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An Efficient and Scalable One-Pot Double Michael Addition-Dieckmann Condensation for the Synthesis of 4,4-Disubstituted Cyclohexane β-Keto Esters

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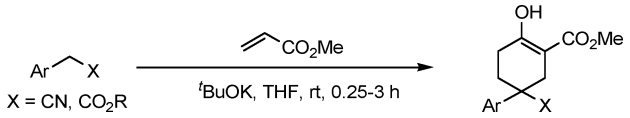

A simple, scalable, and efficient one-pot methodology for the synthesis of 4,4-disubstituted cyclohexane β-keto esters from benzylic nitriles or esters and methyl acrylate promoted by potassium *tert*-butoxide is described. The process relies on a tandem double Michael addition-Dieckmann condensation reaction, which results in the formation of three discrete carbon−carbon bonds in a single pot, including a quaternary center. The method allows for the convenient and rapid synthesis of a variety of 4-aryl-4-cyano-2-carbomethoxycyclohexanone and 4-aryl-2,4-biscarbomethoxycyclohexanone building blocks for use in natural products synthesis and medicinal chemistry.

The 4,4-disubstituted cyclohexanone structural unit has served as a useful synthetic intermediate in a wide range of applications. For example, 4-aryl-4-cyano-2-carbomethoxycyclohexanones (**1**, Figure 1) have been employed in the synthesis of natural products such as the *Amaryllidaceae* alkaloids[1] lycoramine (**2**)[2] and analogs of the anticholinesterase galanthamine (**3**),[3] and the *Sceletium* alkaloids[4] mesembrine (**4**)[5] and tortuosamine (**5**).[6] Additionally, 4-aryl-4-cyano-2-carbomethoxycyclohexanone intermediates have found synthetic utility in the preparation of non-natural products, such as phosphodiesterase 4 (PDE4) inhibitors **6**[7] and **7**.[8] Advantageously, numerous diverse benzylic nitriles and esters are commercially available, allowing for the rapid synthesis of a variety of 4-aryl-4-cyano-2-carbomethoxycyclohexanone and 4-aryl-2,4-biscarbomethoxycyclohexanone intermediates, which can be especially valuable in the discovery of medicinal chemistry agents. For example, 4,4-disubstituted cyclohexanones **8**, resulting from decarboxylation of **1**, have been used as a nucleus for the preparation of biologically active hypotensive[9] and analgesic[10] agents, as well as calcium channel antagonists.[11]

Despite the wide applicability that these intermediates have found in the preparation of biologically active molecules, we were unable to identify a general and operationally simple synthesis of this class of intermediates. The most commonly used method in the literature for the synthesis of 4-aryl-4-cyano-2-carbomethoxycyclohexanones involves a two-step procedure, initially reported by Irie and co-workers (Scheme 1).[12] In this reaction sequence, arylacetonitrile **9** undergoes a double Michael addition reaction with methyl acrylate in the presence of benzyl-(trimethyl) ammoniumhydroxide (Triton B) to afford the diester **12**. Subsequently, in a separate step, diester **12** is treated with 95% sodium hydride (although a few cases have been reported which replace the sodium hydride with potassium *tert*-butoxide) to effect the Dieckmann cyclization providing the 4-aryl-4-cyano-2-carbomethoxycyclohexanone **1**.[9,10] In our hands, we found this reaction sequence to be problematic, particularly on a larger scale. In the first step, the Triton B addition was found to be extremely vigorous, requiring long addition times. Additionally, the sodium hydride promoted Dieckmann condensation was often unpredictable with a variable induction period which led to poor reproducibility and significant issues of lab safety, especially when conducted on a larger scale. Although a more recent report describes a one-pot transformation for the double Michael addition-Dieckmann cyclization of the parent unsubstituted phenylacetonitrile and phenylacetate promoted by $Na_2Fe(CO)_4$ or sodium methoxide, this method affords the 4-phenyl-4-cyano-2-carbomethoxycyclohexanone and 4-phenyl-2,4-biscarboalkoxycyclohexanone products in only moderate yields (56 and 52%, respectively).[13] Due to the limitations with existing approaches, we set out to investigate an improved method to effect the double Michael addition-Dieckmann condensation reaction sequence. This effort has

