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A simple and highly efficient procedure for construction of quaternary carbons centers by tributylphosphine catalyzed bis-Michael addition

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ABSTRACT

The tributylphosphine-catalyzed bis-Michael addition reaction of various kinds of α,β-unsaturated carbonyl compounds with active methylenes is described. This is a convenient and rapid method for generating quaternary carbons centers and useful procedure for the synthesis of branched core and highly substituted *trans* cyclohexanones. All the reactions were completed in 60 min and afford the corresponding products in excellent yields.

1. Introduction

The synthesis of compounds with carbon atoms having four different nonhydrogen substituents is an attractive area of research because of their stereochemistry and biological activity.[1] As a result of extreme steric congestion, the construction of quaternary carbons is a formidable challenge for chemical synthesis. In the last two decades, much attention was paid on construction of quaternary carbons. In terms of catalytic C–C bond-forming generations of quaternary centers, Heck reactions,[2] enolate α-arylations,[3] enolate α-allylations[4], and allylic substitution[5] reactions have proven to be valuable strategies.

The Michael reaction is widely recognized as one of the most important carbon–carbon bond-forming procedures, and it plays an important role in organic synthesis.[6] Michael addition is a powerful method to construct the quaternary carbons centers. This procedure was often carried out in the presence of strong base[7] that often lead to undesirable side reactions.[8] A number of reagents have been developed for this transformation, and most of the reactions referred to mono-Michael addition reaction.[9] But to date, only a few reagents have been reported on the bis-Michael addition to construct the quaternary carbons centers.[10] However there are still disadvantages of these reagents. For example, the reagents were expensive,[11] the reaction time was too long,[10d] and the reaction needed other special conditions,[10f] such as microwave irradiation. In most cases, the range of α,β-unsaturated carbonyl compounds was limited to conjugated carboxylic esters, and a few examples used conjugated ketones with good yields. Thus, there is a demand for the development of a milder reagent for a general bis-Michael addition to construct the quaternary carbons centers from active methylenes and various kinds of α,β-unsaturated compounds in a single step.

In the early years of this century, an impressive development took place in metal free catalytic methods. Exciting results in organocatalysis attracted a deep attention, taking the advantages of often simple, inexpensive and commercially available catalysts.[12] Organocatalysis induced by phosphines is a topic of increasing interest. Owing to their comparatively strong and readily tunable nucleophilicity, nucleophilic phosphine catalysis has been shown to be a powerful tool in organic synthesis.[13] As a part of our continuing interests in phosphine catalysis,[14] here, we wish to disclose our study on the use of tributylphosphine as catalysts in construction of quaternary carbons from α,β-unsaturated carbonyl compounds and active methylenes by bis-Michael addition.

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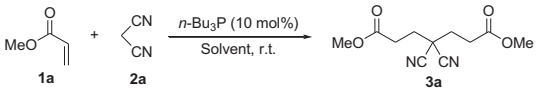
2. Results and discussion

Initially, we selected the Michael addition of malononitrile (**2a**) with methyl acrylate (**1a**) catalyzed by 10 mol % tributylphosphine as a model reaction for investigation of different reaction parameters. As shown in Table 1, the yields of bis-adduct **3a** differed significantly in different solvents at room temperature (Table 1, entries 1–6). Initially, the reaction was carried out under solvent-free conditions, bis-adducts **3a** was formed in a high yield of 83% within 1 h (Table 1, entry 1). When H_2O and THF were used as the solvent, the product was obtained in very low yields (Table 1, entries 2 and 3). When the reaction was carried in other organic solvent, such as toluene, CH_2Cl_2, CH_3CN, moderate to excellent yields were obtained (Table 1, entries 4–6). We were pleased to observe the formation of bis-adduct **3a** with near quantitative yield in CH_3CN (Table 1, entry 6). In absence of catalyst tributylphosphine, this Michael addition reaction did not progress at all (Table 1, entry 7). Other organic bases, such as triethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), were also used in the reaction, but no better results were provided (Table 1, entries 8, 9).

