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Synthesis of pyran annulated heterocyclic scaffolds: a highly convenient protocol using dimethylamine

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Abstract A facile and rapid three-component synthesis of pharmaceutically diverse pyran annulated heterocycles has been developed via a one-pot condensation of aromatic aldehydes, malononitrile, and different enolizable C–H-activated acidic compounds in the presence of dimethylamine as a newer and effective organo-catalyst in ethanol under mild reaction conditions. Selectivity of various pyran derivatives depends on the structure of enolates. The present protocol has synthetic advantages of excellent yields in much shorter reaction times with no chromatography.

Keywords Three-component reaction · Pyran annulated heterocycles · Click synthesis · Dimethylamine

Introduction

The development of newer synthetic methodologies for the construction of heterocyclic scaffolds is a fast-developing area in the field of drug-delivery research. Dihydropyran derivatives are 'privileged' structural motifs, which constitute the significant core of several natural products [1]. They exhibit potential activities against TNF-mediated diseases such as, Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson and Huntington diseases [2, 3]. In addition, 2-amino-4*H*-pyrans bearing nitrile functionality show greater applications in the treatment of psoriatic arthritis, rheumatoid arthritis, and cancer therapy [4–7] and are also useful intermediates for the synthesis of diverse organic molecules such as, pyridones, lactones, imidoesters, and aminopyrimidines [8, 9]. It is valuable to reveal that a

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number of drug molecules containing 4*H*-pyran moiety are used in the treatment of several disorders, such as asthma, ischemia, hypertension, and urinary incontinence [10–14]. Very interestingly, 4*H*-pyrans can be converted into pyridine analogues, which are related to the calcium antagonists of the dihydropyridines [15, 16]. Due to the wide applications of the pyran nucleus, a number of synthetic methods have been reported with catalysts like, DMAP [17], K_3PO_4 [18], $CaCl_2$ [19], piperazine [20], NH_2–SiO_2 [21], SBSSA [22], lactose [23], etc., many of them suffered from any one of the demerits such as, prolonged reaction times, expensive catalysts, low yields, and harsh reaction conditions. Hence, still there is a need for the development of alternate high-yielding newer methodologies using very inexpensive catalysts under mild reaction conditions. In this paper, we report for the first time the dimethylamine catalyzed one-pot, click synthesis of pyran annulated heterocyclic compounds in excellent yields.

Experimental

Reagents and equipment

All of the reagents and solvents were purchased from commercial sources and were freshly used after being purified by standard techniques. Reactions were monitored by TLC using silica gel pre-coated plates with ethyl acetate/hexanes as the mobile phase. Melting points were measured using an Electrothermal apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DRX-300 spectrometer at 300 MHz and were referenced to the solvent (DMSO-d_6 at 2.51 ppm) relative to TMS (0 ppm) as an internal standard. ^{13}C NMR spectra were recorded at 75 MHz and were referenced to the solvent (DMSO-d_6 at 39.49 ppm). Infrared spectra were recorded on a Bruker FT-IR27 spectrometer using KBr pellets.

General procedure for the synthesis of pyran annulated heterocycles

To a stirred mixture of aromatic aldehyde (2.0 mmol) and malononitrile (2.0 mmol) in ethanol (10 ml), a catalytic amount of DMA (5 mol%) was added at room

Table 1 Optimization of suitable solvent for the synthesis of **4b**

Entry	Solvent	Time (min)	Yield (%)[a]
1	CH_3OH	12	89
2	EtOH	4	98
3	*i*-PrOH	30	81
4	H_2O	45	83
5	EtOH:H_2O(1:1)	17	86
6	CH_3CN	45	74

Reaction conditions: 4-chlorobenzaldehyde, malononitrile, dimedone (2 mmol each) and DMA (5 mol%) in ethanol (10 ml) at room temperature

[a] Isolated yield of 4b

temperature. To the precipitated solid materials, ethanolic solution of dimedone or ethyl acetoacetate or barbituric acid (2.0 mmol) was added and from the resulting solution, the products get precipitated within the time mentioned in Tables 1, 2, 3, and 4. For 4*H*-benzo[*h*]chromenes, 1-naphthol (2.0 mmol) was added to the arylidenemalononitrile and stirred at 70 °C until the solid appeared. The products were filtered, air-dried, and recrystallized from ethanol.

