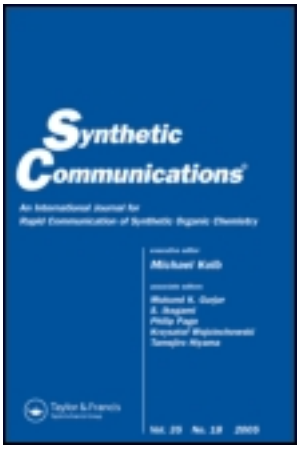

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One-Pot Multicomponent Michael and Thorpe-Ziegler Reaction of Aryl Methyl Ketones

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ONE-POT MULTICOMPONENT MICHAEL AND THORPE–ZIEGLER REACTION OF ARYL METHYL KETONES

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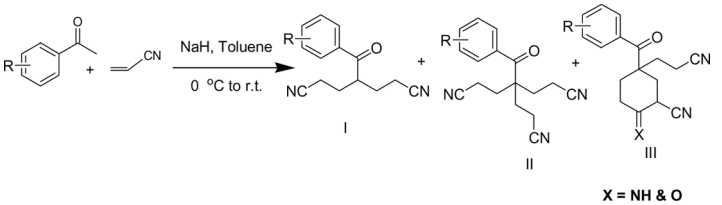
Institute of Himalayan Bioresource Technology, Palampur, India

GRAPHICAL ABSTRACT



Abstract *A regioselective base-promoted Michael and Thorpe–Ziegler reaction between aryl methyl ketones and α,β-unsaturated nitrile was carried out in a single step. Different functional groups in addition to active positions were tolerated under this condition. Results indicated that the reaction proceeds in a consecutive manner as double Michael, triple Michael, and Thorpe–Ziegler condensation. By applying click chemistry, double Michael adducts were converted to bis-tetrazoles, which have broad applications in coordination and medicinal chemistry.*

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Keywords Aryl methyl ketone; tetrazoles; Thorpe–Ziegler condensation; triple Michael reaction

INTRODUCTION

The Michael reaction involves C-C bond formation and has wide applications in organic synthesis.[1–3] Several acidic and basic conditions have been tried to improve the Michael reaction. Side products, frequently encountered in the presence of strong basic conditions, are due to secondary condensation, polymerization, and simultaneous addition at all the reactive sites.[4] Few reactions have been reported for

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C-C bond formation through double Michael reaction in one pot.[5] Forrester et al.[6] reported partial double Michael adduct formation while preparing the mono-adduct from aryl methyl ketone and methacrylonitrile in the presence of potassium methoxide in benzene.

Over the past few years, we have been actively engaged in the development of the Michael reaction under basic and Lewis acidic conditions.[7,8] We report here an efficient one-pot regioselective triple Michael reaction and Thorpe–Ziegler condensation under basic conditions using NaH. The reaction resulted in the formation of three C-C bonds, involving construction of a quaternary carbon center, which has attracted much attention in recent years.[9,10] To the best of our knowledge, this is the first example of regioselective triple Michael and Thorpe–Ziegler condensation under an efficient atom-economical conversion of aryl methyl ketones to electron-deficient alkenes in the presence of NaH in toluene.

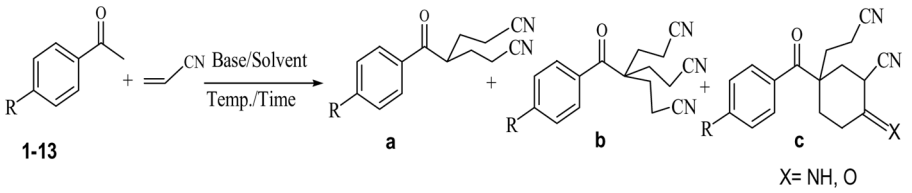
RESULTS AND DISCUSSION

According to Basu et al.[7] aryl methyl ketones react with α,β-unsaturated compounds on a KF-alumina surface, yielding selectively double Michael products. Further addition to the double Michael adduct has not been reported earlier, probably because of the large size of bases used such as KO^{t}Bu and KF-Al_2O_3, which were successful only in double Michael addition. In triple Michael addition, these bases might have caused steric hindrance and were unable to create the carbanion required to produce the triple Michael adduct. A set of different bases were tested in the reactions at 0 °C to room temperature using toluene and a solid surface (Table 1). However, success was achieved with the formation of double Michael adduct. Although aryl methyl ketone (*pKa* ca. 18–30) is not a superior Michael

