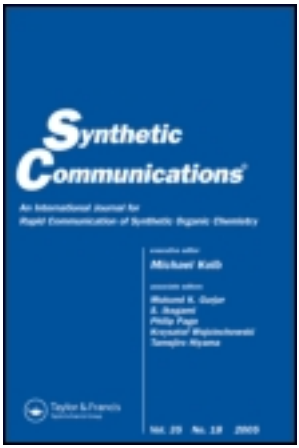

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Efficient and Convenient Method for the Synthesis of Poly Functionalised 4H-Pyrans

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Efficient and Convenient Method for the Synthesis of Poly Functionalised 4H-Pyrans[#]

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ABSTRACT

An efficient single-pot method for the synthesis of polyfunctionalized 4H-pyrans using alkaline metal fluoride as a catalyst is described.

Key Words: Aldehydes; Active methylene compound; Diethyl 1,3-acetone dicarboxylate; Michael addition; Polyfunctionalized 4H-pyran.

The chemistry of polyfunctionalized 4H-pyrans is an ongoing area of interest because of their wide range of applications.[1,2] These 4H-pyrans

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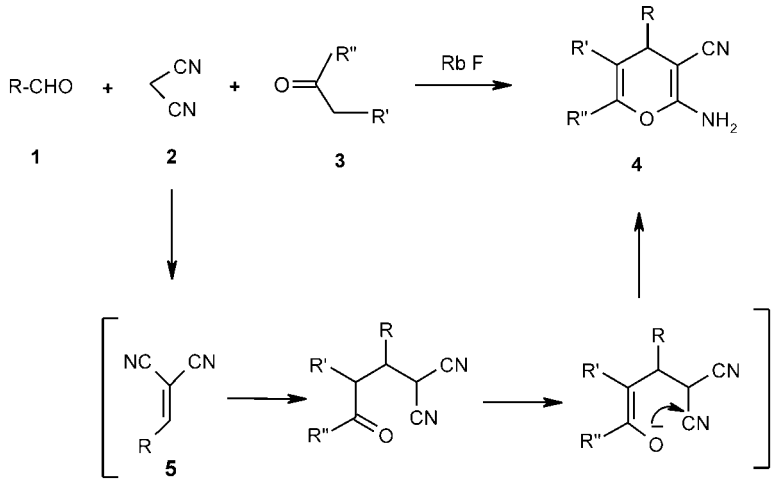
are isosters of 1,4-dihydro pyridine[3] with potential pharmacological interest and active synthons that have been extensively used in heterocyclic synthesis.[2] The 4H-pyrans are synthesized mainly by a three-component coupling reaction of aromatic aldehydes, malononitrile, and ß-ketones/ß-diketones[4] catalyzed by bases like triethylamine,[5] piperidine,[6] etc. Alkali metal fluorides are also used in solid–liquid reactions more specifically for halogen exchange reactions,[7,8] and the reactivity increases from sodium fluoride to cesium fluoride. Alkaline metal fluorides or metal salts are also used in amination process[9] and Michael addition reactions.[10,11] In continuation of our interest in the development of new procedures[12,13] by using suitable catalysts from simple available starting materials, we wish to report here for the first time a novel methodology for the synthesis of polyfunctionalized 4H-pyrans in the shortest time using rubidium fluoride as a catalyst.

The methodology involves an aldehyde **1**, active methylene compound **2**, and a third component 1,3-diethyl acetone dicarboxylate/ethylacetoacetate/1,3-diketones/diethyl malonate **3** in presence of a catalytic amount of rubidium fluoride under thermal conditions to give the desired pyrans. The rubidium fluoride acts as a base and promotes reaction by abstracting a proton from active methylenes sequentially in twofold. As a result, the Knoevenagel condensation with aromatic/aliphatic aldehydes and malononitrile form an alkene intermediate that, in situ, reacts with 1,3-diethyl acetone dicarboxylate/ethylacetoacetate/1,3-diketones/diethyl malonate by Michael addition to give polyfunctionalized 4H-pyrans **4** in good yields. The most probable mechanism is depicted in Scheme 1. The mode of formation of **4** is further confirmed by the initial preparation of dicyanoalkenes **5** from aromatic aldehyde and malononitrile in the presence of rubidium fluoride. The compound **5** further reacted with 1,3-diethylacetone dicarboxylate in the presence of rubidium fluoride resulted the desired pyran **4**. However, in the absence of rubidium fluoride, the initial Knoevenagel condensation reaction did not proceed.

