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Tandem cross-Rauhut–Currier/cyclization reactions of activated alkenes to give densely functionalized 3,4-dihydropyrans

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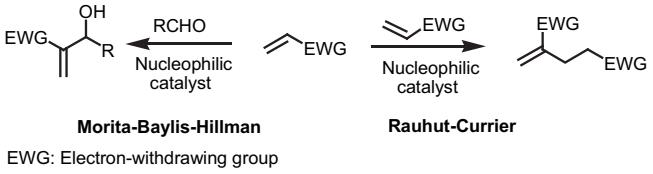
ABSTRACT

A novel tandem cross-Rauhut–Currier/cyclization reaction between α,β-unsaturated ketones was developed. Using DABCO (20 mol%) as the catalyst, a series of densely functionalized 3,4-dihydropyrans were obtained in excellent yields and stereoselectivities (up to 98% yield, >99:1 dr). A tentative catalytic cycle was proposed with key intermediates confirmed by ESIMS studies.

1. Introduction

The Rauhut–Currier (RC) reaction, which is also known as the vinylogous Morita–Baylis–Hillman (MBH) reaction, provides a unique atom-economical way to create a new C–C bond between two activated alkenes under the catalysis of nucleophilic catalysts (Scheme 1).[1] In comparison to the numerous researches on the MBH reaction, the RC reaction is much less investigated. This is partly attributable to the low reactivity of the substrates and the problem of selectivity when two different activated alkenes were involved. Recently, in the domain of intramolecular RC reaction, where the above two problems are somewhat extenuated, significant progress has been made, which also demonstrated the value of the reaction in synthetic chemistry.[2] However, the intermolecular RC reaction between different activated alkenes remains a great challenge.[3] It goes without saying that a right choice of the two reactants with appropriate reactivity would serve as a direct solution to this challenge. Nevertheless, partly due to the restriction of the reactivity of commonly known substrates, very limited success has been achieved with this strategy. Recently, Ma et al. attained a success by using the highly activated β,γ-unsaturated α-keto ester as the Michael acceptor and cyclic β-halo-α,β-unsaturated



Scheme 1. Comparison of MBH and RC reactions.

aldehydes as the other reaction partner (known as the latent enolate), which was followed by acetalization to give useful spiro-3,4-dihydrofurans.[4] In contrast, much less satisfactory results were reported for reactions using cheap, simple activated alkenes, such as methyl vinyl ketone (MVK) and acrylates as the reaction partners, which are probably due to their relatively lower reactivity and susceptibility to homodimerization.

As part of our ongoing project on the development of organocatalyzed reactions utilizing α,β-unsaturated ketones to construct synthetically useful structures, we report herein a novel tandem cross-Rauhut–Currier/cyclization reaction featuring the use of α-cyano-α,β-unsaturated ketones **2** as the Michael acceptor, with which simple activated alkenes (MVK and acrylates) are well tolerated as reaction partners. The resultant densely functionalized 3,4-dihydropyrans **1** are a common structural unit present in many biologically active compounds, and the construction of this kind of structures has aroused many interests among chemists.[5]

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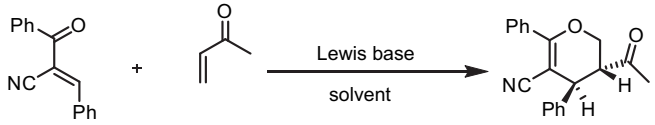
2. Results and discussion

We assumed that a suitable Michael acceptor in this reaction should have a proper electrophilicity for the Michael addition step, whereas be less reactive with the nucleophilic catalyst. With our experience with α,β-unsaturated ketones, it seems the chalcone derivative **2a** bearing a doubly activated alkene may be a suitable candidate. To our delight, when (*E*)-2-benzoyl-3-phenylacrylonitrile **2a** and MVK **3a** were treated with DABCO (20 mol %) in CH_3CN at room temperature for 6 h, a 3,4-dihydropyran product **1a** was isolated in good yield as a single diastereoisomer (Table 1, entry 1).[6] Apparently, the formation of **1a** could result from the expected cross-Rauhut–Currier followed by an intramolecular S_N2 reaction. Decreasing the catalyst loading to 10 mol % slowed down the reaction remarkably (Table 1, entry 2). When three other tertiary amines DBU, DMAP, and Et_3N were used instead of DABCO, much less successful results were obtained (Table 1, entries 3–6). In addition, nucleophilic phosphine catalysts (n-Bu)$_3$P and Ph_3P also proved unsuitable for this reaction (Table 1, entries 7–8). Polar solvents were favored in the reaction, however, the other solvents examined all gave inferior results to the originally used CH_3CN (Table 1, entries 9–14). Thus, the present reaction was best performed with 20 mol % of DABCO in CH_3CN at room temperature.