Table 1. Michael and Thorpe–Ziegler reaction

Entry (%)	Reactant (R)	Base/ equivalent	Conditions (temp./time)	Solvent	Yield (%)[a] a	b	c	Total yield (%)
1	H	NaH/1	rt/12 h	Toluene	10	15	—	25
2	H	NaH/2	rt/12 h	Toluene	15	20	5[b]	40
3	H	NaH/3	rt/12 h	Toluene	10	40	15[b]	65
4	H	NaH/4	rt/12 h	Toluene	20	25	5[b]	50
5	H	NaH/5	rt/12 h	Toluene	5	10	—	15
6	Br	NaH/3	rt/12 h	Toluene	10	35	15[c]	60
7	OMe	NaH/3	rt/12 h	Toluene	15	30	b + c[c]	45
8	Me	NaH/3	rt/12 h	Toluene	10	35	b + c[c]	45
9	H	NaOEt/3	rt/12 h	Toluene	15	Trace	Trace[b]	15
10	H	KO^{t}Bu/3	rt/12 h	Toluene	20	Trace	Trace[b]	20
11	H	KF-Al_2O_3	60 °C/12 h	—	50	—	—	50
12	H	NaH/3	rt/12 h	THF	5	Trace	—	5
13	H	NaH/3	rt/12 h	DMF	3	Trace	—	3

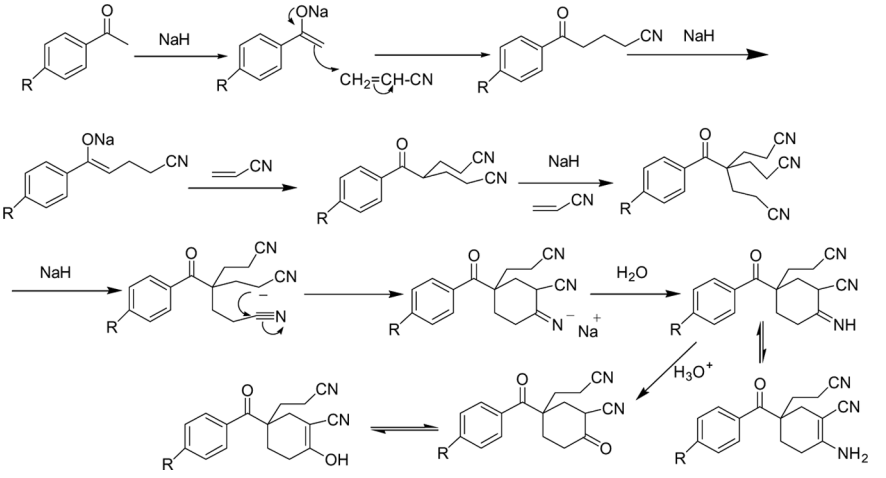
[a]Isolated yields for pure compounds.
[b]X=NH.
[c]X=O.



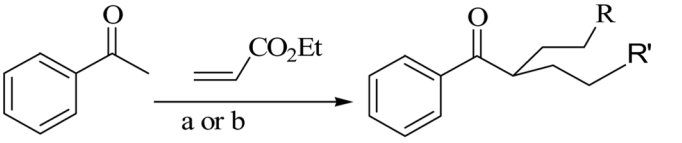
Scheme 1. Regioselective Michael and Thorpe–Ziegler reaction.

donor, we developed a novel and efficient triple Michael and Thorpe–Ziegler condensation reaction using acetophenone in the presence of NaH to solve the problem in basic chemistry (Scheme 1). The small size of NaH could be a good choice to minimize steric hindrance and facilitate the generation of carbanion, leading to the formation of a triple Michael adduct in good yields. NaH (3 eq.) at 0 °C to room temperature was most suitable to generate the carbanion of aryl methyl ketone to produce **3a** (10%), **3b** (40%), and **3c** (15%) in a consecutive manner. Final compounds were characterized by infrared (IR), NMR, and high-resolution mass spectroscopic (HRMS) (electrospray ionization) data. The overall isolated yield of the reaction was 65% in toluene. Under similar reaction conditions, 4-bromoacetophenone also produced **6a** (10%), **6b** (35%), and a mixture of **6b** and **6c**. Repeated silica-gel column chromatography of the mixture of **6b** and **6c** yielded **6c** (15%). Under such conditions, the halogen group of 4-bromoacetophenone was tolerated. 4-Methoxy acetophenone **7** and 4-methylacetophenone **8** under the same conditions yielded double Michael (**7a** 15% and **8a** 10%), triple Michael (**7b** 30% and **8b** 35%), and Thorpe–Ziegler products (**7b, 7c** and **8b, 8c** as mixtures).

By using NaOEt and KO^{t}Bu (3 eq.) in toluene, double Michael products **9a** and **10a** were obtained in 15–20% yield (Table 1) and traces of **9b, 10b** and **9c, 10c** were isolated. KF-Al_2O_3 (Table 1, entry 11) gave the maximum yield of double



Scheme 2. Proposed mechanism of Michael and Thorpe–Ziegler reaction.