Different aldehydes containing electron-withdrawing and electron-releasing substituents and ß-diketoesters are used for universal applicability of the method for the preparation of pyrans. It is found that in all cases, the yields are in the range 68–89%, irrespective of the substituent present in the phenyl ring of aromatic aldehyde. The main advantage of the method is its easy workup procedure with good yields of product. The substituent pattern and yields are given in Table 1, and spectral data are given in Table 2.

In conclusion, a methodology has been developed for the synthesis of polyfunctionalized 4H-pyrans using rubidium fluoride catalyst for the first time by an efficient three-component coupling reaction.



Scheme 1.

EXPERIMENTAL SECTION

Melting points were determined in open glass capillaries on a Mettler FP51 melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on Fourier transform infrared (FT-IR) Schimadzu Perkin-Elmer 1310 infrared spectrophotometer. ^{1}H NMR spectra were recorded on Varian Gemini (200 MHz) spectrometer, and tetramethylsilane (TMS) was

Table 1. The reaction time and yields of polyfunctionalized pyrans **(4)**.

Entry	*R*	*R′*	*R″*	Time (min)	Mp. (°C)	Lit. Mp. (°C)	Yield (%)
4a	C_6H_5	COOEt	CH_2COOEt	20	117–118	—	89
4b	*p*-Cl-C_6H_4	COOEt	CH_2COOEt	25	128–129	—	80
4c	*p*-CH_3-C_6H_4	COOEt	CH_2COOEt	25	135–136	—	82
4d	*p*-OH-C_6H_4	COOEt	CH_2COOEt	35	159–160	—	81
4e	*p*-NO_2-C_6H_4	COOEt	CH_2COOEt	20	131–132	—	78
4f	*m*-Oph-C_6H_4	COOEt	CH_2COOEt	35	116–117	—	78
4g	C_6H_5	COOEt	OEt	30	118–119	—	68
4h	C_6H_5	$COCH_3$	CH_3	25	205–206	210	72
4i	*p*-CH_3-C_6H_4	$COCH_3$	CH_3	30	132–133	135	71
4j	C_6H_5	COOEt	CH_3	25	172–173	176	87
4k	C_2H_5	COOEt	CH_2COOEt	50	106–107	—	68

Table 2. Spectral data of polyfunctionalized 4H-pyrans (4).