Table 1
Screening of solvents and Lewis bases



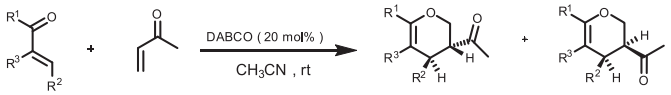
2a **3a** **1a**

E	Lewis base (equiv)	Solvent	T (h)	dr[a]	Yield[b] %
1	DABCO (0.2)	CH_3CN	6	>99:1	84
2	DABCO (0.1)	CH_3CN	24	>99:1	73
3	DBU (0.2)	THF	48	—	Trace
4	DBU (0.2)	CH_3CN	12	—	Complex
5	DMAP (0.2)	CH_3CN	48	>99:1	52
6	Et_3N (0.2)	CH_3CN	48	—	Trace
7	Ph_3P (0.2)	CH_3CN	48	—	Trace
8[c]	n-Bu_3P (0.2)	CH_3CN	48	—	Complex
9	DABCO (0.2)	Toluene	48	>99:1	45
10	DABCO (0.2)	THF	48	>99:1	70
11	DABCO (0.2)	DMF	12	>99:1	75
12	DABCO (0.2)	CH_2Cl_2	48	>99:1	35
13	DABCO (0.2)	$CHCl_3$	48	>99:1	40
14	DABCO (0.2)	Et_2O	48	>99:1	Trace

[a] Determined by ^{1}H NMR assay.
[b] Isolated yields.
[c] Run in the nitrogen atmosphere.

Having established optimal reaction conditions, we next studied the scope of the reaction with regard to different α-cyano-α,β-unsaturated ketones **2** using MVK **3a**. When R^1 is a phenyl group (**2a**–**k**), the reaction proceeded smoothly to give the desired products in good to excellent yields when R^2 is also an aryl group, including heterocyclic groups, such as 2-thienyl and 3-indyl groups (Table 2, entries 1–11). Substrates bearing electron-withdrawing substituents on the aryl group of R^2 in general were significantly more reactive than those with electron-donating ones. In addition, substrates **2e** and **2i** with *ortho* substituents also seemed less reactive probably due to steric reasons (Table 2, entries 5 and 9). The reaction hardly proceeded when R^2 is an alkyl group (Table 2, entry 12). In contrast, variation of the substituents with different electronic nature on the aryl group of R^1 has little influence on the reaction rate (Table 2, entries 13–15). Notably, the cyano group at the α-position of enone **2a** was essential for the reaction. When it

Table 2
Scope of the tandem reaction of enones **2** and MVK **3a**



2a-r **3a** **1a-r** **1a'-r'**

E	**2** (R^1, R^2)	R^3	T (h)	Prod.	dr[a]	Yield[b] %
1	**2a** (R^1=R^2=Ph)	CN	12	**1a**	>99:1	86
2	**2b** (R^1=Ph, R^2=4-Cl–C_6H_4)	CN	4	**1b**	>99:1	92
3	**2c** (R^1=Ph, R^2=4-Br–C_6H_4)	CN	4	**1c**	>99:1	95
4	**2d** (R^1=Ph, R^2=3-Br–C_6H_4)	CN	4	**1d**	>99:1	92
5	**2e** (R^1=Ph, R^2=2-Br–C_6H_4)	CN	12	**1e**	>99:1	98
6	**2f** (R^1=Ph, R^2=4-F–C_6H_4)	CN	4	**1f**	>99:1	98
7	**2g** (R^1=Ph, R^2=4-MeO–C_6H_4)	CN	18	**1g**	>99:1	96
8	**2h** (R^1=Ph, R^2=4-NO_2–C_6H_4)	CN	2	**1h**	>99:1	71
9	**2i** (R^1=Ph, R^2=2,4-dichlorophenyl)	CN	12	**1i**	>99:1	87
10	**2j** (R^1=Ph, R^2=2-thienyl)	CN	12	**1j**	>99:1	70
11	**2k** (R^1=Ph, R^2=*N*-methyl-3-indyl)	CN	24	**1k**	>99:1	96
12	**2l** (R^1=Ph, R^2=$PhCH_2CH_2$)	CN	72	**1l**	—	n.r.[c]
13	**2m** (R^1=4-MeO–C_6H_4, R^2=Ph)	CN	12	**1m**	>99:1	82
14	**2n** (R^1=4-Me–C_6H_4, R^2=Ph)	CN	12	**1n**	>99:1	84
15	**2o** (R^1=4-Br–C_6H_4, R^2=Ph)	CN	12	**1o**	>99:1	85
16	**2p** (R^1=R^2=Ph)	H	72	**1p**	—	n.r.[c]
17	**2q** (R^1=R^2=Ph)	SO_2Ph	72	**1q**	—	n.r.[c]
18	**2r** (R^1=R^2=Ph)	CO_2Me	72	**1r**	—	n.r.[c]

[a] Determined by ^{1}H NMR assay. The relative configuration was determined by NOESY assay.
[b] Isolated yields.
[c] The n.r. stands for no reaction.

was replaced by H, SO_2Ph or CO_2Me, basically no reaction took place (Table 2, entries 16–18). In all of these cases examined, only the trans diastereoisomer was observed (Fig. 1).[6]

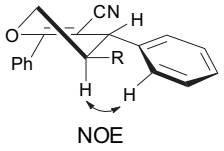
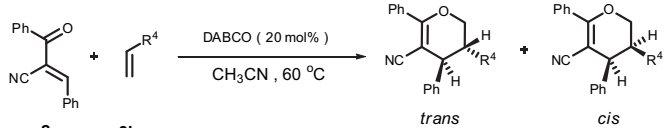


Fig. 1. Nuclear Overhauser effect.