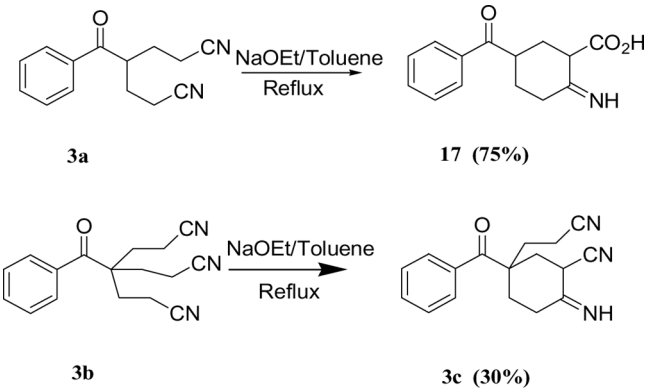


1

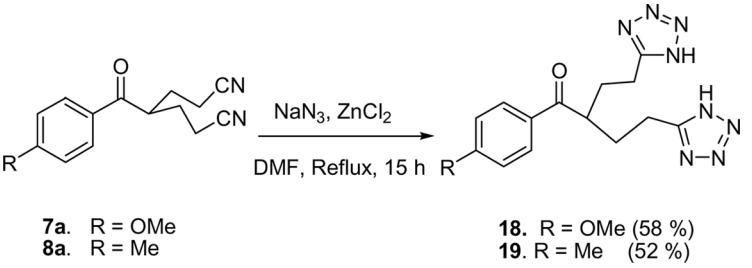
14. R= -CO_2Et, R' = -CO_2Et (30[a] % & 25[b] %)
15. R=-CO_2Et, R' = -CO_2H (5[a] % & 7[b] %)
16. R= -CO_2H, R' = -CO_2H (10[a] % & 12[b] %)

Scheme 3. Michael reaction using KF-Al_2O_3–NaH and NaOEt conditions. (a) KF-alumina NaH (1:1) at 0 °C to rt for 12 h; (b) NaOEt, toluene at 0 °C to rt for 12 h.

Michael product **11a** (50%) under solvent-free conditions. In another study, the reaction was performed using different solvents [tetrahydrofuran (THF) and dimethylformamide (DMF)] under various concentrations of NaH. Contrary to toluene, THF and DMF solvents under the same basic conditions afforded poor yields of double and traces of triple Michael products (Table 1, entries 12 and 13). Encouraged by the significant results obtained with 3 eq. of NaH in toluene at 0 °C to room temperature (entry 3), we further planned to convert aryl methyl ketone directly to the Thorpe–Ziegler condensation product by increasing NaH upto 5 eq. in the reaction mixture. This did not happen, and very poor yields (5–10%) of **5a** and **5b** were obtained. After several parallel studies, we concluded that 3 eq. NaH in toluene was a highly selective method for obtaining double and triple Michael and Thorpe–Ziegler condensation products. Change of substituents in the aromatic ring of the aryl methyl ketone had no effect on carbonyl methyl. Enolates of acetophenones were produced under NaH basic conditions (Scheme 2), which further participated in the Michael reaction. Substituted carbon of acetophenone is more efficient Michael donor than unsubstituted carbon, and therefore the substituted ketone picked up one unsaturated nitrile to produce double Michael adduct. Triple Michael addition also occurred on the same carbon atom and produced triple Michael adducts. After triple Michael addition, further carbanion generated next to the nitrile carbon participated



Scheme 4. Thorpe–Ziegler condensation of double (**3a**) and triple Michael (**3b**) products.



Scheme 5. Bis-tetrazoles from double Michael product.

in Thorpe–Ziegler-type condensation in one pot. Final products were obtained as double and triple Michael adducts along with Thorpe–Ziegler condensation product. When we treated acetophenone with ethyl acrylate (Scheme 3) in the presence of KF-Al_2O_3–NaH and NaOEt in basic conditions at 0 °C to room temperature for 12 h, the reaction ended with the formation of major pimelate ester **14** and its mono and bis-carboxylic acids (**15** and **16**).

Thorpe–Ziegler condensation reaction was also performed independently from **3a** and **3b** under NaOEt (0.44 mmol) base in dry toluene (3 mL), refluxing for 4 h. Completion of the reaction was monitored by thin-layer chromatography (TLC), and purification was performed by silica-gel column chromatography, affording **17** (75%) and **3c** (30%) (Scheme 4). This proved that Thorpe–Ziegler condensation products are also possible directly from double and triple Michael adducts. To broaden the scope of the reaction, bis-tetrazoles were prepared from double Michael products using click chemistry, which have wide applications in coordination chemistry[11–14] and as surrogates for carboxylic acids.[15] Compounds **12a** and **13a** were treated separately with NaN_3 and $ZnCl_2$ in DMF (3 mL) and refluxed for 15 h. Progress of the reaction was monitored on TLC, and products were purified by silica-gel column chromatography yielding **18** (58%) and **19** (52%) (Scheme 5). In addition to tetrazoles, derivatives of this reaction have applications for the synthesis of oxadiazoles,[16] which have analgesic, herbicidal, muscle relaxant and tranquilizing effects. The reaction products are also useful in development of dendrimers required in drug delivery systems.[17–19] The reaction will also facilitate the synthesis of β-amino acids, which have many therapeutic uses in medicines.[20]