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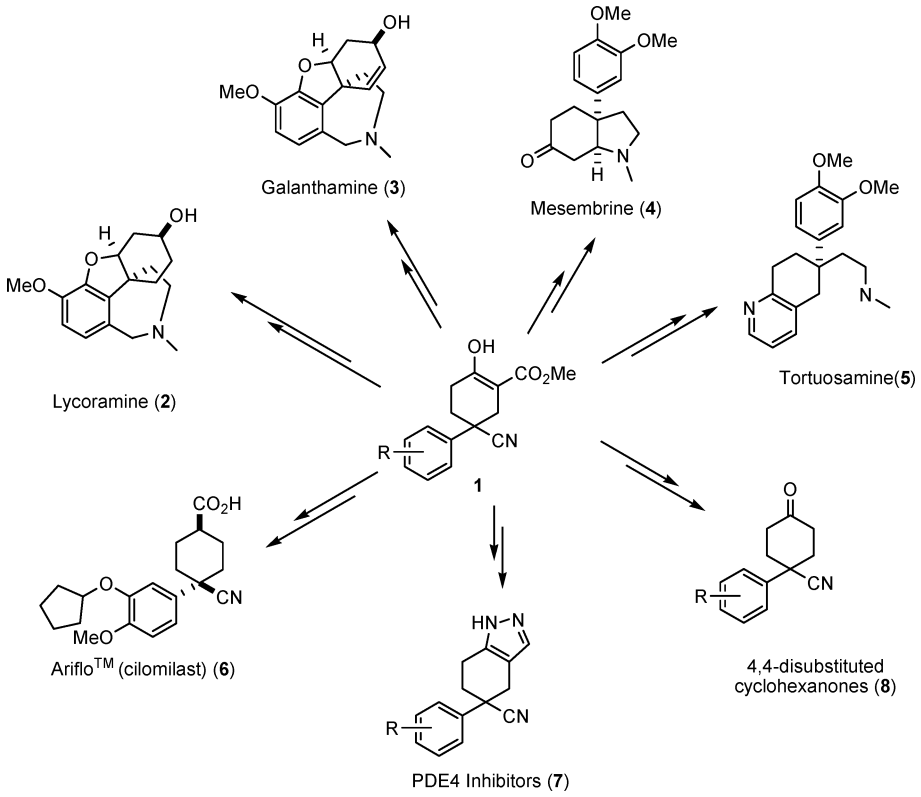
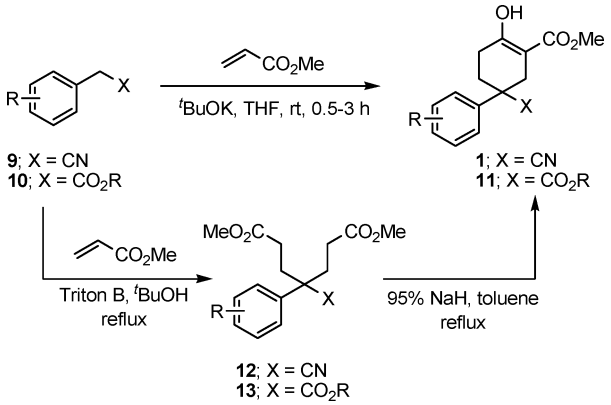


FIGURE 1. 1. Biologically active molecules obtained from 4-aryl-4-cyano-2-carbomethoxycyclohexanones.

SCHEME 1. One-Pot vs Two-Pot Method for the Synthesis of 4,4-Disubstituted-2-carbomethoxycyclohexanones



resulted in the development of a safe, efficient, and scalable method for the synthesis of 4-aryl-4-cyano-2-carbomethoxycyclohexanones **1** and 4-aryl-2,4-biscarbomethoxycyclohexanones **11**.

We chose to initially examine formation of 4-aryl-4-cyano-2-carbomethoxycyclohexanones **1** using a stoichiometric amount (3.0 equiv) of potassium *tert*-butoxide as the base for the tandem double Michael addition-Dieckmann condensation of arylacetonitriles **9** and methyl acrylate (2.0 equiv). As summarized in Table 1, we found the reaction to proceed at room temperature in good to excellent yields (70−92%) with short reaction times (0.25−3 h). The reactions were generally found to be very clean with little side product formation. Further experimentation revealed that reducing the potassium *tert*-butoxide to a substoichiometric amount (1.2 equiv), afforded the desired products in comparable yields (65−91%). Under either set of conditions, the reaction was found to be slightly exothermic with a temperature peak of ∼50 °C (≤5 g scale). On this scale, when the reaction was attempted at 0 °C, it typically did not go to completion and yields were lowered to 40−50%. However, the larger scale experiments (>50 g) were initiated at 0 °C, then allowed to warm to room temperature to ensure minimization of potentially rigorous exotherms.[14] These conditions were found to be applicable to a wide variety of substituted arylacetonitriles **9**, including electron rich (e.g., entry 15), electron deficient (e.g., entry 6), and sterically encumbered (e.g., entry 9) arylacetonitriles and heteroarylacetonitriles (entries 24−29). The substrates limiting the scope of this method were the 4-nitrophenylacetonitrile (entry 19) and 3-nitrophenylacetonitrile (entry 20), which gave only trace or no desired product.