To our delight, besides MVK, methyl acrylate **3b** also participated in the reaction with **2a** to give the corresponding products in moderate to good yields, albeit with a long reaction time at room temperature and a poor diastereoselectivity (Table 3, entry 1). Increasing the reaction temperature to 60 °C could shorten the reaction time dramatically and improve the dr value slightly (Table 3, entry 2). The use of bulkier acrylates **3c** and **3d** provided inferior

Table 3
Substrate scope of activated alkenes **3**



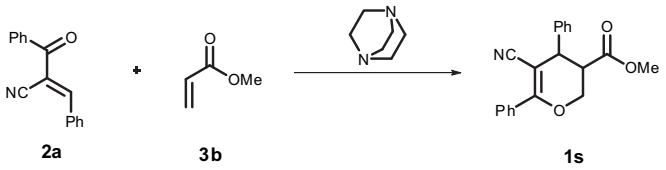
2a **3b-e** *trans* **1s-v** *cis* **1s'-v'**

Entry	**3** (R^4)	T (h)	Product	dr[a] (trans/cis)	Total yield[b] (%)
1[c]	**3b** (CO_2Me)	120	**1s**	1.5:1	71
2	**3b** (CO_2Me)	24	**1s**	2.4:1	78
3	**3c** (CO_2Et)	24	**1t**	1.4:1	61
4	**3d** (CO_2-*t*-Bu)	120	**1u**	—	Trace
5[c]	**3e** (COEt)	12	**1v**	>99:1	81

[a] Determined by ^{1}H NMR analysis. The relative configuration was determined by NOESY assay.
[b] Isolated yields.
[c] The reaction was run at room temperature.

results (Table 3, entries 3 and 4), while the homolog of MVK, ethyl vinyl ketone gave the product with a good yield, and only the trans diastereoisomer was detected (Table 3, entry 5).

Based on previous studies on the RC reaction, a tentative catalytic cycle was proposed for the current tandem reaction (Scheme 3). Conjugate addition of DABCO to the activated alkene **3b** provided intermediate **4**, which would add onto α,β-unsaturated ketone **2a** to afford intermediate **7**. The latter then underwent an intramolecular S_N2 reaction to yield dihydropyran **1s** with regeneration of the amine catalyst. And another possible reaction path was that the intermediate **7** first underwent elimination of the DABCO moiety, then the pyranyl ring **1** was generated from **10** by means of a 6-*endo*-*trig*-*O*-1,4-addition. Given the several neutral zwitterionic intermediates in this proposed mechanism,[7] which are suitable for detection by ESIMS in their protonated/cationic forms,[8] we also employed this technique to gain some insight into this reaction. With the standard procedure for MS detection, possible intermediates in the model reaction between **2a** and **3b** were captured by gradual addition of the reactants (Scheme 2). All the intermediates in the catalytic cycle were found in ESIMS analysis, which supported the speculation (Fig. 2).



Scheme 2. Model reaction for ESIMS study.

(1) A solution of activated alkene **3b** (0.0025 mmol) and DABCO (0.0025 mmol) in CH_3CN (6 mL) was stirred at room temperature. After 1 min, 5 μL of the solution was taken and diluted with 100 μL of CH_3CN and transferred into the ESI source by a syringe pump at a flow rate of 10 μL min^{-1} for the MS detection. After this standard treatment, the signal of intermediate ions **5** (*m*/*z* 199), a protonated form of the proposed intermediate **4**, was detected (Fig. 2a).

(2) A solution of α,β-unsaturated ketones **2a** (0.0025 mmol), methyl acrylate **3b** (0.0025 mmol) and DABCO (0.0025 mmol) in CH_3CN (6 mL) was stirred at room temperature. In the first 5 min, intermediate ions **5** (*m*/*z* 199) were detected (Fig. 2b); at 20 min, inter-mediate ions **5** (*m*/*z* 199) and **8** (*m*/*z* 432) were detected (Fig. 2c); at 40 min, ions **9** formed from the product **1** started to appear while intermediate ions **5** and **8** existed (Fig. 2c). After 5 h, the signal of ion **5** and **8** became very weak, and strong signals of ions **9** could be detected. All these intermediate ions were structurally characterized by tandem mass spectrometric (MS/MS) analysis.