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded using a Bruker Avance 300 spectrometer operating at 300 MHz (^1H) and 75 MHz (^{13}C). Spectra were recorded at 25 °C in $CDCl_3$, C_3D_6O, or C_5D_5N with tetramethylsilane (TMS) as internal standard. Chemical shifts were recorded in δ (ppm) relative to the TMS signal, coupling constants (J) are given in hertz, and multiplicities of signals are reported as follows: s, singlet; d, doublet; t, triplet; m, multiplet; and br, broad singlet. Mass spectra were recorded on a Waters Q-TOF-MS with ESI using Waters Masslynx software. Each sample was dissolved in acetonitrile–water (50:50) and directly injected into the ESI

source at a flow rate of 5 μL/min. All reagents of high quality were purchased from Sigma Aldrich. Solvents were procured from SD Fine chemicals. Toluene was freshly distilled before use and dried over 4-Å molecular sieves. NaH (60%) was washed with hexane and dried under reduced pressure. Commercial reagents and solvents were of analytical grade and were purified by standard procedures prior to use. TLC was performed using precoated silica-gel plates 60 F_{254}.

General Procedure for Michael and Thorpe–Ziegler Reaction

Acetophenone (1 g, 8.32 mmol) was dissolved in 3 mL toluene and cooled to 0 °C, and then NaH (24.96 mmol, 3.0 eq.) was added. After 5 min, acrylonitrile (16.64 mmol, 2 eq.) was added at 0 °C. The reaction mixture was stirred at room temperature for 12 h until completion, monitored by TLC. The reaction mixture was acidified with 2 N HCl and extracted with ethylacetate (3 × 10 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The reaction product was purified by silica-gel column chromatography eluted with ethylacetate–hexane, 1:9 to 3:7 (v/v), to afford corresponding products (**3, 6, 7**, and **8**).

Selected Data for 3a–c, 6a–c, 7a, 7b, 8a, and 8b

4-Benzoyl heptanedinitrile (3a). Yield: 188 mg (10%); colorless oil. IR (KBr): 2926, 2854, 2246, 1659, 1583, 1470, 1421, 1391, 1256, 1201, 1171, 1075, 965, 838, 766 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.87–1.92 (m, 2H), 2.14–2.47 (m. 6H), 3.78–3.84 (m, 1H), 7.52 (m, 2H), 7.64 (m, 1H), 8.02 (d, J = 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.94 (2C), 28.43 (2C), 42.98, 118.87 (2C), 128.40 (2C), 129.94 (2C), 134.21, 135.91, 200.82. HRMS (ESI) data: m/z calcd. for $C_{14}H_{15}N_2O$ $[M + H]^+$: 227.2818; found: 227.2881.

4-Benzoyl-4(2-cyanoethyl) heptanedinitrile (3b). Yield: 930 mg (40%); white solid; mp 96–98 °C. IR (KBr): 2926, 2854, 2246, 1659, 1583, 1470, 1421, 1391, 1256, 1201, 1171, 1075, 965, 838, 766 cm^{-1}. ^1H NMR (300 MHz, C_3D_6O): δ = 2.30–2.36 (m, 6H), 2.51–2.56 (m, 6H), 7.51–7.55 (m, 2H), 7.59–7.64 (m, 1H), 7.81–7.83 (m, 2H). ^{13}C NMR (75 MHz, C_3D_6O): δ = 12.54 (3C), 29.44 (3C), 53.63, 119.98 (3CN), 128.27 (2C), 129.62 (2C), 132.59, 138.87, 204.97. HRMS (ESI) data: m/z calcd. for $C_{17}H_{18}N_3O$ $[M + H]^+$: 280.3444; found: 280.3444.

5-Benzoyl-5-(2-cyanoethyl)-2-iminocyclohexane carbonitrile (3c). Yield: 348 mg (15%); colorless oil. IR (KBr): 3433, 3321, 2925, 2242, 2199, 1714, 1675, 1629, 1507, 1458, 1378, 1266, 1227, 694. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.87 (m, 4H), 2.24–2.25 (m, 2H), 2.30–2.33 (m, 2H), 2.35–2.39 (m, 2H), 2.97–3.03 (m, 1H), 7.45–7.48 (m, 2H), 7.56–7.58 (m, 1H), 7.69–7.72 (m, 2H), 7.81 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.36, 24.52, 25.31, 29.40, 30.95, 33.03, 33.38, 49.06, 88.48, 117.26, 118.92, 127.61 (2C), 128.57 (2C), 132.58, 136.68, 150.56, 168.80, 203.21 HRMS (ESI) data: m/z calcd. for $C_{17}H_{18}N_3O$ $[M + H]^+$: 280.3444; found 280.3446.

4-p-Bromo-benzoyl heptanedinitrile (6a). Yield: 153.5 mg (10%); colorless oil. IR (KBr): 2926, 2854, 2250, 1659, 1583, 1478, 1428, 1391, 1256, 1201, 1178, 1075,

975 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.83–1.94 (m, 2H), 2.12–2.22 (m, 2H), 2.24–2.35 (m, 2H), 2.38–2.48 (m, 2H), 3.76–3.81 (m, 1H), 7.66–7.70 (m, 2H), 7.86–7.92 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.39 (2C), 27.56 (2C), 43.32, 119.03 (2CN), 127.12, 130.31 (2C), 132.99 (2C), 134.98, 200.25. HRMS (ESI) data: m/z calcd. for $C_{14}H_{14}BrN_2O$ $(M+H)^+$: 306.1778; found: 306.1707.