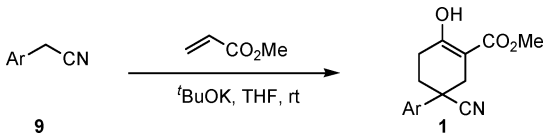
In addition to arylacetonitriles, methyl arylacetates **10** were demonstrated to be effective substrates in the one-pot double Michael addition-Dieckmann cyclization sequence (Table 2). Similarly to the arylacetonitriles, heretoaryl and electron rich and poor arylacetates were tolerated in the reaction to afford the 4-aryl-2,4-biscarbomethoxycyclohexanone products **11** in good to excellent yields (66−89%).

This method was also applicable to 1,3-phenylene- and 1,4-phenylenediacetonitrile subtrates **14** and **16**, in which two 4-aryl-4-cyano-2-carbomethoxycyclohexanones could be generated simultaneously to afford the highly functionalized meso products **15** and **17**, respectively (Scheme 2). The corresponding C1 symmetric isomers were not detected.[15] It should be noted that 1,2-phenylenediacetonitrile **18** gave only the monocyclized product **19** under the standard conditions, which could be

(14) See supporting information for large scale (≥50 g) experimental procedures for the synthesis of compounds **1p** and **11c**.

(15) A small impurity was observed in the crude reaction mixture, but was not identified.

TABLE 1. Scope of the One-Pot Synthesis of 4-Aryl-4-cyano-2-carbomethoxy-cyclohexanones[a]

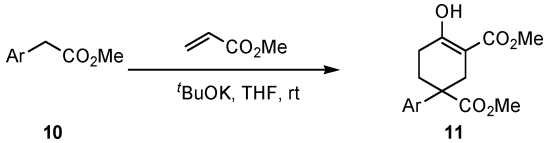


9 1

entry	product	Ar	time (h)	yield[b] (1.2 equiv ^{t}BuOK)	yield[b] (3.0 equiv ^{t}BuOK)
1	**1a**	Ph	1, 0.25	73	82
2	**1b**	4-BrPh	1	88	82
3	**1c**	4-ClPh	2	87	82
4	**1d**	3-ClPh	1	87	85
5	**1e**	2-ClPh	1	85	83
6	**1f**	3,4-ClPh	3	84	81
7	**1g**	4-MePh	2	89	86
8	**1h**	3-MePh	1	86	92
9	**1i**	2-MePh	1	nd[c]	76
10	**1j**	2-(CF_3)Ph	1	80	84
11	**1k**	4-(OCF_3)Ph	0.33	91	nd
12	**1l**	2-OMePh	1	nd	76
13	**1m**	3-OMePh	1	nd	87
14	**1n**	4-OMePh	1	nd	85
15	**1o**	3,4-OMePh	1	65	90
16	**1p**	4-FPh	0.25	nd	76
17	**1q**	3-FPh	0.25	nd	79
18	**1r**	2-FPh	0.25	nd	84
19	**1s**	4-NO_2Ph	18	nd	0
20	**1t**	3- NO_2Ph	1	nd	6
21	**1u**	4-CNPh	1	nd	70
22	**1v**	1-naphthyl	1	nd	84
23	**1w**	2-naphthyl	1	nd	90
24	**1x**	thiazol-2-yl	1	82	nd
25	**1y**	thiazol-5-yl	0.33	88	nd
26	**1z**	thiophen-2-yl	0.5	nd	78
27	**1aa**	pyrid-2-yl	0.5	87	nd
28	**1bb**	pyrid-3-yl	0.5	82	nd
29	**1cc**	pyrid-4-yl	0.5	86	nd

[a] Reactions were conducted in THF at 23 °C with 1.0 equiv of arylacetonitrile, 2.0 equiv of methyl acrylate, and 1.2 or 3.0 equiv of ^{t}BuOK. The arylacetonitrile concentration was 0.37 M. [b] Isolated yield after column chromatography. [c] nd = not determined.