Table 1
Optimization of reaction conditions for the Michael addition of malononitrile to conjugated alkenes[a]

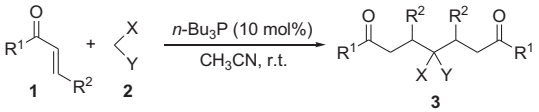


Entry	Solvent	Time (min)	Yield (%)[b]
1	Neat	60	83
2	H_2O	120	<5
3	THF	120	<5
4	Toluene	60	75
5	CH_2Cl_2	25	88
6	CH_3CN	25	98
7[c]	CH_3CN	600	0
8[d]	CH_3CN	40	91
9[e]	CH_3CN	90	0

[a] Reaction conditions: methyl acrylate (271 μL, 3.0 mmol), malononitrile (66 mg, 1.0 mmol), *n*-Bu_3P (25 μL, 10 mol %), solvent (5.0 mL), room temperature (25 °C).
[b] Isolated yield.
[c] Catalyst-free.
[d] DBU (14 μL, 10 mol %) was used.
[e] Et_3N (14 μL, 10 mol %) was used.

Having established the optimal reaction conditions for bis-addition of malononitrile (**2a**) to methyl acrylate (**1a**), we then examined other active methylenes with conjugated carboxylic esters and ketones in CH_3CN catalyzed by tributylphosphine (10 mol %) at room temperature to establish the general utility of this transformation. As shown in Table 2, excellent yields of bis-adducts were obtained with both terminal unsubstituted conjugated carboxylic esters and ketones in very short reaction time. Although a longer reaction time (300 min) was needed when the terminal substituted alkene, ethyl crotonate, was employed in the reaction, the product **3e** was formed in near a quantitative yield (Table 2, entry 5).

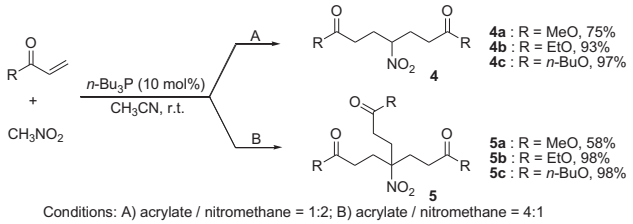
Table 2
Michael addition of active methylene compounds to conjugated alkenes[a]



Entry	Product	R^1	R^2	X	Y	Time (min)	Yield (%)[b]
1	**3a**	MeO	H	CN	CN	25	98
2	**3b**	EtO	H	CN	CN	40	98
3	**3c**	*n*-BuO	H	CN	CN	25	98
4	**3d**	Me	H	CN	CN	20	95
5	**3e**	EtO	Me	CN	CN	300	97
6	**3f**	EtO	H	CN	CO_2Et	30	98
7	**3g**	EtO	H	CO_2Me	CO_2Me	20	94
8	**3h**	EtO	H	CO_2Et	CO_2Et	24	98
9	**3i**	EtO	H	NO_2	Me	5	98

[a] Reaction conditions: conjugated alkene (3.0 mmol), active methylene compound (1.0 mmol), *n*-Bu_3P (25 μL, 10 mol %), CH_3CN (5.0 mL), room temperature (25 °C).
[b] Isolated yield.

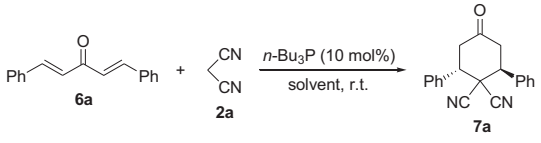
The Michael addition of nitroalkanes with conjugated carboxylic esters is the key step for the synthesis of dendrimers.[15] But long reaction time and low yield often puzzled in the synthesis of the branched core. In the previously reported procedures, a mixture of monoaddition products, double addition products and triple addition products were often formed when nitromethane was used in the Michael reaction with acrylates.[16] Here, we report a synthetic method to yield pure double addition products and triple addition products near a quantitative yield just by controlling the ratio of substrates between acrylates and nitromethane in a very short time. Under the optimal reaction conditions, double Michael adducts were formed when the ratio of acrylates/nitromethane was 1:2. While a 4:1 ratio of the substrates acrylates/nitromethane was used, the reaction gave treble Michael adducts as the main products (Scheme 1). This new synthetic method reported here would greatly contribute to synthesize of dendrimers.



Scheme 1. Michael reaction of nitromethane to acrylates.