4-p-Bromo-benzoyl-4(2-cyanoethyl) heptanedinitrile (6b). Yield: 628.92 mg (35%); white solid; mp 128–130 °C. IR (KBr): 2946, 2894, 2246, 1659, 1588, 1470, 1421, 1391, 1276, 1201, 1161, 1095, 965, 848, 776 cm^{-1}. ^1H NMR (300 MHz, C_3D_6O): δ = 2.25–2.31 (m, 6H), 2.46–2.51 (m, 6H), 7.68–7.73 (m, 2H), 7.78–7.82 (m, 2H). ^{13}C NMR (75 MHz, C_3D_6O): δ = 12.48 (3C), 29.90 (3C), 53.68, 119.86 (3CN), 127.07, 130.97 (2C), 132.81 (2C), 137.57, 203.91. HRMS (ESI) data: m/z calcd. for $C_{17}H_{17}BrN_3O$ $(M+H)^+$: 359.2405; found: 359.2433.

5-p-Bromo-benzoyl-5-(2-cyanoethyl)-2-oxo-cyclohexanecarbonitrile (6c). Yield: 270.70 mg (15%); colorless oil. IR: 3434, 2926, 2360, 2342, 2247, 1670, 1583, 1508, 1458, 1204, 1073, 1008, 721. ^1H NMR (300 MHz, C_3D_6O): δ = 2.38–2.55 (m, 8H), 2.65–2.68 (m, 2H), 3.33–3.36 (m, 1H), 7.72 (d, J = 7.9 Hz, 2H), 7.84 (d, J = 7.9 Hz, 2H). ^{13}C NMR (75 MHz, C_3D_6O): δ = 12.64, 26.69, 28.17, 29.44, 36.09, 49.34, 119.20, 121.21, 127.40, 129.10 (2C), 132.43 (2C), 137.70, 203.84, 205.77. HRMS (ESI): m/z calcd. for $C_{17}H_{16}BrN_2O_2$ $(M+H)^+$: 360.2252; found: 360.2250.

4-p-Methoxy-benzoyl heptane dinitrile (7a). Yield: 256.04 mg (15%); colorless oil. IR (KBr): 2926, 2246, 1659, 1583, 1470, 1421, 1201, 1171, 1075, 965. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.86–1.91 (m, 2H), 2.16–2.32 (m, 4H), 2.36–2.40 (m, 2H), 3.77–3.81(m, 1H), 3.89 (s, 3H), 6.97–7.02 (m, 2H), 7.99–8.03 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.12 (2C), 27.69 (2C), 42.52, 55.73, 114.48 (2C), 118.97 (2CN), 129.14, 130.98 (2C), 164.60, 199.24. HRMS (ESI) data: m/z calcd. for $C_{15}H_{17}N_2O_2$ $(M+H)^+$: 257.3078; found: 257.3006.

4-p-Methoxy-benzoyl-4(2-cyanoethyl) heptane dinitrile (7b). Yield: 618.12 mg (30%); white solid; mp 99–101 °C. IR (KBr): 2936, 2844, 2276, 1669, 1573, 1490, 1421, 1371, 1256, 1214, 1171, 1075, 975, 848; ^1H NMR (300 MHz, C_3D_6O): δ = 2.41–2.43 (m, 6H), 2.48–2.55 (m, 6H), 3.93 (s, 3H), 7.03–7.06 (m, 2H), 7.96–7.99 (m, 2H). ^{13}C NMR (75 MHz, C_3D_6O): δ = 13.30 (3C), 30.40 (3C), 54.13, 56.53, 115.25 (2C), 120.72 (3CN), 129.69, 130.56, 132.16 (2C), 164.50, 202.51. HRMS (ESI) data: m/z calcd. for $C_{18}H_{20}N_3O_2$ $(M+H)^+$: 310.3704; found: 310.3704.

4-p-Methyl benzoyl heptane dinitrile (8a). Yield: 179 mg (10%); colorless oil. IR (KBr): 2956, 2824, 2249, 1654, 1582, 1460, 1431, 1371, 1258, 1181, 1095, 968, 858, 762. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.90–1.91 (m, 2H), 2.14–2.32 (m, 4H), 2.36–2.40 (m, 2H), 2.43 (s, 3H), 3.78–3.84 (m, 1H), 7.34 (d, J = 7.9 Hz, 2H), 7.93 (d, J = 8.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.21 (2C), 21.82, 27.54 (2C), 42.87, 118.91 (2CN), 128.68 (2C), 130.02 (2C), 133.64, 145.58, 200.51. HRMS (ESI): m/z calcd. for $C_{15}H_{17}N_2O$ $(M+H)^+$: 241.3084; found: 241.3044.

