2 - 7.6 (m, 4H, aromatic protons).
3d	3320 (NH ₂); 1750, 1740, 1720 (CO)	1.17 (t, 3H, CH ₃); 2.4 (s, 3H, CH ₃); 3.8(s, 3H, OCH ₃); 4.2(q, 2H, CH ₂); 4.4(s, 1H, H-4); 6.9(s, 2H, NH ₂); 7.1-7.8 (m, 9H, aromatic protons).

3e	3400, 3340, 3200 (NH ₂); 2200 (CN); 1690 (CO).	1.2 (t, 3H, CH ₃); 2.3 (s, 3H, CH ₃); 4.2 (q, 2H, CH ₂); 4.5 (s, 1H, H-4); 6.17 (d, 1H, furan H-3); 6.39 (m, 1H, furan H-4); 6.9 (s, 2H, NH ₂); 7.6 (d, 1H, furan H-5).
3f	3500, 3400 (NH ₂); 2220 (CN); 1720 (CO).	2.1 (s, 3H, CH ₃); 2.2 (s, 3H, CH ₃); 4.5 (s, 1H, H-4); 5.1 (s, 2H, NH ₂); 7.2 - 7.4 (m, 5H, aromatic protons).
3g	3400 (NH ₂); 1770, 1760 (CO).	1.17 (t, 3H, CH ₃); 2.2 (s, 3H, CH ₃); 3.6 (s, 2H, NH ₂); 4.4 (s, 1H, H-4); 7.4-7.9 (m, 10H, aromatic protons).
3h	3300, 3200 (NH ₂); 2220 (CN); 1730 (CO).	
3i	3450, 3350 (NH ₂); 2200 (CN); 1720 (CO).	
4a	2200 (CN); 1720 (CO)	1.2 (t, 3H, CH ₃); 1.9 (s, 3H, CH ₃); 3.7 (s, 3H, OCH ₃); 4.5 (s, 1H, H-4); 7.1-7.9 (m, 9H, aromatic protons).
4b	2200 (CN); 1690 (CO).	

* 3a (M⁺ = 284); ¹³CNMR (Chart 1).

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