This procedure was also applicable to the intramolecular double Michael reaction of active methylenes to dienones, and afforded the compound, containing a new quaternary carbon center, 1,1-disubstituted-2,6-diarylcyclohexane-4-ones, which were often employed as starting materials for the synthesis of compounds with possible biological activity[17] and used to prepare a variety of spiro heterocycles.[18] As can be seen from the solvents screened results summarized in Table 3, when the reaction was performed in CH_2Cl_2 in the presence of 10 mol % of tributylphosphine as the catalyst, the reaction proceeded smoothly and gave exclusively the

Table 3
Optimization of reaction conditions for the Michael addition of malononitrile to dibenzylidene acetone[a]



Entry	Solvent	Time (min)	Yield (%)[b]
1	CH_3CN	90	32
2	THF	300	0
3	Toluene	90	21

(*continued on next page*)

Table 3 (*continued*)

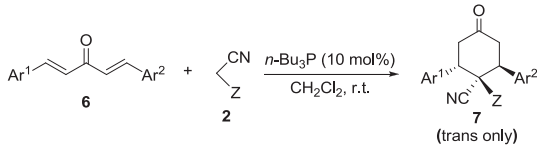
Entry	Solvent	Time (min)	Yield (%)[b]
4	CH_2Cl_2	5	95
5	H_2O	90	10

[a] Reaction conditions: dibenzal acetone (234 mg, 1.0 mmol), malononitrile (66 mg, 1.0 mmol), *n*-Bu_3P (25 μL, 10 mol %), solvent (5.0 mL), room temperature (25 °C).
[b] Isolated yield.

trans-1,1-disubstituted-2,6-diarylcyclohexane-4-one (**7a**) in the best yield of 95% within only 5 min (Table 3, entry 4).

Under the standard reaction conditions, a variety of dienones (**6**) and active methylenes (**2**) were examined to explore the scope of the reaction. The results are shown in Table 4, high isolated yields were obtained for all the products, regardless of the electronic nature of the aromatic substituents. Compared to the Michael reactions of malononitrile with dibenzal acetone, which contained donating and moderately electron withdrawing groups, the reactions of ethyl cyanoacetate with the same substrates needed a longer reaction time. When the substrates **6** with strong electron withdrawing groups (4-CN and 4-NO_2), the opposite results were obtained. A shorter time was often needed when they reacted with ethyl cyanoacetate.

Table 4
n-Bu_3P catalyzed Michael addition of active methylenes to dienones[a]