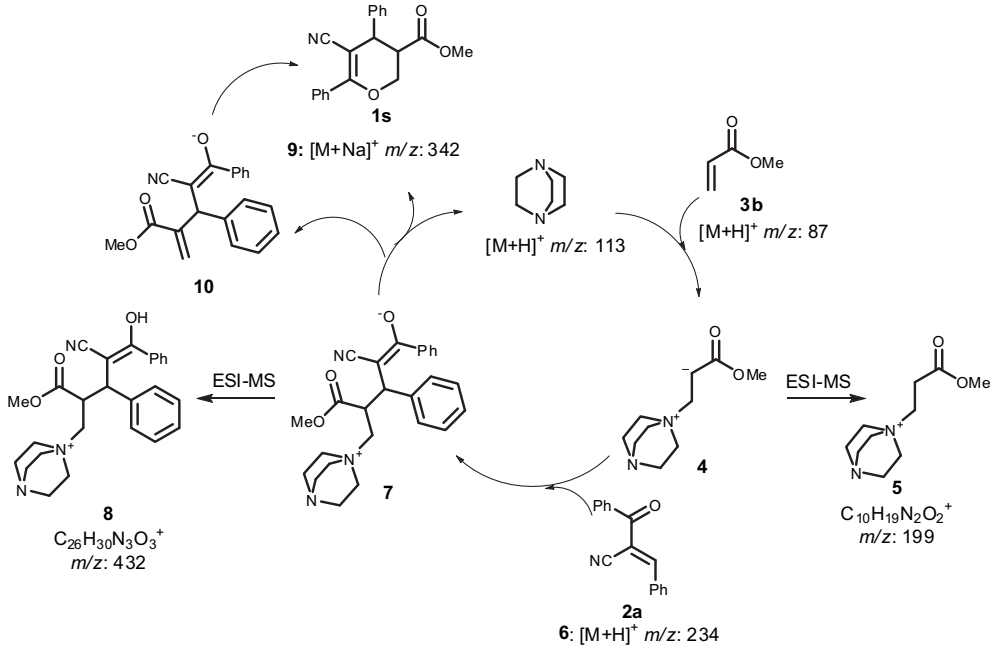
3. Conclusion

In conclusion, we have discovered an efficient, amine-catalyzed tandem cross-Rauhut–Currier coupling/cyclization reaction of activated alkenes and investigated the mechanism with ESIMS. The mild reaction conditions, good to excellent yields, and easily available substrates make this reaction an attractive method for the preparation of densely functionalized 3,4-dihydropyrans. Efforts toward the development of an asymmetric variant of this reaction are ongoing in our laboratory.

4. Experiment section

4.1. General information

Unless otherwise indicated, all compounds and reagents were purchased from commercial suppliers and used without further



Scheme 3. Proposed catalytic cycle for the cross-Rauhut–Currier/cyclization reaction of **2a** and **3b**.

purification. ^1H nuclear magnetic resonance spectra are recorded at 400 MHz. All chemical shifts (δ) are given in parts per million. Data are reported as follows: chemical shift, integration, multiplicity (s=single, d=doublet, t=triplet, q=quartet, m=multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on Bruker AMX-400 NMR spectrometer. IR spectra were recorded on a Perkin–Elmer 983 G instrument. MS or HRMS was recorded on a HP-5989A spectrometer.