Spectral data

*2-Amino-4-(4-fluorophenyl)-7,7′-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4c**)*

Colorless crystals; mp 186–188 °C; IR (KBr) (ν_{max}, cm^{-1}) 3,371, 3,318 (NH_2), 2,208 (CN), 1,687 (C=O), 1,248 (C–O–C); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 0.94 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.13 (d, 2H, CH_2, J = 16.2 Hz), 2.28 (d, 2H, CH_2, J = 16.2 Hz), 4.21 (s, 1H, CH) 7.02 (s, 2H, NH_2), 7.13 (d, 2H, ArH, J = 8.7 Hz), 7.18 (d, 2H, ArH, J = 8.7 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 26.80, 28.28, 31.74, 34.89, 49.94, 58.14, 112.59, 114.84, 119.58, 128.95, 140.86, 158.47, 159.27, 162.47, 195.68.

*2-Amino-7,7′-dimethyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**4i**)*

Colorless crystals; mp 214–216 °C; IR (KBr) (ν_{max}, cm^{-1}) 3,382, 3,319 (NH_2), 2,198 (CN), 1,689 (C=O), 1,246 (C–O–C); ^{1}H NMR (300 MHz, DMSO-d_6) δ

Table 2 Synthesis of 2-amino-7,7′-dimethyl-5-oxo-tetrahydro-4*H*-chromene-3-carbonitriles

Entry	R	Product[a] 4(a–k)	Time (min)	Yield (%)[b]	M.p. (°C)	
					Found	Reported (Refs.)
1	H	4a	6	95	228–230	232–233 [20]
2	4-Cl	4b	4	98	212–214	213–215 [20]
3	4-F	4c	5	97	186–188	189–191 [20]
4	4-NO_2	4d	5	97	180–182	183–185 [20]
5	4-OH	4e	9	93	200–202	203–204 [20]
6	4-Br	4f	6	96	218–220	219–220 [20]
7	4-OMe	4g	7	94	196–198	201–202 [20]
8	3-OH	4h	10	92	232–234	238–240 [24]
9	3-NO_2	4i	6	96	214–216	214–216 [20]
10	2-Cl	4j	7	95	210–212	214–215 [20]
11	2-NO_2	4k	6	95	228–230	232–233 [20]

[a] Synthesis of 2-amino-7,7′-dimethyl-5-oxo-tetrahydro-4*H*-chromene-3-carbonitrile derivatives. Reaction conditions: aldehyde (2.0 mmol), malononitrile (2.0 mmol), DMA (5 mol%), and dimedone (2.0 mmol) at RT

[b] Isolated yield

Table 3 Synthesis of 6-amino-5-cyano-4*H*-pyran-3-carboxylates

Entry	R	Product[a] 6(a–k)	Time (min)	Yield (%)[b]	M.p. (°C)	
					Found	Reported (Refs.)
1	H	6a	8	93	188–190	191–192 [20]
2	4-Cl	6b	6	96	174–176	174–175 [20]
3	4-F	6c	7	94	172–174	170–172 [20]
4	4-NO_2	6d	7	96	170–172	174–176 [20]
5	4-OH	6e	10	92	192–194	196 [25]
6	4-Br	6f	8	95	176–178	176–178 [20]
7	4-OMe	6g	9	92	138–140	136–137 [20]
8	3-OH	6h	11	90	158–160	162–164 [26]
9	3-NO_2	6i	8	95	178–180	183–185 [20]
10	2-Cl	6j	9	95	190–192	191–193 [20]
11	2-NO_2	6k	8	94	178–180	180–181 [20]