4-p-Methyl-benzoyl-4(2-cyanoethyl) heptane dinitrile (8b). Yield: 764.96 mg (35%); white solid; mp 150–152 °C. IR (KBr): 2916, 2824, 2236, 1669, 1593, 1480, 1428, 1398, 1251, 1214, 1170, 1078, 964, 834. ^1H NMR (300 MHz,

C_3D_6O): δ = 2.06–2.09 (br, 2H), 2.31–2.36 (m, 2H), 2.41 (s, 3H), 2.49–2.54 (m, 6H), 7.36 (d, J = 8.0, 2H), 7.79 (d, J = 8.0 Hz, 2H). ^{13}C NMR (75 MHz, C_3D_6O): δ = 13.19 (3C), 21.88, 31.09 (3C), 54.21, 120.64 (3CN), 129.38 (2C), 130.56 (2C), 136.52, 144.17, 204.64. HRMS (ESI): m/z calcd. for $C_{18}H_{20}N_3O$ $(M + H)^+$: 294.3710; found: 294.3710.

General Procedure for 14, 15, and 16

Condition a. A mixture of acetophenone (240.38 mg, 2 mmol) and ethylacrylate (600 mg, 6 mmol) was added separately to dry KF-alumina–NaH (1:1), and the solid was stirred at 0 °C to room temperature for 12 h and monitered by TLC. The reaction mixture was acidified with 2 N HCl and extracted with ethylacetate (3 × 10 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The reaction product was purified by silica-gel column chromatography, eluted with ethylacetate–hexane 1:9 to 5:5 (v/v), and yielded corresponding products **14**–**16**.

Condition b. Acetophenone (0.833 mmol, 1.0 eq.) was dissolved in 3 mL toluene and cooled to 0 °C, and NaOEt (2.499 mmol, 3.0 eq.) was added. After 5 min, ethylacrylate (1.66 mmol, 2 eq.) was added at 0 °C. The reaction mixture was stirred at room temperature for 12 h until completion and was monitored by TLC. The reaction mixture was acidified with 2 N HCl and extracted with ethylacetate (3 × 10 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica-gel column chromatography, eluted with ethylacetate–hexane 1:9 to 5:5 (v/v), and yielded corresponding products **14**–**16**.

Selected Data for 14–17

Diethyl-4-benzoyl heptanedioate (14). Yield: condition a, 192.2 mg (30%); condition b, 66.5 mg (25%); colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10–1.17 (m, 6H), 1.77 (m, 2H), 1.99–2.28 (m, 6H), 3.55–3.59 (m, 1H), 3.97–4.04 (m, 4H), 7.42 (m, 2H), 7.52 (m, 1H), 7.92 (d, J = 7.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.03 (2C), 26.72 (2C), 31.48 (2C), 43.65, 60.30 (2C), 128.23 (2C), 128.64 (2C), 133.20, 136.82, 172.90, 202.82. HRMS (ESI) data: m/z calcd. for $C_{18}H_{25}O_5(M + H)^+$: 321.3881; found: 321.3881.

6-(Ethoxycarbonyl)-4-benzoyl hexanoic acid (15). Yield: condition a, 29 mg (5%); condition b, 17 mg (7%); colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (m, 3H), 1.73–1.75 (m, 2H), 2.00–2.07 (m, 2H), 2.18–2.34 (m, 4H), 3.56–3.58 (br, 1H), 3.98–4.05 (m, 2H), 7.37–7.50 (m, 3H), 7.89–7.91 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.29, 26.53, 27.01, 31.41, 31.70, 43.90, 60.68, 128.52 (2C), 128.96 (2C), 133.56, 136.97, 173.27, 178.46, 203.03. HRMS (ESI) data: m/z calcd. for $C_{16}H_{21}O_5$ $(M + H)^+$: 293.3349; found: 293.3350.

4-Benzoyl heptanedioic acid (16). Yield: condition a, 53 mg (10%); condition b, 26.3 mg (12%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78–1.83 (m, 2H), 2.13–2.19 (m, 2H), 2.35–2.39 (m, 2H), 2.49–2.54 (m, 2H), 3.77–3.81 (m, 1H),

7.44–7.49 (m, 2H), 7.54–7.57 (m, 1H), 8.02–8.05 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.86$ (2C), 31.44 (2C), 43.41, 128.66 (2C), 129.0 (2C), 133.61, 136.73, 179.54, 202.90. HRMS (ESI) data: m/z calcd. for $C_{14}H_{17}O_5$ $(M+H)^+$: 265.2818; found: 265.2818.

5-Benzoyl-2-iminocyclohexane carboxylic acid (17). To a solution of NaOEt (30 mg, 0.440 mmol) in toluene (3 mL), **3a** (100 mg, 0.440 mmol) was added at room temperature and stirred for 5 min. The reaction mixture was refluxed for 4 h and monitored by TLC. The reaction mixture was acidified with 2 N HCl and extracted with ethylacetate (3×10 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure gave oil **17**.