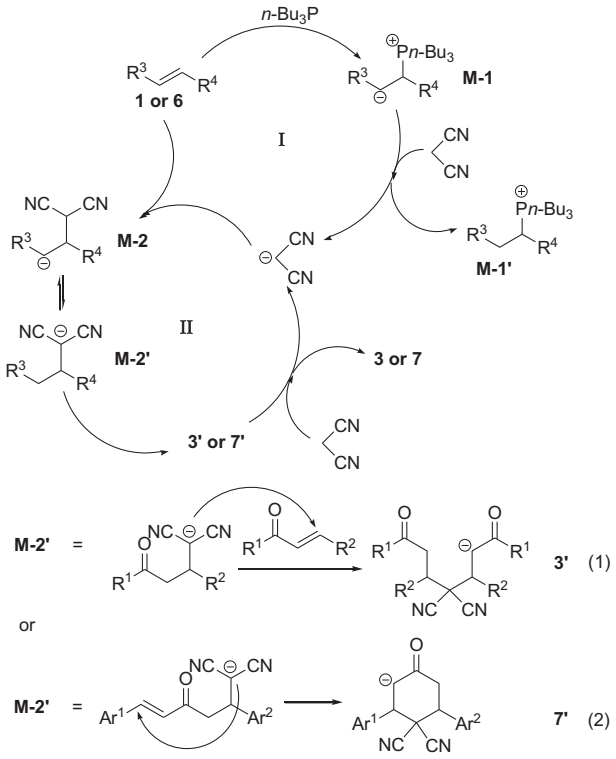


Entry	Product	Ar^1	Ar^2	Z	Time (min)	Yield (%)[b]
1	**7a**	Ph	Ph	CN	5	95
2	**7b**	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	CN	25	82
3	**7c**	*p*-$OCH_3C_6H_4$	*p*-$OCH_3C_6H_4$	CN	16	95
4	**7d**	*p*-ClC_6H_4	*p*-ClC_6H_4	CN	2	95
5	**7e**	*p*-CNC_6H_4	*p*-CNC_6H_4	CN	120	93
6	**7f**	*p*-$NO_2C_6H_4$	*p*-$NO_2C_6H_4$	CN	60	89
7	**7g**	*o*-ClC_6H_4	*o*-ClC_6H_4	CN	10	88
8	**7h**	*m*-ClC_6H_4	*m*-ClC_6H_4	CN	10	>99
9	**7i**	*m*-$CH_3C_6H_4$	*m*-$CH_3C_6H_4$	CN	7	85
10	**7j**	*p*-$CH_3C_6H_4$	Ph	CN	20	93
11	**7k**	*p*-ClC_6H_4	Ph	CN	4	90
12	**7l**	*p*-CNC_6H_4	Ph	CN	70	94
13	**7m**	*p*-$NO_2C_6H_4$	Ph	CN	60	97
14	**7n**	Ph	Ph	CO_2Et	60	>99
15	**7o**	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	CO_2Et	40	85
16	**7p**	*p*-ClC_6H_4	*p*-ClC_6H_4	CO_2Et	60	96
17	**7q**	*p*-$NO_2C_6H_4$	*p*-$NO_2C_6H_4$	CO_2Et	20	90
18	**7r**	*m*-$CH_3C_6H_4$	*m*-$CH_3C_6H_4$	CO_2Et	60	91
19	**7s**	*m*-ClC_6H_4	*m*-ClC_6H_4	CO_2Et	40	85
20	**7t**	*p*-$CH_3C_6H_4$	Ph	CO_2Et	50	91
21	**7u**	*p*-$NO_2C_6H_4$	Ph	CO_2Et	15	98

[a] Reaction conditions: dienone (1.0 mmol), active methylene compound (1.0 mmol), *n*-Bu_3P (25 μL, 10 mol %), CH_2Cl_2 (5.0 mL), room temperature (25 °C).
[b] Isolated yield.

We also tried this intramolecular double Michael reaction out on grams scale, compound **7a** was chosen as the target compound. The reaction was carried out on a ten-mmol scale with only 5 mol % of tributylphosphine as the catalyst. Product **7a** could be obtained in 2.82 g with 94% yield within 30 min.

Base on the results and the reported literature,[19] a proposed mechanism for the double Michael addition reaction is shown in Scheme 2. Initial attack of the tributylphosphine on the substrate of olefin (**1** or **6**) generates a zwitterion **M-1**, which deprotonates a molecule of the active methylene. The addition of deprotonated active methylene to the olefin (**1** or **6**) followed by proton transfer generates **M-2′**, which reacts again to olefin through intermolecular (1) or intramolecular (2) Michael addition. Then product **3** or **7** was released, and deprotonated active methylene was regenerated.



Scheme 2. Possible mechanism for the bis-addition catalyzed by tributylphosphine.

3. Conclusion

In conclusion, we have successfully demonstrated a new procedure for construction of quaternary carbons centers in a single step by intermolecular and intramolecular bis-Michael addition. The compound tributylphosphine was employed as a highly efficient catalyst for the Michael reaction of a broad range of α,β-unsaturated carbonyl compounds and active methylenes. The reaction condition is mild and the method is operationally simple. The products, containing a new quaternary carbons center, were obtained in good to excellent yields in short times.

4. Experimental section

4.1. General procedure for the Michael addition of active methylene compounds to conjugated alkenes (3a as an example)

A mixture of malononitrile (**2a**) (66 mg, 1 mmol), methyl acrylate (**1a**) (271 μL, 3 mmol), tributylphosphine (25 μL, 0.1 mmol), and anhydrous CH_3CN (5.0 mL) was magnetically stirred in a flask under nitrogen atmosphere at room temperature. The reaction progress was monitored by thin layer chromatography (TLC) until malononitrile was consumed. Then, the reaction mixture was diluted with H_2O (10 mL) and extracted with AcOEt (3×10 mL), the organic phase was washed with brine (10 mL), dried over anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the residue was subjected to chromatography on a silica gel (200–300 mesh) column using petroleum ether/ethyl acetate (4:1) as eluent to afford **3a** (233 mg, 98% yield) as a colorless liquid.

