HETEROCYCLES, Vol. 104, No. 3, 2022, pp. 541 - 548. © 2022 The Japan Institute of Heterocyclic Chemistry
Received, 18th October, 2021, Accepted, 29th November, 2021, Published online, 6th December, 2021
DOI: 10.3987/COM-21-14574

FUNCTIONALIZATION OF MELDRUM'S ACID BY DIELS–ALDER APPROACH

Sambasivarao Kotha* and Vidyasagar Gaikwad

Department of Chemistry, Indian Institute of Technology-Bombay, Powai, Mumbai-400076, India, Fax: +91(22)-2572 7152; E-mail: srk@chem.iitb.ac.in

Abstract – We have synthesized several Meldrum's acid derivatives using Diels–Alder reaction as a key step. Here, the key sultine derivative is prepared by rongalite and the sultine derivative is useful as a latent diene.

Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione, a cyclic ester, with an acidic CH_2 group with pKa 4.83[1,2] is valuable synthon to design heterocycles and polycycles.[3] It is widely used in multicomponent reactions.[4] Meldrum's acid derivatives are also beneficial to assemble natural products and also used for synthesis of reactive intermediates and polymers.[5] They are also used in aza-Diels–Alder reaction with different dienophiles.[6] Uracil derivatives[7] are synthesized from trifloroacetyl Meldrum's acid. Gillena and co-workers[8] recently synthesized an antimicrobial compounds from Meldrum's acid. Various Meldrum's acid derivatives **1-5**, shown in Figure 1 are useful in designing diverse polycycles.[9-18]

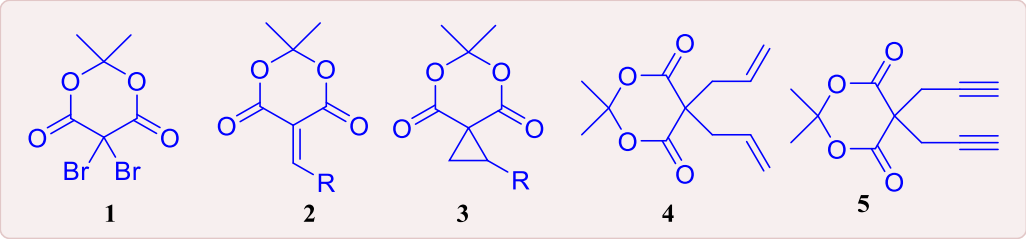
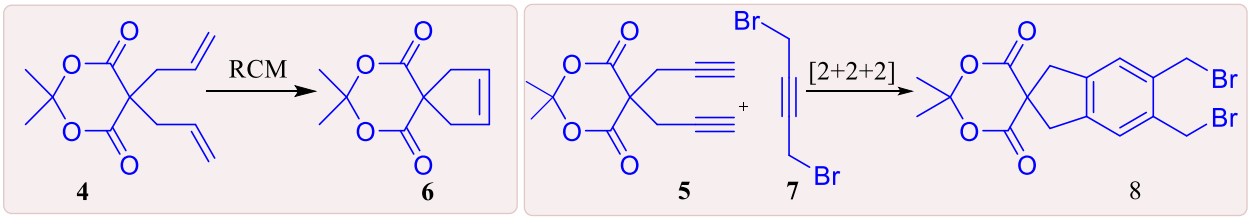


Figure 1. Meldrum's acid derivatives used in organic synthesis

Recently, Kotha and co-workers reported diverse Meldrum's acid derivatives involving a [2+2+2] cycloaddition reaction as a key step. Compound **4** undergo ring-closing metathesis (RCM) to generate cyclopentene derivative **6**. Whereas, dialkyne derivative **5** and monoalkyne **7** undergo cyclotrimerization to generate the dibromo compound **8** with the aid of $Mo(CO)_6$ (Scheme 1) under microwave irradiation conditions in acetonitrile.[19,20] Furthermore, we developed a new route for the synthesis of tetrahydroisoquinoline carboxylic acid derivatives via a [2+2+2] cyclotrimerization.[21,22] In view of our

interest in developing new synthetic strategies,[23a,23b] dibromo compound **8** was identified as a key synthon for the construction of numerous targets. For this purpose, we envisioned an alternative route to the synthesis of dibromo Meldrum's acid derivative **8** starting with commercially available inexpensive materials such as 1,2,4,5-tetramethylbenzene and Meldrum's acid.