[a] Synthesis of 6-amino-5-cyano-4*H*-pyran-3-carboxylates. Reaction conditions: aldehyde (2.0 mmol), malononitrile (2.0 mmol), DMA (5 mol %), and ethyl acetoacetate (2.0 mmol) at RT

[b] Isolated yield

Table 4 Synthesis of 7-amino-2,4-dioxo-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile derivatives

Entry	R	Product[a] 8(a–k)	Time (min)	Yield (%)[b]	M.p. (°C)	
					Found	Reported (Refs.)
1	H	8a	20	90	220–222	222–224 [27]
2	4-Cl	8b	15	93	238–240	242–243 [27]
3	4-F	8c	16	92	218–220	–
4	4-NO_2	8d	15	93	236–238	237–238 [27]
5	4-OH	8e	25	88	>300	>300 [27]
6	4-Br	8f	16	92	208–210	–
7	4-OMe	8g	25	89	252–254	–
8	3-OH	8h	25	87	202–204	–
9	3-NO_2	8i	15	92	248–250	–
10	2-Cl	8j	18	91	204–206	–
11	2-NO_2	8k	18	91	216–218	–

[a] Synthesis of 7-amino-2,4-dioxo-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitriles. Reaction conditions: aldehyde (2.0 mmol), malononitrile (2.0 mmol), DMA (5 mol %), and barbituric acid (2.0 mmol) at RT

[b] Isolated yield

(ppm): 0.96 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.15 (d, 2H, CH_2, J = 16.2 Hz), 2.30 (d, 2H, CH_2, J = 15.9 Hz), 4.43 (s, 1H, CH) 7.18 (s, 2H, NH_2), 7.67 (d, 2H, ArH, J = 5.7 Hz), 7.99 (s, 1H, ArH), 8.09 (t, 1H, ArH, J = 6.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 26.71, 28.29, 31.79, 35.41, 49.85, 57.22, 111.77, 119.31, 121.64, 121.74, 129.98, 134.15, 146.97, 147.76, 158.62, 163.13, 195.72.

*Ethyl-6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate (**6a**)*

Light yellowish white crystals; mp 188–190 °C; IR (KBr) (ν_{max}, cm^{-1}) 3,404, 3,329 (NH_2), 2,190 (CN), 1,694 (C=O), 1,260 (C–O–C); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.02 (t, 3H, CH_3, J = 7.2 Hz), 2.31 (s, 3H, CH_3), 3.95 (q, 2H, CH_2, J = 3.6 Hz), 4.29 (s, 1H, CH), 6.90 (s, 2H, NH_2), 7.15 (d, 2H, ArH, J = 7.8 Hz), 7.21 (t, 1H, ArH J = 7.5 Hz), 7.31 (t, 2H, ArH, J = 7.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 13.68, 18.09, 38.93, 57.23, 60.11, 107.22, 119.68, 126.77, 127.15, 128.40, 144.85, 156.55, 158.44, 165.41.

*Ethyl-6-amino-5-cyano-2-methyl-4-(3-nitrophenyl)-4H-pyran-3-carboxylate (**6i**)*

Colorless crystals; mp 178–180 °C; IR (KBr) (ν_{max}, cm^{-1}) 3,396, 3,325 (NH_2), 2,197 (CN), 1,688 (C=O), 1,252 (C–O–C); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.02 (t, 3H, CH_3, J = 7.2 Hz), 2.35 (s, 3H, CH_3), 3.97 (q, 2H, CH_2, J = 6.6 Hz), 4.53 (s, 1H, CH), 7.10 (s, 2H, NH_2), 7.64 (d, 2H, ArH, J = 7.5 Hz), 7.99 (s, 1H, ArH), 8.12 (t, 1H, ArH, J = 3.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 13.61, 18.27, 38.91, 56.31, 60.30, 106.22, 119.33, 121.70, 121.95, 130.16, 134.17, 147.32, 147.75, 157.78, 158.62, 165.06.