*4.1.1. Diethyl 4,4-dicyano-3,5-dimethylheptanedioate (**3e**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.21–1.30 (12H, m), 2.36–2.53 (2H, m), 2.63–2.78 (4H, m), 4.16 (4H, q, J_1=14.0 Hz, J_2=7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.15, 16.10, 34.41, 37.09, 47.97, 61.35, 113.72, 170.40. MS (ESI): m/z=317.1 $[M+Na]^+$. HRMS calcd for $C_{15}H_{22}N_2O_4Na^+$ $[M+Na]^+$ 317.1477; found 317.1479.

*4.1.2. 1,5-Diethyl 3,3-dimethyl pentane-1,3,3,5-tetracarboxylate (**3g**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.19 (t, 6H, J=7.2 Hz), 2.12–2.17 (m, 4H), 2.21–2.26 (m, 4H), 3.67 (s, 6H), 4.06 (q, 4H, J_1=7.2 Hz, J_2=14.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.34, 28.46, 29.67, 52.77, 56.35, 60.79, 171.26, 172.65. MS (ESI): m/z=355.4 $[M+Na]^+$. HRMS calcd for $C_{15}H_{24}O_8Na^+$ $[M+Na]^+$ 355.1363; found 355.1366.

*4.1.3. Dimethyl 4-nitroheptanedioate (**4a**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.09–2.31 (m, 4H), 2.37–2.48 (m, 4H), 3.69 (s, 6H), 4.65 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=28.76, 30.02, 52.15, 86.80, 172.37. MS (ESI): m/z=256.1 $[M+Na]^+$. HRMS calcd for $C_9H_{15}O_6NNa^+$ $[M+Na]^+$ 256.0795; found 256.0799.

*4.1.4. Dibutyl 4-nitroheptanedioate (**4c**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.93 (t, 3H, J=7.2 Hz), 2.31–1.43 (m, 4H), 1.56–1.65 (m, 4H), 2.07–2.49 (m, 8H), 4.10 (t, 6H, J=6.8 Hz), 4.61–4.69 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.27, 14.34, 14.41, 28.85, 30.38, 61.14, 92.12, 171.90. MS (ESI): m/z=340.2 $[M+Na]^+$. HRMS calcd for $C_{15}H_{27}O_6NNa^+$ $[M+Na]^+$ 340.1733; found 340.1735.

*4.1.5. Dimethyl 4-(2-(methoxycarbonyl)ethyl)-4-nitroheptanedioate (**5a**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.17–2.62 (m, 12H), 3.62 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=28.58, 30.35, 52.20, 92.03, 172.33. MS (ESI): m/z=342.3 $[M+Na]^+$. HRMS calcd for $C_{13}H_{21}NO_8Na^+$ $[M+Na]^+$ 342.1159; found 342.1156.

*4.1.6. Dibutyl 4-(2-(butoxycarbonyl)ethyl)-4-nitroheptanedioate (**5c**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.89 (t, 9H, J=7.2 Hz), 1.28–1.37 (m, 6H), 1.52–1.59 (m, 6H), 2.23 (s, 6H), 2.24 (s, 6H), 4.03 (t, 6H, J=6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.85, 19.27, 28.84, 30.42, 30.73, 65.07, 92.10, 171.98. MS (ESI): m/z=368.5 $[M+Na]^+$. HRMS calcd for $C_{22}H_{39}NO_8Na^+$ $[M+Na]^+$ 468.2568; found 468.2568.

4.2. General procedure for the Michael addition of active methylenes to dienones (7a as an example)

A mixture of malononitrile (**2a**) (66 mg, 1 mmol), dibenzylidene acetone (**6a**) (234 mg, 1 mmol), tributylphosphine (25 μL, 0.1 mmol), and anhydrous CH_2Cl_2 (5.0 mL) was magnetically stirred in a flask under nitrogen atmosphere at room temperature. The reaction progress was monitored by thin layer chromatography (TLC) until the starting materials were completely consumed. Then, the reaction mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3×10 mL), the organic phase was washed with brine (10 mL), dried over anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the residue was subjected to chromatography on a silica gel (200–300 mesh) column using petroleum ether/ethyl acetate (4:1) as eluent to afford **7a** (286 mg, 95% yield) as a light yellow solid (mp 170–171 °C).