TABLE 2. One-Pot Synthesis of 4-Aryl-2,4-biscarbomethoxycyclohexanones[a]



10 11

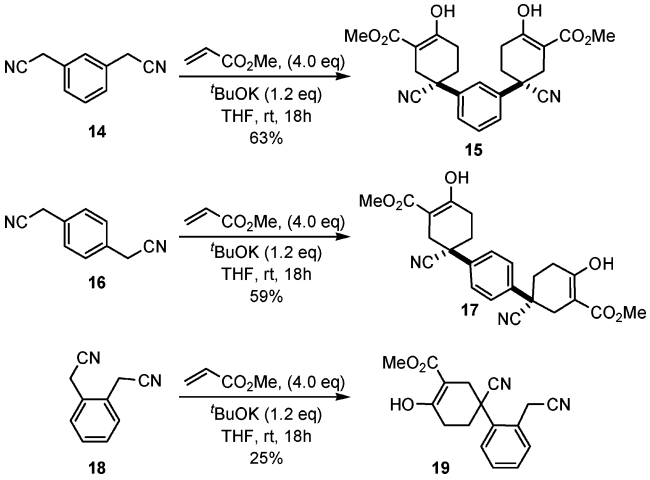
entry	product	Ar	time (h)	yield[b]
1	**11a**	Ph	1	89
2	**11b**	2-FPh	3	75
3[c]	**11c**	4-FPh	2	66
4	**11d**	4-OMePh	0.5	89
5	**11e**	pyrid-2-yl	3	74

[a] Reactions were conducted in THF at 23 °C with 1.0 equiv of methyl arylacetate, 2.0 equiv of methyl acrylate, and 3.0 equiv of ^{t}BuOK. The methyl arylacetate concentration was 0.37 M. [b] Isolated yield after column chromatography. [c] Reaction carried out with 1.2 equiv of ^{t}BuOK.

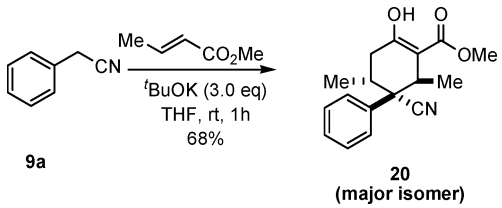
attributed to the increased steric demand required for the formation of the second ring.

It had been previously reported in the literature that attempts to utilize methyl crotonate in the tandem double Michael addition-Dieckmann cyclization led to only monoalkylated products.[13] However, under our conditions, we found that

SCHEME 2. One-Pot Synthesis of Bis-4-aryl-2,4-biscarbomethoxycyclohexanones



SCHEME 3. Double Michael Addition-Dieckmann Condensation Employing Methyl Crotonate



treatment of phenylacetonitrile with 3.0 equiv of potassium *tert*-butoxide in the presence of methyl crotonate gave the cyclization product in 68% yield as a mixture of diastereomers (3:2:1:0.1), further expanding the scope of the present methodology (Scheme 3).[16]

The β-keto ester products obtained from the one-pot double Michael addition-Dieckmann cyclization reaction described above were found to undergo facile decarboxylation to afford the corresponding 4,4-disubstituted ketones. We demonstrated that, in addition to the standard Krapcho decarboxylation method[17] (method A), 4-aryl-4-cyano-2-carbomethoxycyclohexanones **1** and 4-aryl-2,4-biscarbomethoxycyclohexanones **11** underwent decarboxylation at lower temperatures in the presence of potassium hydroxide (method B) in comparable yields (Table 3). Gratifyingly, the diester substrate **11c** could be selectively decarboxylated to give the desired product **22**; however, prolonged reaction times (under both methods) resulted in hydrolysis of the 4-carbomethoxy group and ultimately gave the monosubstituted 4-arylcyclohexanone byproducts (X = H).[18]

Having discovered the decarboxylation reaction of β-keto esters **1** and **11** could be accomplished by simply heating in the presence of aqueous potassium hydroxide, we speculated that the entire reaction sequence (double Michael addition-Dieckmann condensation-decarboxylation) could be achieved in one-pot facilitated by potassium *tert*-butoxide. Indeed, we found that this was a viable approach to obtain 4,4-disubstituted

(16) Ratio of diastereomers determined via ^{1}H NMR analysis. Only the major diastereomer could be obtained in sufficient purity for full characterization (see supporting information).