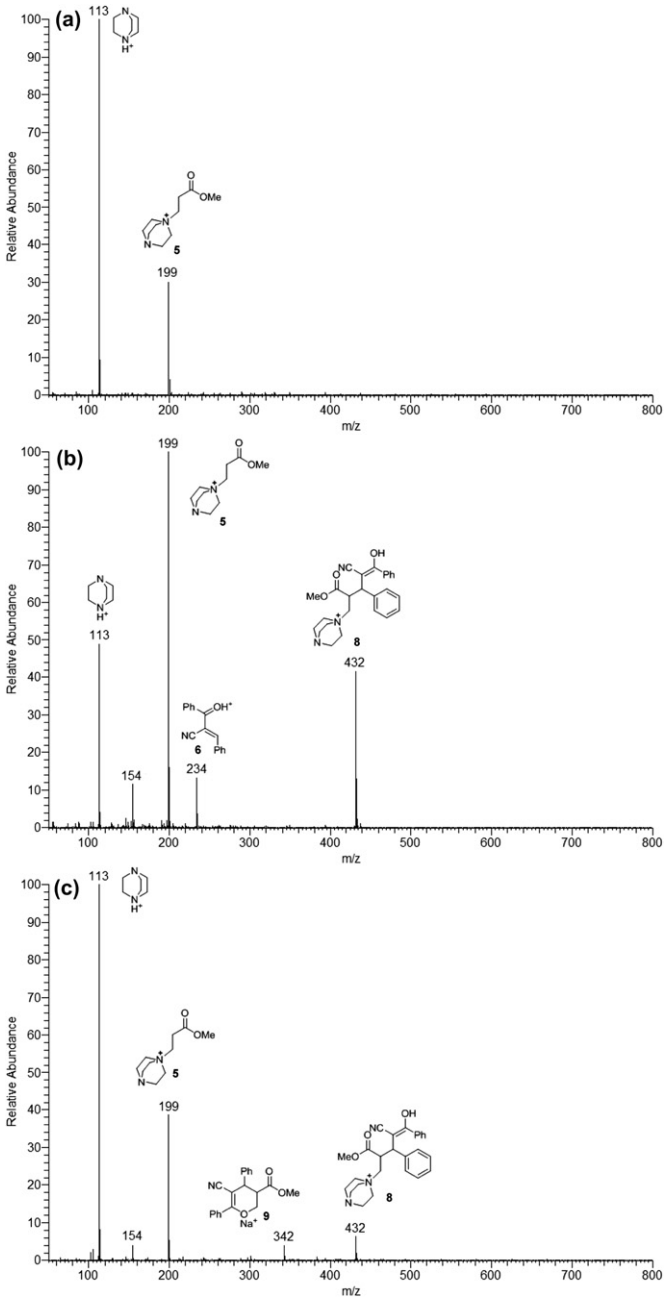


Fig. 2. ESIMS carried out with the standard procedure for MS detection for the sample taken from the reaction mixture of α,β-unsaturated ketones **2a** (0.0025 mmol), methyl acrylate **3b** (0.0025 mmol), and DABCO (0.0025 mmol) in CH_3CN (6 mL) stirred at room temperature at the reaction time of (a) 5 min, (b) 20 min, and (c) 40 min.

4.2. General procedure for the synthesis of 3-oxo-3-phenyl propanenitrile[9]

A dry and nitrogen-flushed 150 mL three-neck flask equipped with a magnetic stirring bar was charged with a solution of sodium hydride (60%) (3.8 g, 1.5 equiv) and ethyl benzoate (9.2 mL, 64 mmol) in dry toluene (100 mL). The reaction mixture was stirred at 90 °C, and acetonitrile (8.0 mL) was dropped with stirring in 1 h, thereafter, the solvent was stirred at 90 °C for 6 h. Then saturated NH_4Cl (10 mL) and 70 mL of water were added at 0 °C to quench the reaction. The suspension was extracted with ethyl acetate (3×100 mL), the solvent was evaporated and the crude mixture was recrystallized to yield 6.0 g (41 mmol, 64%) of the desired product as a yellow solid.

4.3. General procedure for the synthesis of 2a–o[10]

A dry 50 mL round flask equipped with a magnetic stirring bar was charged with a solution of 3-oxo-3-phenylpropanenitrile (0.87 g, 6.0 mmol), benzaldehyde (0.61 mL, 6.0 mmol), piperidine (0.12 mL, 0.2 equiv), and acetic acid (0.069 mL, 0.2 equiv) in toluene (20 mL). The mixture was heated at 60 °C for 12 h. After cooling to room temperature, the mixture was washed with water (10 mL) and the aqueous phase was extracted with ethyl acetate (3×10 mL). The crude mixture was subjected to column chromatography (PE/EA 98:2) to yield 0.68 g (2.9 mmol, 48%) of the desired product as a white solid.

*4.3.1. 2-Benzoyl-3-(1-methyl-1H-indol-3-yl)acrylonitrile (**2k**).* Orange solid; mp: 139–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (3H, s), 7.32–7.44 (3H, m), 7.51 (2H, t, J=7.2 Hz), 7.60 (1H, t, J=7.2 Hz), 7.78 (1H, d, J=8.0 Hz), 7.88–7.90 (2H, m), 8.63 (2H, d, J=16.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.16, 101.27, 110.56, 110.73, 118.58, 120.07, 122.94, 124.19, 128.46, 128.70, 128.92, 132.47, 135.18, 137.12, 137.45, 147.14, 189.19 ppm; IR (KBr): ν 3117, 3060, 2928, 2203, 1650, 1549, 1517, 1472, 1325, 1263, 1124, 1074, 741, 720, 654 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{14}N_2O$ (M^+) 286.1106. Found 286.1100.

4.4. General procedure for the tandem cross-Rauhut–Currier/ cyclization reactions

To a mixture of enone **2** (0.10 mmol) and MVK **3** (0.30 mmol) in acetonitrile (1.0 mL), DABCO (0.02 mmol) was added at ambient temperature. After stirring for 6 h, the solvent was concentrated, the crude product was directly purified by flash column chromatography on silica gel (PE/EA 95:5 to 90:10) to afford the desired product **1** as a solid.

*4.4.1. 3-Acetyl-4,6-diphenyl-3,4-dihydro-2H-pyran-5-carbonitrile (**1a**).* White solid; mp: 124–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (3H, s), 3.05 (1H, m), 4.15 (1H, d, J=6.0 Hz), 4.36–4.38 (2H, m), 7.30–7.33 (3H, m), 7.37–7.47 (5H, m), 7.78 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.77, 42.00, 53.23, 65.93, 87.21, 119.10, 127.99, 128.08, 128.30, 128.46, 129.23, 131.14, 132.53, 140.26, 165.70, 205.46 ppm; IR (KBr): ν 3063, 3023, 2206, 1713, 1618, 1492, 1449, 1359, 1150, 769, 698 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{17}NO_2$ (M^+) 303.1259. Found 303.1263.