*4.2.1. 2,6-Bis(4-cyanophenyl)-4-oxocyclohexane-1,1-dicarbonitrile (**7e**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.84–2.91 (4H, m), 3.64 (2H, t, J=6.0 Hz), 7.23 (4H, d, J=7.6 Hz), 8.32 (4H, d, J=7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=41.72, 45.48, 53.59, 112.93, 113.94, 117.79, 129.25, 129.87, 133.05, 139.50, 202.83. MS (ESI): m/z=349.6 $[M-H]^-$. HRMS calcd for $C_{22}H_{13}N_4O^-$ $[M-H]^-$ 349.1168; found 349.1165.

*4.2.2. 4-Oxo-2,6-dim-tolylcyclohexane-1,1-dicarbonitrile (**7i**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.36 (6H, s), 3.01–3.14 (4H, m), 3.77 (2H, t, J=6.4 Hz), 7.09–7.31 (8H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.71, 30.52, 42.64, 45.74, 114.20, 126.09, 129.23, 130.01, 130.52, 135.36, 139.17, 205.03. MS (ESI): m/z=327.6 $[M-H]^-$. HRMS calcd for $C_{22}H_{19}N_2O^-$ $[M-H]^-$ 327.1503; found 327.1507.

*4.2.3. 2-(4-Cyanophenyl)-4-oxo-6-phenylcyclohexane-1,1-dicarbonitrile (**7l**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.04 (1H, dd, J_1=16.4 Hz, J_2=5.2 Hz), 3.12–3.18 (3H, m), 3.85–3.93 (2H, m), 7.31–7.33 (2H, m), 7.42–7.47 (5H, m), 7.71 (2H, d, J=7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=41.96, 42.07, 44.49, 44.87, 46.05, 113.35, 113.60, 118.60, 129.11, 129.32, 129.81, 132.95, 134.75, 140.07, 203.85. MS (ESI): m/z=324.2 $[M-H]^-$. HRMS calcd for $C_{21}H_{14}N_3O^-$ $[M-H]^-$ 324.1215; found 324.1219.

*4.2.4. Ethyl 1-cyano-4-oxo-2,6-dip-tolylcyclohexanecarboxylate (**7o**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.92 (3H, t, J=7.2 Hz), 2.31 (3H, s), 2.33 (3H, s), 2.77 (1H, dd, J_1=16.4 Hz, J_2=3.6 Hz), 3.02 (1H, dd, J_1=16.4 Hz, J_2=5.6 Hz), 3.10–3.17 (2H, m), 3.78–3.87 (2H, m), 3.90–3.93 (2H, m), 7.03–7.26 (8H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.69, 21.31, 42.13, 42.26, 43.35, 47.99, 56.00, 62.94, 128.55, 128.61, 129.60, 133.96, 134.64, 138.32, 138.66, 166.53, 207.73. MS (ESI): m/z=375.1 M^+. HRMS calcd for $C_{24}H_{24}NO_3^-$ $[M-H]^-$ 374.1746; found 374.1770.

*4.2.5. Ethyl 2,6-bis(4-chlorophenyl)-1-cyano-4-oxocyclohexanecarboxylate (**7p**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.96 (3H, t, J=7.2 Hz), 2.77 (1H, dd, J_1=16.6 Hz, J_2=3.6 Hz), 3.00 (1H, dd, J_1=16.6 Hz, J_2=5.6 Hz), 3.08–3.17 (2H, m), 3.84–3.93 (4H, m, $COCH_2$), 7.09–7.33 (8H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.76, 42.67, 42.14, 42.78, 47.43, 55.61, 63.37, 118.21, 129.20, 130.07, 134.64, 134.98, 135.26, 135.82, 166.20, 206.52. MS (ESI): m/z=415.9 M^+. HRMS calcd for $C_{22}H_{18}Cl_2NO_3^-$ $[M-H]^-$ 414.0669; found 414.0663.

*4.2.6. Ethyl 1-cyano-2,6-bis(4-nitrophenyl)-4-oxocyclohexanecarboxylate (**7q**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.80 (3H, t, J=7.2 Hz), 2.77 (1H, dd, J_1=16.4 Hz, J_2=2.8 Hz), 2.91 (1H, dd, J_1=16.8 Hz, J_2=5.2 Hz), 3.03–3.10 (2H, m), 3.72–3.97 (4H, m), 7.23 (2H, d, J=8.4 Hz); 7.35 (2H, d, J=8.0 Hz); 8.03 (4H, t, J=9.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.63, 41.08, 42.07, 42.49, 47.27, 54.73, 63.74, 117.34, 124.02, 129.67, 143.85, 148.02, 165.54, 204.96. MS (ESI): m/z=437.0 M^+. HRMS calcd for $C_{22}H_{18}N_3O_7^-$ $[M-H]^-$ 436.1223; found 436.1220.