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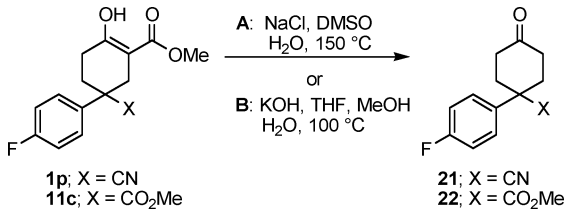
TABLE 3. Decarboxylation of β-Keto Esters to 4,4-Disubstituted Cyclohexanones



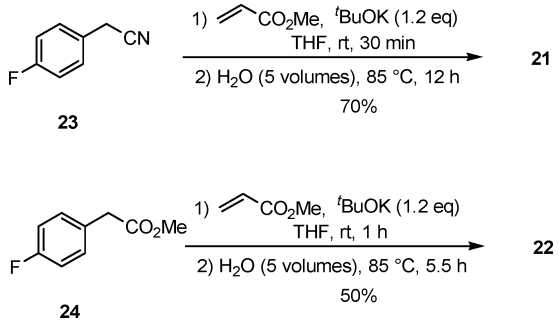
1p; X = CN
11c; X = CO_2Me

21; X = CN
22; X = CO_2Me

entry	substrate	product	conditions	yield[a]
1	**1p**	**21**	A[b]	53
2	**1p**	**21**	B[c]	62
3	**11c**	**22**	A	75
4	**11c**	**22**	B	71

[a] Isolated yield after column chromatography. [b] Reactions carried out with 1.0 equiv of NaCl. [c] Reactions carried out with 0.6 equiv of KOH.

SCHEME 4. One-Pot Double Michael Addition-Dieckmann Condensation-Decarboxylation



cyclohexanones as exemplified with substrates 4-fluorophenylacetonitrile **23** and methyl 2-(4-fluorophenyl)acetate **24** (Scheme 4). The double Michael addition-Dieckmann condensation was carried out according to our standard procedure with 1.2 equiv of potassium *tert*-butoxide. Upon completion, the reaction mixture was diluted with water (5× the volume of THF) and heated to 85 °C to afford the desired cyclohexanones (i.e., **21**, **22**) in moderate to good yields.

In summary, a tandem one-pot double Michael addition-Dieckmann condensation of arylacetonitriles and arylacetates promoted by potassium *tert*-butoxide affords the corresponding 4,4-disubstituted cyclohexane β-keto esters. Owing to the operational simplicity, generality, and scalability, this method represents a notable improvement over existing procedures described in the literature.

Experimental

General Procedure for the Tandem One-Pot Double Michael Addition-Dieckmann Condensation. To a solution of arylacetonitrile or methyl arylacetate (1.0 equiv) and methyl acrylate (2.0 equiv) in THF (0.37 M) was added solid potassium *tert*-butoxide (1.2 or 3.0 equiv). After being stirred for 0.25−3 h at 25 °C, the reaction mixture was acidified with aqueous 3 N HCl and extracted with CH_2Cl_2 (×3). The organic layers were combined, dried with Na_2SO_4, and concentrated *in vacuo*. Purification of the crude product by flash chromatography on silica gel provided the title compounds.

4-Phenyl-4-cyano-2-carbomethoxycyclohexanone (1a): Prepared according to the general procedure using phenylacetonitrile (5.0 g, 42.7 mmol), methyl acrylate (7.7 mL, 85.4 mmol), and ^{t}-BuOK (14.4 g, 128.1 mmol) in THF (115 mL). Flash column chromatography using a gradient elution (SiO_2, 10% to 25% EtOAc/hexanes) afforded 8.96 g of **1a** (82%) as a white solid. Analytical data for **1a**: mp 96−98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.28 (s, 1 H), 7.53 (d, J = 8.3 Hz, 2 H), 7.45 (t, J = 7.6 Hz, 2 H), 7.38 (dt, J = 8.3, 1.2 Hz, 1 H), 3.80 (s, 3 H), 3.03 (d, J = 16.1 Hz, 1 H), 2.85 (m, 1 H), 2.71 (dd, J = 16.1, 1.0 Hz, 1 H), 2.52 (m, 1 H), 2.32 (*A*BXY, J_{AB} = 13.2 Hz, J_{AX} = 6.1 Hz, J_{AY} = 3.1 Hz, 1 H) 2.24 (A*B*XY, J_{AB} = 13.2 Hz, J_{BX} = 11.9 Hz, J_{BY} = 5.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.8, 170.7, 139.4, 129.1, 128.3, 125.6, 122.0, 95.0, 51.7, 41.2, 34.8, 31.5, 27.1; IR (neat, cm^{-1}) 3100−2800, 1660, 1617, 1443, 1354, 1291, 1219; MS (ESI) 256.0 $[M - H]^-$; Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.02; H, 5.88; N, 5.45.

Acknowledgment. We thank David Chow for assistance with NMR spectrometric analysis of compound **20** and Manuel Ventura for purification support of this compound.

Supporting Information Available: Full characterization data for all new compounds and details of experimental procedures are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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