*4.4.2. 3-Acetyl-4-(4-chlorophenyl)-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (**1b**).* White solid; mp: 131–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (3H, s), 3.03 (1H, m), 4.16 (1H, d, J=6.8 Hz), 4.31–4.42 (2H, m), 7.24 (2H, d, J=8.8 Hz), 7.36 (2H, d, J=8.0 Hz), 7.42–7.48 (3H, m), 7.77 (2H, d, J=7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.86, 41.37, 53.20, 66.01, 86.91, 119.16, 124.50, 128.27, 128.50, 129.45, 131.29, 132.29, 133.95, 138.74, 165.90, 204.93 ppm; IR (KBr): ν 2988, 2923, 2206, 1714, 1614, 1489, 1455, 1361, 1151, 1082, 697 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{17}ClNO_2$ ($[M+H]^+$) 338.0942. Found 338.0947.

*4.4.3. 3-Acetyl-4-(4-bromophenyl)-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (**1c**).* White solid; mp: 141–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (3H, s), 3.03 (1H, m), 4.15 (1H, d, J=6.8 Hz), 4.31–4.43 (2H, m), 7.18 (2H, d, J=8.8 Hz), 7.42–7.53 (5H, m), 7.77 (2H, d, J=7.6 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.83, 41.35, 53.12, 65.98, 86.74, 118.93, 122.02, 128.28, 128.51, 129.82, 131.32, 132.27, 132.39, 139.32, 165.95, 204.92 ppm; IR (KBr): ν 3063, 2925, 2206, 1715, 1615, 1472, 1360, 1151, 776, 696 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{16}BrNO_2$ (M^+) 381.0364. Found 381.0370.

*4.4.4. 3-Acetyl-4-(3-bromophenyl)-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (**1d**).* White solid; mp: 142–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (3H, s), 3.02 (1H, m), 4.17 (1H, d, J=6.0 Hz), 4.36–4.38 (2H, m), 7.24–7.26 (2H, m), 7.42–7.48 (5H,

m), 7.78 (2H, d, J=6.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.58, 41.29, 53.12, 65.76, 86.43, 118.88, 123.28, 126.92, 128.31, 128.51, 130.76, 131.06, 131.23, 131.32, 132.26, 142.75, 166.05, 204.66 ppm; IR (KBr): ν 3001, 2933, 2206, 1716, 1611, 1512, 1460, 1359, 1249, 1150, 833, 776 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{16}BrNO_2$ (M^+) 381.0364. Found 381.0364.

*4.4.5. 3-Acetyl-4-(2-bromophenyl)-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (**1e**).* White solid; mp: 148–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (3H, s), 3.02 (1H, s), 4.14–4.17 (1H, dd, ^3J=11.6 Hz, ^4J=2.4 Hz), 4.61–4.67 (2H, m), 7.23 (1H, m), 7.38–7.51 (5H, m), 7.67 (1H, d, J=8.0 Hz), 7.82–7.84 (2H, d, J=7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.03, 40.46, 50.56, 64.27, 84.65, 119.24, 124.11, 128.06, 128.26, 128.46, 129.50, 130.37, 131.20, 132.45, 133.86, 139.43, 166.58, 204.03 ppm; IR (KBr): ν 3059, 2998, 2206, 1713, 1621, 1464, 1445, 1361, 1153, 768, 697 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{16}BrNO_2$ (M^+) 381.0364. Found 381.0369.

*4.4.6. 3-Acetyl-4-(4-fluorophenyl)-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (**1f**).* White solid; mp: 121–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (3H, s), 3.05–3.10 (1H, m), 4.20 (1H, d, J=7.2 Hz), 4.38–4.44 (2H, m), 7.12 (2H, t, J=8.8 Hz), 7.30–7.50 (5H, m), 7.81 (2H, d, J=6.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.70, 41.34, 53.32, 66.06, 87.24, 116.20 (d, J_{F-C}=21.2 Hz), 118.93, 128.27, 128.49, 129.71 (d, J_{F-C}=8.2 Hz), 131.25, 132.33, 135.90 (d, J_{F-C}=3.3 Hz), 162.40 (d, J_{F-C}=246.9 Hz), 165.77, 205.18 ppm; IR (KBr): ν 2958, 2920, 2207, 1715, 1615, 1506, 1449, 1223, 1146, 695 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{16}FNO_2Na$ ([M+Na]$^+$) 344.1057. Found 344.1066.

*4.4.7. 3-Acetyl-4-(4-methoxyphenyl)-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (**1g**).* Yellow solid; mp: 123–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (3H, s), 3.04 (1H, m), 3.80 (3H, s), 4.08 (1H, d, J=6.8 Hz), 4.33–4.41 (2H, m), 6.91 (2H, d, J=8.8 Hz), 7.21 (2H, d, J=8.4 Hz), 7.43–7.50 (3H, m), 7.77 (2H, d, J=7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.01, 41.44, 53.26, 55.32, 66.12, 87.71, 114.64, 119.19, 128.28, 128.44, 129.12, 131.09, 132.05, 132.56, 159.30, 165.45, 205.82 ppm; IR (KBr): ν 2956, 2926, 2204, 1715, 1608, 1512, 1455, 1256, 1176, 1029, 837, 701 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{19}NO_3$ (M^+) 333.1365. Found 333.1362.