*7-Amino-5-(4-chlorophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d] pyrimidine-6-carbonitrile (**8b**)*

White solid; mp 238–240 °C; IR (KBr) (ν_{max}, cm^{-1}) 3,388, 3,327 (NH_2), 3,170 (N–H), 2,195 (CN), 1,715 (C=O), 1,487 (C–N), 1,247 (C–O–C); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 4.24 (s, 1H, CH), 7.17 (s, 2H, NH_2), 7.23 (d, 2H, ArH, J = 5.8 Hz), 7.34 (d, 2H, ArH, J = 5.8 Hz), 11.12 (s, 1H, NH), 11.96 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 35.50, 58.67, 88.44, 119.49, 128.64, 129.69, 131.71, 149.47, 149.91, 152.74, 158.04, 162.95.

*7-Amino-5-(4-nitrophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d] pyrimidine-6-carbonitrile (**8d**)*

White solid; mp 236–238 °C; IR (KBr) (ν_{max}, cm^{-1}) 3,380, 3,322 (NH_2), 3,181 (N–H), 2,197 (CN), 1,698 (C=O), 1,483 (C–N), 1,245 (C–O–C); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 4.41 (s, 1H, CH), 7.19 (s, 2H, NH_2), 7.57 (d, 2H, ArH, J = 8.7 Hz), 8.12 (d, 2H, ArH, J = 8.7 Hz), 11.13 (s, 1H, NH), 12.16 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 35.54, 58.12, 87.39, 119.08, 124.92, 130.36, 146.62, 149.71, 151.73, 152.76, 157.37, 162.58.

*2-Amino-4-(4-chlorophenyl)-4H-benzo[h]chromene-3-carbonitrile (**10b**)*

White solid; mp 230–232 °C; IR (KBr) (ν_{max}, cm^{-1}) 3,394, 3,337 (NH_2), 2,206 (CN), 1,667 (C=O), 1,283 (C–O–C); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 4.84 (s, 1H, CH), 6.42 (s, 2H, NH_2), 7.06 (d, 1H, ArH, J = 9.0 Hz), 7.24–7.28 (m, 4H, ArH), 7.48 (d, 2H, ArH, J = 9.0 Hz), 7.77 (d, 2H, ArH, J = 9.0 Hz), 8.27 (d, 1H,

ArH, J = 6.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 39.12, 55.73, 119.80, 120.22, 122.14, 122.36, 123.62, 125.53, 125.87, 126.55, 127.63, 128.21, 129.84, 132.73, 133.90, 142.36, 146.98, 160.42.

*2-Amino-4-(4-nitrophenyl)-4H-benzo[h]chromene-3-carbonitrile (**10d**)*

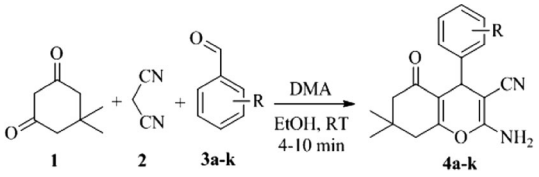
White solid; mp 186–188 °C; IR (KBr) (ν_{max}, cm^{-1}) 3,387, 3,329 (NH_2), 2,196 (CN), 1,663 (C=O), 1,278 (C–O–C); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 4.79 (s, 1H, CH), 6.47 (s, 2H, NH_2), 6.92 (d, 1H, ArH, J = 9.0 Hz), 7.31–7.36 (m, 4H, ArH), 7.49 (d, 2H, ArH, J = 9.0 Hz), 7.68 (d, 2H, ArH, J = 9.0 Hz), 8.24 (d, 1H, ArH, J = 6.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 38.92, 55.32, 118.98, 121.02, 122.21, 122.42, 123.57, 125.48, 125.13, 125.94, 127.42, 128.54, 130.68, 132.03, 134.12, 142.53, 147.62, 161.28.