Entry	IR (cm^{-1})	Mass (m/z)	^{1}H NMR (DMSO-d_6). δ
4a	3407, 3331, 2197, 1745, 1692, 1647	356$[M]^+$, 279, 205, 141	1.18 (*t*, 3H), 1.35 (*t*, 3H), 3.70 (*d*, 1H, $J = 17.2$ Hz), 3.9 (*d*, 1H, $J = 17.2$ Hz), 4.0 (*q*, 2H), 4.25 (*q*, 2H), 4.45 (*s*, 1H), 4.54 brs, 2H), 7.28 (*m*, 5H)
4b	3440, 3302, 2200, 1693, 1647, 1604	390$[M]^+$, 345, 303, 279, 205	1.1 (*t*, 3H), 1.35 (*t*, 3H), 3.62 (*d*, 1H, $J =$ Hz), 3.98 (*d*, 1H, $J = 17.1$ Hz), 4.05 (*q*, 2H), 4.25 (*q*, 2H), 4.45 (*s*, 1H), 4.6 (brs, 2H), 7.3 (*m*, 4H)
4c	3402, 3331, 2190, 1740, 1697, 1647	370$[M]^+$, 325, 297, 279	1.1 (*t*, 3H), 1.34 (*t*, 3H), 2.34 (*s*, 3H), 3.65 (*d*, 1H, $J = 17.1$ Hz), 3.96 (*d*, 1H, $J = 17.1$ Hz),4.05 (*q*, 2H), 4.2 (*q*, 2H), 4.42 (*s*, 1H), 4.48 (brs, 2H), 7.16 (*m*, 4H)
4d	3342, 3261, 2196, 1695, 1679, 1605	372$[M]^+$, 327, 279, 205, 167	1.1 (*t*, 3H), 1.23 (*t*, 3H), 3.52 (*d*, 1H, $J = 17.1$ Hz), 3.85 (*d*,1H, $J = 17.1$ Hz), 4.0 (*q*, 2H), 4.15 (*q*, 2H), 4.22 (*s*, 1H), 4.40 (brs, 2H), 6.74 (*d*, 2H), 7.02 (*d*, 2H), 9.05 brs, 1H)
4e	3315, 3300, 2189, 1692, 1655, 1635	401$[M]^+$, 355, 328, 279, 167	1.1 (*t*, 3H), 1.32 (*t*, 3H), 3.60 (*d*, 1H, $J = 17.1$ Hz), 3.78 (*d*, 1H, $J = 17.1$ Hz), 4.0 (*q*, 2H), 4.2 (*q*, 2H), 4.29 (*s*, 1H), 4.54 (brs, 2H), 7.5 (*d*, 2H), 8.18 (*d*, 2H)
4f	3385, 3204, 2201, 1769, 1681, 1613	448$[M]^+$, 375, 355, 279, 205	1.1 (*t*, 3H), 1.3 (*t*, 3H), 3.68 (*d*, 1H, $J = 17.1$ Hz), 3.94 (*d*, 1H, $J = 17.1$ Hz), 4.08 (*q*, 2H), 4.2 (*q*, 2H), 4.42 (*s*, 1H), 4.55 (brs, 2H), 7.02 (*m*, 5H), 7.35 (*m*, 4H)
4g	3404, 3295, 2196, 1754, 1729, 1704	314$[M]^+$, 269, 241, 223, 203	0.98 (*t*, 3H), 1.32 (*t*, 3H), 3.95 (*q*, 2H), 4.28 (*q*, 2H), 4.40 (*s*, 1H), 4.62 (brs, 2H), 7.59 (*m*, 5H)

(*continued*)

Table 2. Continued.

Entry	IR (cm^{-1})	Mass (m/z)	^{1}H NMR (DMSO-d_6). δ
4k	3355, 3340, 2987, 2221, 1702, 1690	308[M] + , 280, 263, 235	0.81 (*t*, 3H), 1.23 (*t*, 3H), 1.30 (*t*, 3H), 2.82 (*m*, 2H), 3.38 (*t*, 1H), 3.58 (*d*, 1H, $J = 17.1$ Hz), 3.70 (*d*, 1H, $J = 17.1$ Hz), 4.12 (*q*, 2H), 4.21 (*q*, 2H), 5.88 (brs, 2H)

All the compounds give satisfactory elemental data.

used as the internal standard. Mass spectra were recorded on a VG-micro mass 7070H instrument at 70 ev. Elemental analyses were performed on a Vario EL analyzer.

General Procedure for the Preparation of 4H-Pyran (4)

A mixture of 1,3-diethyl acetone dicarboxylate **3** (1.88 mmol), aromatic/aliphatic aldehyde **1** (1.88 mmol), malononitrile **2** (1.88 mmol), and rubidium fluoride (0.94 mmol) in methanol (10 mL) was refluxed for a specified time. After completion of the reaction, the solvent was distilled off and treated with water (10 mL). The precipitated solid was filtered off and recrystallized from methanol to give the title compound.

Benzylidene Malononitrile

Benzaldehyde (0.2 g, 1.88 mmol) and malononitrile (0.124 g, 1.88 mmol) were dissolved in methanol (10 mL) and rubidium fluoride (0.098 g, 0.94 mmol) was added. The mixture was reacted at room temperature for 5 min. After completion of the reaction, the solvent was distilled off and diluted with water. The precipitated solid was filtered, washed with water, and dried. It is further used without purification.

Condensation of Benzylidene Malononitrile with Diethylacetone Dicarboxylate

To a mixture of benzylidene malononitrile (0.2 g, 1.29 mmol) and 1,3-diethyl acetone dicarboxylate (0.262 g, 1.29 mmol) in methanol rubidium

fluoride (0.06 g, 0.57 mmol) was added to it. The mixture was refluxed for 20 min, cooled, solvent was removed, and the residue was treated with water (10 mL). The precipitated solid was filtered off and recrystalized from methanol to obtain pyran **4**.

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