*4.4.8. 3-Acetyl-4-(4-nitrophenyl)-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (**1h**).* Yellow solid; mp: 146–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (3H, s), 3.10 (1H, m), 4.33–4.38 (2H, m), 4.48 (1H, m), 7.47–7.53 (5H, m), 7.80 (2H, d, J=8.0 Hz), 8.27 (2H, d, J=8.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.36, 41.43, 53.11, 65.99, 86.05, 123.99, 124.44, 128.28, 128.60, 129.21, 131.57, 131.93, 147.69, 166.42, 203.93 ppm; IR (KBr): ν 2957, 2925, 2206, 1715, 1614, 1597, 1519, 1494, 1348, 1151, 969, 696 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{17}N_2O_4$ ([M+H]$^+$) 349.1183. Found 349.1195.

*4.4.9. 3-Acetyl-4-(2,4-dichlorophenyl)-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (**1i**).* Pale yellow solid; mp: 143–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (3H, s), 3.00 (1H, d, J=2.4 Hz), 4.15 (1H, dd, ^3J=11.6 Hz, ^4J=2.4 Hz), 4.58–4.62 (2H, m), 7.28–7.30 (2H, m), 7.43–7.47 (4H, m), 7.77 (2H, d, J=8.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.16, 37.85, 50.30, 64.50, 84.24, 119.05, 127.75, 128.26, 128.50, 130.34, 131.08, 131.37, 132.25, 134.31, 134.53, 136.52, 166.75, 203.79 ppm; IR (KBr): ν 3054, 3002, 2206, 1715, 1613, 1557, 1471, 1385, 1154, 1103, 696 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{15}Cl_2NO_2$ (M^+) 371.0480. Found 371.0478.

*4.4.10. 3-Acetyl-6-phenyl-4-(thienyl-2-yl)-3,4-dihydro-2H-pyran-5-carbonitrile (**1j**).* Yellow solid; mp: 95–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (3H, s), 3.12 (1H, m), 4.46–4.49 (3H, m), 6.99–7.03 (2H, m), 7.28 (1H, d, J=4.8 Hz), 7.41–7.47 (3H, m), 7.75 (2H, d, J=6.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.24, 36.83, 53.52, 65.83, 87.44, 118.90, 125.40, 126.79, 127.29, 128.34, 128.45, 131.22, 132.33, 143.69, 165.26, 204.61 ppm; IR (KBr): ν 2956, 2854, 2203, 1714, 1614, 1495, 1463, 1456, 1361, 1154, 1186, 1081, 968, 693 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{15}NO_2SNa$ ([M+Na]$^+$) 332.0716. Found 332.0726.

*4.4.11. 3-Acetyl-4-(1-methyl-1H-indyl-3-yl)-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (**1k**).* Orange solid; mp: 169–171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (3H, s), 3.27 (1H, m), 3.77 (3H, s), 4.38–4.48 (3H, m), 6.99 (1H, s), 7.13 (1H, t, J=7.2 Hz), 7.28–7.35 (2H, m), 7.43–7.45 (3H, m), 7.56 (1H, m), 7.79 (2H, d, J=6.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.23, 31.44, 33.71, 51.25, 65.96, 87.25, 109.86, 113.56, 118.47, 119.55, 122.25, 125.73, 128.29, 128.35, 128.44, 131.00, 132.73, 137.78, 165.19, 205.82 ppm; IR (KBr): ν 2925, 2854, 2205, 1712, 1613, 1467, 1360, 1327, 1282, 1150, 1081, 969, 909, 739, 697 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{20}N_2O_2Na$ ([M+Na]$^+$) 379.1417. Found 379.1423.

*4.4.12. 3-Acetyl-6-(4-methoxyphenyl)-4-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (**1m**).* White solid; mp: 121–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (3H, s), 3.04 (1H, m), 3.84 (3H, s), 4.14 (1H, d, J=7.2 Hz), 4.34–4.38 (2H, m), 6.93 (2H, d, J=9.2 Hz), 7.26–7.38 (5H, m), 7.75 (2H, d, J=8.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.87, 42.15, 53.41, 55.42, 65.92, 85.78, 113.80, 119.55, 124.79, 127.93, 128.06, 129.19, 129.96, 140.44, 161.83, 165.43, 205.60 ppm; IR (KBr): ν 2956, 2926, 2853, 2204, 1715, 1608, 1512, 1455, 1256, 1176, 1150, 1029, 837, 701 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{19}NO_3Na$ ([M+Na]$^+$) 356.1257. Found 356.1261.

*4.4.13. 3-Acetyl-4-phenyl-6-p-tolyl-3,4-dihydro-2H-pyran-5-carbonitrile (**1n**).* White solid; mp: 122–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (3H, s), 3.13 (3H, s), 3.05 (1H, m), 4.14 (1H, d, J=6.4 Hz), 4.35–4.38 (2H, m), 7.22–7.25 (2H, m), 7.28–7.31 (3H, m), 7.36–7.39 (2H, m), 7.68 (2H, d, J=8.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.50, 29.87, 42.01, 53.31, 65.93, 86.59, 119.32, 127.95, 128.07, 128.22, 129.14, 129.21, 129.66, 140.34, 141.59, 165.82, 205.59 ppm; IR (KBr): ν 3036, 2925, 2849, 2205, 1716, 1609, 1454, 1360, 1189, 1150, 824, 701 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{19}NO_2Na$ ([M+Na]$^+$) 340.1308. Found 340.1317.