Yield: 81 mg (75% yield); colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.60$–1.61 (m, 2H), 2.17–2.20 (br, 2H), 2.42 (br, 2H), 2.48–2.49 (m, 1H), 7.27–7.38 (m, 5H), 7.85 (brs,1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.06$, 24.55, 29.74, 43.35, 51.51, 126. 45 (2C), 129.15 (2C), 133.41, 143.81, 172.65, 177.87, 203.72. HRMS (ESI) data: m/z calcd. for $C_{14}H_{16}NO_3(M+H)^+$: 246.2818; found: 246.2807.

5-Benzoyl-5-(2-cyanoethyl)-2-iminocyclohexane Carbonitrile 3c (Scheme 4)

To a solution of NaOEt (24.3 mg, 0.358 mmol) in toluene (3 mL), **3b** (100 mg, 0.358 mmol) was added at room temperature and stirred for 5 min. The reaction mixture was refluxed for 4 h, monitored by TLC, acidified with 2 N HCl, and extracted with ethylacetate (3×10 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to yield oil **3c** (30 mg, 30% yield); NMR, HRMS (ESI), and IR data were given previously.

General Procedure for the Synthesis of Bis-Tetrazoles (18 and 19) from Double Michael Product

To a solution of NaN_3 (84.52 mg, 1.3 mmol) in DMF (3 mL), **7a** (125 mg, 0.52 mmol) was added at room temperature. To this, $ZnCl_2$ (88.59 mg, 0.65 mmol) was added. The reaction mixture was refluxed for 15 h until completion and was monitored by TLC. The reaction mixture was acidified with 2 N HCl and extracted with ethylacetate (3×10 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. Compound **18** (58%) was purified by column chromatography, eluting with hexane–ethylacetate 5:5 to 3:7 (v/v) respectively.

2-[2-(1H-Tetrazol-5-yl)ethyl]-1-(4-methoxy phenyl)-4-(1H-tetrazol-5-yl) butan-1-one (18). Yield: 77 mg (58%); brown solid; mp 140–142 °C. IR (KBr): 3447, 3138, 3027, 2958, 2862, 2736, 2634, 2486, 2360, 1666, 1603, 1560, 1458, 1426, 1250, 1098, 1070, 1053. ^{1}H NMR (300 MHz, C_5D_5N): $\delta = 2.28$–2.33 (m, 2H), 2.49–2.57 (m, 2H), 3.22 (br, 4H), 3.68 (s, 3H), 4.01–4.03 (m, 1H), 6.92–6.95 (m, 2H), 8.11–8.14 (m, 2H), 8.70 (s, 2H). ^{13}C NMR (75 MHz, C_5D_5N): $\delta = 21.87$ (2C), 30.39 (2C), 44.30, 55.77, 114.64 (2C), 130.27, 131.36, (2C), 156.89, 164.29, 201.34. HRMS (ESI) data: m/z calcd. for $C_{15}H_{19}N_8O_2(M+H)^+$: 343.3641; found: 343.3641.

2-[2-(1H-Tetrazol-5-yl)ethyl]-4-(1H-tetrazol-5-yl)-1-p-tolylbutan-1-one (19). Yield: 88 mg (52%); brown solid; mp 133–135 °C. IR (KBr): 3447, 3138, 3027, 2958, 2862, 2736, 2634, 2486, 2360, 1666, 1603, 1560, 1458, 1426, 1250, 1098, 1070, 1053. ^{1}H NMR (300 MHz, C_5D_5N): $\delta = 2.20$ (s, 3H), 2.22–2.29 (m, 2H), 2.49–2.56 (m, 2H), 3.13–3.18 (m, 4H), 4.03–4.07(m, 1H), 7.13–7.15 (m, 2H), 8.69–8.70 (m, 2H), 13.20 (br, 2H). ^{13}C NMR (75 MHz, C_5D_5N): $\delta = 21.54$, 21.93 (2C), 30.70 (2C), 44.48, 129.07 (2C), 130.04 (2C), 134.90, 144.66, 157.12, 202.44. HRMS (ESI) data: m/z calcd. for $C_{15}H_{19}N_8O$ $(M + H)^+$: 327.3647; found: 327.3647.

CONCLUSION

In summary, we developed a simple and efficient one-pot method for the synthesis of double and triple Michael and Thorpe–Ziegler condensation reactions of aryl methyl ketones in a consecutive manner. Further, double Michael products were used for synthesis of tetrazoles, which have versatile applications as bidented ligands. We believe that the present innovation will open new vistas in supramolecular chemistry.[21–23] Synthesis of tetrazoles from triple Michael adducts will be reported subsequently.

SUPPORTING INFORMATION

Spectral data for all compounds have been given (see the Supplemental Materials available online).