Results and discussion

To optimize reaction conditions, the experiment was initially carried out with 4-chlorobenzaldehyde (**3b**) and malononitrile (**2**) in ethanol containing two drops of dimethylamine as an organo-base catalyst. The resulting solution has been stirred at room temperature where the 2-benzylidenemalononitrile was formed as a solid within 2 min, to which an ethanolic solution of 5,5′-dimethylcyclohexane-1,3-dione or dimedone (**1**) was added, resulting in a clear solution. The product, 2-amino-4-(4-chlorophenyl)-7,7′-dimethyl-5-oxo-tetrahydro-4*H*-chromene-3-carbonitrile (**4b**) precipitated within 2 min with high purity, but in the absence of DMA, the reaction was sluggish with low conversions.

In order to fix a suitable reaction medium and amount of catalyst, the model reaction was performed with different solvents such as, methanol, ethanol, 2-propanol, acetonitrile, and water, and it was observed that ethanol would be the best medium yielding 98 % of **4b** with 5 mol% of the catalyst. Further increase in the quantity of catalyst did not show any significant change on the yield and reaction time. With these optimized reaction conditions, various aromatic aldehydes (**3a–k**) were utilized to synthesize a series of 2-amino-tetrahydro-4*H*-chromenes (Scheme 1).

From the results shown in Table 2, it is evident that almost all the studied aldehydes bearing both electron-withdrawing and electron-donating substituents provided a very good yield of the corresponding tetrahydro-4*H*-chromenes. The formation of the cyclized tetrahydro-4*H*-chromene derivatives was confirmed by the ^{1}H NMR spectrum in which the two singlets at 0.94 and 1.03 ppm indicate the two



Scheme 1 Synthesis of 2-amino-tetrahydro-4*H*-chromene-3-carbonitrile derivatives

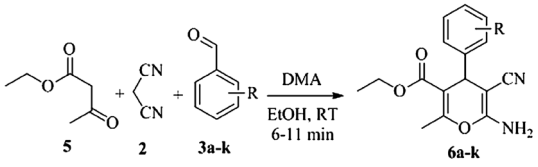
methyl groups of the dimedone moiety, another singlet at δ 4.21 ppm corresponds to the (–CH–) methine proton and the peak at δ 7.02 ppm as singlet represents the existence of an amino group. The IR spectrum shows a strong peak at 2,208 cm^{-1} that specifies the nitrile functionality and peaks at 3,371 and 3,318 cm^{-1} representing the presence of free NH_2 group.

In continuation of this multicomponent reaction, we have also tried to examine the catalytic efficiency of DMA with other C–H-activated acidic compounds such as ethyl acetoacetate (**5**) and barbituric acid (**7**) under the above optimized reaction conditions, where also good yields of the corresponding pyran derivatives (**6a–k**) and (**8a–k**) have been observed and the results are summarized in Tables 3 and 4 (Scheme 2 and 3).

In the case of 1-naphthol (**9**), the reaction proceeded smoothly at higher temperature and the best results (**10a–k**) were achieved while refluxing the reaction mixture at 70 °C (Table 5; Scheme 4). From the results obtained in all the cases, it is clear to state that the reaction proceeded in a rapid manner and provided excellent yields with higher purity. All the synthesized pyran annulated heterocycles were characterized by IR, ^{1}H NMR, ^{13}C NMR, and their melting points compared with literature.

A plausible mechanism for the three-component synthesis of pyran annulated heterocycles using DMA in ethanol has been proposed in Scheme 5. Initially, aromatic aldehyde was made to react with malononitrile in the presence of catalyst to provide the Knoevenagel product, i.e., arylidenemalononitrile (**I**). Then, ethanolic solution of diketone was added to the reaction mixture, leading to the Michael addition with the arylidenemalononitrile followed by cyclization where the reaction occurs very rapidly, and within a few minutes resulting in the formation of highly pure target molecule (**III**).