*4.4.14. 3-Acetyl-6-(4-bromophenyl)-4-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (**1o**).* White solid; mp: 138–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (3H, s), 3.06 (1H, m), 4.14 (1H, d, J=6.8 Hz), 4.37–4.39 (2H, m), 7.26–7.41 (5H, m), 7.57 (2H, d, J=8.8 Hz), 7.66 (2H, d, J=8.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.81, 41.98, 53.08, 66.01, 87.71, 118.78, 125.68, 128.02, 128.10, 129.28, 129.80, 131.31, 131.74, 140.00, 164.49, 205.31 ppm; IR (KBr): ν 2955, 2924, 2852, 2206, 1715, 1621, 1615, 1487, 1455, 1150, 1010, 831, 701, 674 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{16}NO_2BrNa$ ([M+Na]$^+$) 404.0257. Found 404.0267.

*4.4.15. Methyl 5-cyano-4,6-diphenyl-3,4-dihydro-2H-pyran-3-carboxylate (**1s**).* The title compound was obtained according to the general procedure (78% yield) and a mixture of two diastereoisomers (major and minor); dr: trans/cis=2.4:1. Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.97 (m, 1H; major), 3.31 (m, 1H; minor), 3.55 (s, 3H; minor), 3.71 (s, 3H; major), 4.23–4.27 (m, 1H; both diastereoisomers), 4.32 (d, 1H, J=11.6 Hz; minor), 4.36 (d, 1H, J=3.2 Hz; major), 4.46–4.51 (m, 1H; both diastereoisomers), 7.23–7.48 (m, 8H; both diastereoisomers), 7.80–7.84 (m, 2H; both diastereoisomers) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.86, 42.00, 42.77, 46.21, 52.55, 62.94, 65.62, 85.37, 86.25, 119.25, 119.36, 127.93, 128.10, 128.17, 128.29, 128.34, 128.45, 128.49, 128.69, 129.10, 129.12, 131.12, 132.59, 132.68, 137.39, 140.35, 165.64, 165.85, 169.42, 170.64 ppm; IR (KBr): ν 3054, 3026, 2954, 2925, 2854, 2207, 1737, 1617, 1494, 1453, 1437, 1345, 1246, 1203, 1152, 1080, 1011, 975, 771, 698 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{17}NO_3$ (M^+) 319.1208. Found 319.1205.

*4.4.16. Ethyl 5-cyano-4,6-diphenyl-3,4-dihydro-2H-pyran-3-carboxylate (**1t**).* The title compound was obtained according to the

general procedure (61% yield) and a mixture of two diastereoisomers (major and minor); dr: trans/cis=1.4:1. Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, 3H, J=3.0 Hz; minor), 1.21 (t, 3H, J=3.0 Hz; major), 2.95 (m, 1H; major), 3.28 (m, 1H; minor), 3.96–4.00 (m, 1H; both diastereoisomers), 4.14–4.25 (m, 2H; both diastereoisomers), 4.30–4.37 (m, 1H; both diastereoisomers), 4.46–4.50 (m, 1H; both diastereoisomers), 7.23–7.42 (m, 5H; both diastereoisomers), 7.44–7.55 (m, 3H; both diastereoisomers), 7.79–7.84 (m, 2H; both diastereoisomers) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.93, 14.09, 41.97, 42.01, 42.81, 46.30, 61.02, 61.57, 63.04, 65.79, 85.50, 86.33, 119.28, 119.40, 127.90, 128.13, 128.17, 128.26, 128.44, 128.48, 128.62, 128.76, 128.80, 128.84, 129.08, 129.26, 131.08, 132.66, 132.72, 137.41, 140.32, 165.58, 165.85, 168.99, 170.18 ppm; IR (KBr): ν 3065, 3027, 2961, 2925, 2853, 2207, 1707, 1598, 1492, 1459, 1449, 1341, 1247, 1186, 1153, 1081, 1029, 771, 699 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{19}NO_3$ (M^+) 333.1365. Found 333.1369.

*4.4.17. 4,6-Diphenyl-3-propionyl-3,4-dihydro-2H-pyran-5-carbonitrile (**1v**).* Pale yellow solid; mp: 115–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J=7.2 Hz), 2.13 (1H, m), 2.44 (1H, m), 3.07 (1H, m), 4.13 (1H, d, J=7.8 Hz), 4.29–4.42 (2H, m), 7.26–7.47 (8H, m), 7.78 (2H, d, J=6.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.23, 36.37, 42.65, 52.49, 66.57, 87.65, 119.01, 128.00, 128.29, 128.44, 129.20, 131.09, 132.56, 140.05, 165.67, 208.46 ppm; IR (KBr): ν 3060, 3023, 2924, 2854, 2206, 1715, 1614, 1575, 1494, 1455, 1308, 1214, 1151, 1078, 1029, 969, 768, 698 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{19}NO_2$ (M^+) 317.1416. Found 317.1419.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.01.036.

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