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REFERENCES

1. Oare, D. A.; Heathcock, C. H. Stereochemistry of the base-promoted Michael addition reaction. In *Topics in Stereochemistry*; E. L. Eliel, S. H. Eilen (Eds.); John Wiley and Sons: New York, 1989; vol. 19, pp. 277–290.
2. Angelo, J. D.; Revial, G.; Costa, P. R. R.; Castro, R. N.; Antunes, O. A. C. Asymmetric Michael addition of chiral imines to phenylvinylsulfone: Preparation of key chiral building blocks for the synthesis of *Aspidosperma* and *Hunteria* alkaloids. *Tetrahedron: Asymmetry* **1991**, *2*, 199–202.
3. Alexakis, A.; Andrey, O. Diamine-catalyzed asymmetric Michael additions of aldehydes and ketones to nitrostyrene. *Org. Lett.* **2002**, *4*, 3611–3614.
4. Beergmann, E. D.; Ginsburg, D.; Pappo, R. *The Michael Reaction in Organic Reaction*; Wiley: London, 1959; vol. 10, pp. 179–555.
5. Giardini, A.; Lesma, G.; Passarella, D.; Perez, M.; Silvani, A. Double Michael reaction of N-carboethoxy-2,3-dihydropyridin-4-one. *Synlett* **2001**, 132–134.
6. Forrester, A. R.; Irikawa, H.; Thomson, R. H.; Woo, S. O.; King, T. J. Iminyls, part 8: Intramolecular addition to nitrile groups. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1712–1720.

7. Basu, B.; Das, P.; Hossain, I. KF-alumina-mediated selective double Michael additions of aryl methyl ketones: A facile entry to the synthesis of functionalized pimelate esters and derivatives. *Synlett* **2004**, *12*, 2224–2226.
8. Basu, B.; Das, P.; Hossain, I. Synthesis of β-amino esters via aza-Michael addition of amines to alkenes promoted on silica: A useful and recyclable surface. *Synlett* **2004**, *14*, 2630–2632.
9. Denissova, I.; Barriault, L. Stereoselective formation of quaternary carbon centers and related functions. *Tetrahedron* **2003**, *59*, 10105–10146.
10. Christoffers, J.; Baro, A. Stereoselective construction of quaternary stereocenters. *Adv. Syn. Catal.* **2005**, *347*, 1473–1482.
11. Stassen, A. F.; Grunert, M.; Mills, A. M.; Spek, A. L.; Haasnoot, J. G.; Reedijk, J.; Linert, W. Linkage isomers of dibromobis(1-(2-methoxyethyl)tetrazole)copper (II) containing either a bromide or a unique tetrazole bridge. *Dalton Trans.* **2003**, 3628–3633.
12. Wu, T.; Zhou, R.; Li, D. Crystallographic characterization of the intermediate in the synthesis of tetrazole from nitrile and azide in water. *Inorg. Chem. Commun.* **2004**, *7*, 492–494.
13. Ostrovskii, V. A.; Pevzner, M. S.; Kofman, T. P.; Shcherbinin, M. B.; Tselinskii, I. V. Energetic 1,2,4-triazoles and tetrazoles: Synthesis, structure, and properties. *Targets Heterocycl. Syst.* **1999**, *3*, 467–526.
14. Thornber, C. W. Isosterism and molecular modification in drug design. *Chem. Soc. Rev.* **1979**, *8*, 563–580.
15. Butler, R. N. Advances in tetrazole chemistry. *Adv. Heterocycl. Chem.* **1977**, *21*, 323–435.
16. Ali, M. A.; Shaharyar, M. Oxadiazole Mannich bases: Synthesis and antimycobacterial activity. *Bioorg. Med. Chem.* **2007**, *17*, 3314–3316.
17. Lankau, H. J.; Unverferth, K.; Grunwald, C.; Hartenhauer, H.; Heinecke, K.; Ster, K. B.; Dost, R.; Egerland, U.; Rundfeldt, C. New GABA-modulating 1,2,4-oxadiazole derivatives and their anticonvulsant activity. *Eur. J. Med. Chem.* **2007**, *42*, 873–879.
18. Dutta, T.; Agashe, H. B.; Gargi, M.; Balasubramanium, P.; Kabra, M.; Jain, N. K. Poly(propyleneimine) dendrimer based nanocontainers for targeting of efavirenz to human monocytes/macrophages in vitro. *J. Drug Targeting* **2007**, *15*, 89–98.
19. Pavlov, G. M.; Korneeva, E. V.; Meijer, E. W. Molecular characteristics of poly(propylene imine) dendrimers as studied with translational diffusion and viscometry. *Colloid Polym. Sci.* **2002**, *280*, 416–423.
20. Lelais, G. R.; Seebach, D. 2-Amino acids–Syntheses, occurrence in natural products, and components of β-peptides. *Biopolymers* **2004**, *76*, 206–243.
21. Rajakumar, P.; Kanagalatha, R. Synthesis and optoelectrochemical properties of novel phenothiazinophanes. *Tetrahedron Lett.* **2007**, *48*, 8496–8500.
22. Bond, A. D.; Fleming, A.; Kelleher, F.; Mcginley, J.; Prajapati, V.; Skovsgaard, S. Synthesis and characterisation of tetra-tetrazole macrocycles. *Tetrahedron* **2007**, *63*, 6835–6842.
23. Sprengard, U.; Schudok, M.; Schmidt, W.; Kretzschmar, G.; Kunz, H. Multiple sialyl Lewis N-glycopeptides: Effective ligands for E-selectin. *Angew. Chem. Int. Ed.* **1996**, *35*, 321–324.