Scheme 2 Synthesis of 6-amino-5-cyano-4*H*-pyran-3-carboxylate derivatives



Scheme 3 Synthesis of 7-amino-2,4-dioxo-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitriles

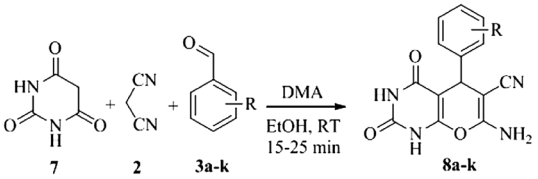


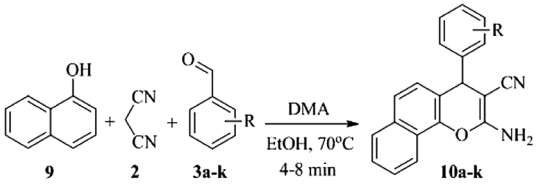
Table 5 Synthesis of 2-amino-4*H*-benzo[*h*]chromene-3-carbonitriles

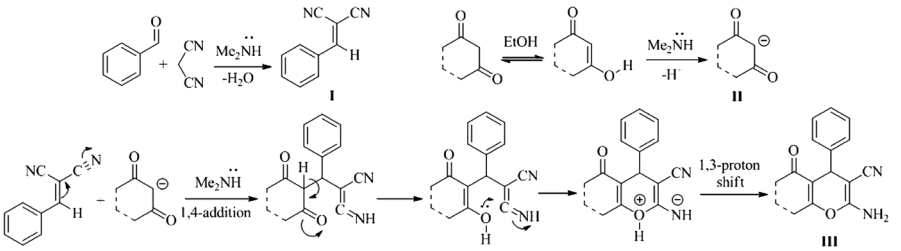
Entry	R	Product[a] 10(a–k)	Time (min)	Yield (%)[b]	M.p. (°C)	
					Found	Reported (Refs.)
1	H	10a	6	92	210–212	215–217 [28]
2	4-Cl	10b	4	96	230–232	230–232 [29]
3	4-F	10c	5	95	228–230	236–237 [30]
4	4-NO_2	10d	4	95	186–188	188–189 [31]
5	4-OH	10e	8	89	240–242	246–248 [30]
6	4-Br	10f	5	96	242–244	239–241 [30]
7	4-OMe	10g	8	90	174–176	176–179 [29]
8	3-OH	10h	8	90	224–226	250–253 [28]
9	3-NO_2	10i	5	94	202–204	208–211 [29]
10	2-Cl	10j	6	92	236–238	250–251 [32]
11	2-NO_2	10k	6	93	206–208	209–210 [33]

[a] Synthesis of 2-amino-4*H*-benzo[*h*]chromene-3-carbonitriles. Reaction conditions: aldehyde (2.0 mmol), malononitrile (2.0 mmol), DMA (5 mol%), and 1-naphthol (2.0 mmol) at 70 °C

[b] Isolated yield

Scheme 4 Synthesis of 2-amino-4*H*-benzo[*h*]chromene-3-carbonitrile derivatives





Scheme 5 A plausible mechanism for the formation of pyran annulated heterocycles

Conclusions

In summary, we have finely developed a rapid and newer protocol for the synthesis of tetrahydro-4*H*-chromene, 4*H*-pyran, 1*H*-pyrano[2,3-*d*]pyrimidine, and 4*H*-benzo[*h*]chromene derivatives under mild reaction conditions via a one-pot, three-component reaction using 5 mol% of dimethylamine as an effective organo-catalyst. The present method offers notable advantages, such as, high atom-economy, easy isolation of products, and operational simplicity, which makes the methodology an important technique for the synthesis of valuable O-heterocycles.

Further applications of densely functionalized pyran derivatives of this protocol are under progress in our laboratory.

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