*4.2.7. Ethyl 1-cyano-4-oxo-2,6-dim-tolylcyclohexanecarboxylate (**7r**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.91 (3H, t, J=7.2 Hz), 2.31 (3H, s), 2.33 (3H, s), 2.78 (1H, dd, J_1=17.2 Hz, J_2=3.6 Hz), 3.02 (1H, dd, J_1=16.6 Hz, J_2=5.6 Hz), 3.11–3.18 (2H, m), 3.77–3.86 (2H, m), 3.90–3.94 (2H, m), 6.96–7.24 (8H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.67, 21.66, 42.03, 42.46, 43.31, 48.38, 55.90, 62.88, 118.70, 125.62, 125.76, 128.79, 128.88, 129.29, 129.54, 137.01, 137.65, 138.50, 138.61, 166.55, 207.58. MS (ESI): m/z=375.1 M^+. HRMS calcd for $C_{24}H_{24}NO_3^-$ $[M-H]^-$ 374.1746; found 374.1751.

*4.2.8. Ethyl 2,6-bis(3-chlorophenyl)-1-cyano-4-oxocyclohexanecarboxylate (**7s**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.97 (3H, t, J=7.2 Hz), 2.78 (1H, dd, J_1=16.6 Hz, J_2=3.6 Hz), 3.02 (1H, dd, J_1=16.6 Hz, J_2=5.2 Hz), 3.08–3.20 (2H, m), 3.87–3.94 (4H, m), 7.06–7.34 (8H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.73, 41.64, 42.27, 42.86, 47.85, 55.50, 63.47, 109.97, 118.01, 126.56, 126.87, 128.96, 129.20, 130.37, 134.75, 134.97, 138.72, 139.25, 166.09, 206.19.

MS (ESI): m/z=415.0 M^+. HRMS calcd for $C_{22}H_{18}Cl_2NO_3^-$ $[M-H]^-$ 414.0669; found 414.0665.

*4.2.9. Ethyl 1-cyano-4-oxo-2-phenyl-6-p-tolylcyclohexanecarboxylate (**7t**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.90 (3H, t, J=7.2 Hz), 2.32 (3H, s), 2.79 (1H, dd, J_1=16.4 Hz, J_1=3.2 Hz), 3.04 (1H, dd, J_1=14.6 Hz, J_2=5.6 Hz), 3.09–3.20 (2H, m), 3.77–3.96 (4H, m), 7.02–7.32 (9H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.64, 21.29, 41.86, 42.16, 42.34, 42.51, 43.12, 43.35, 48.09, 48.17, 62.96, 118.70, 128.51, 128.68, 128.75, 128.91, 129.62, 133.93, 134.52, 137.70, 138.71, 166.58, 207.63. MS (ESI): m/z=361.2 M^+. HRMS calcd for $C_{23}H_{23}NO_3^+$ M^+ 361.1678; found 361.1675.

*4.2.10. Ethyl 1-cyano-2-(4-nitrophenyl)-4-oxo-6-phenylcyclohexane carboxylate (**7u**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.81 (3H, t, J=7.2 Hz), 2.77 (1H, dd, J_1=16.0 Hz, J_2=2.0 Hz), 2.96–3.15 (3H, m), 3.73 (2H, q, J_1=14.0 Hz, J_2=6.8 Hz), 3.96 (1H, t, J=6 Hz), 4.03 (1H, dd, J_1=13.6 Hz, J_2=2.0 Hz), 7.03–7.09 (2H, m), 7.21–7.27 (3H, m), 7.46 (2H, d, J=8.4 Hz), 8.05 (2H, d, J=8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.43, 41.79, 42.49, 48.17, 53.73, 55.06, 63.23, 117.99, 123.82, 128.51, 128.85, 128.92, 129.71, 136.42, 144.78, 147.67, 165.75, 205.89. MS (ESI): m/z=392.2 M^+. HRMS calcd for $C_{22}H_{20}N_2O_5^+$ M^+ 392.1372; found 392.1376.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.11.103

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