Scheme 1. Meldrum's acid derivatives

In view of the importance of Meldrum's acid derivatives,[24] we plan to work out a new methodology for the construction of *o*-xylene intermediate **10** where Meldrum's acid and spiroindane[25] are attached. Dibromo compound **8** may be a key building block for the synthesis of unnatural amino acids[26] and sultine derivatives. Here, we report a new strategy to highly functionalized sultine derivative containing Meldrum's acid via rongalite.[27a,27b] Moreover we also synthesized diverse amino acid derivatives and crownophanes using Diels–Alder reaction and enyne metathesis[28] as well as phenylalanine peptides via cross enyne metathesis and Diels–Alder reaction as key steps.[29]

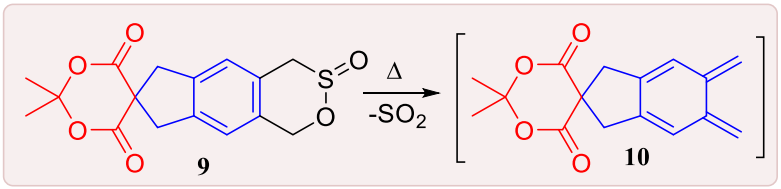
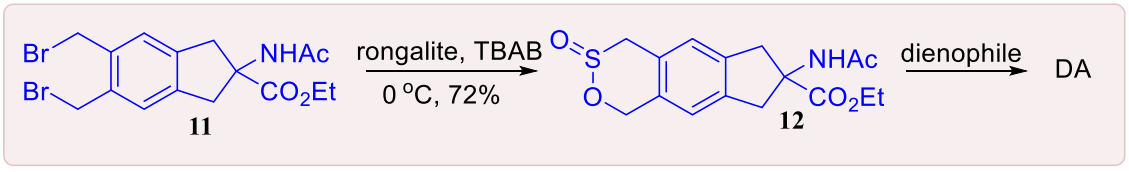


Figure 2. Meldrum's acid containing *o*-xylylene intermediate **10**



Scheme 2. Benzo annulated indane-based AAA derivatives

We found that a selective, one side alkylation of 1,2,4,5-tetrakis(bromomethyl)benzene **13** with an active methylene compound was possible.[30] So, we plan to use this idea with Meldrum's acid (Figure 3).

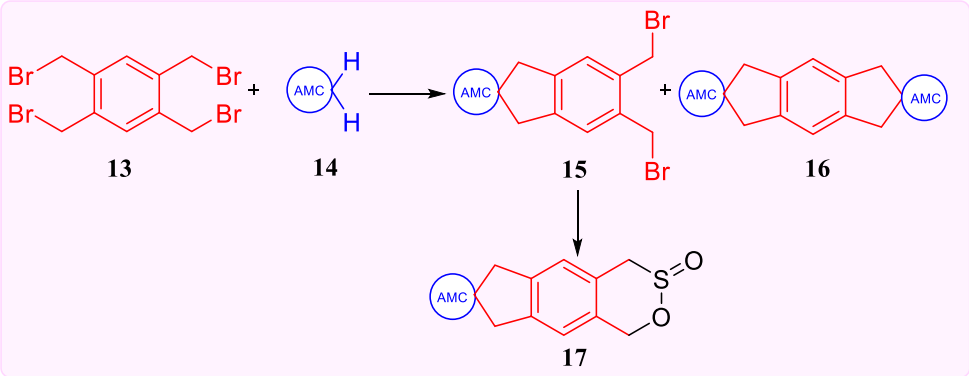
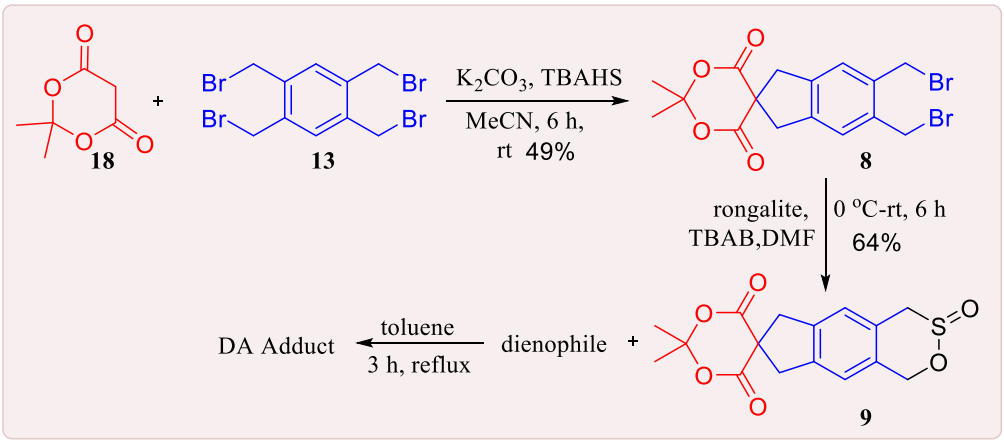


Figure 3. General strategy to synthesize sultine derivatives

To realize the strategy shown in Figure 3, initially, we focused on the synthesis of starting material 1,2,4,5-tetrakis(bromomethyl)benzene **13** using the known procedure.[31] The intermediate **8** was successfully synthesized in 49% yield by coupling of the Meldrum's acid with 1,2,4,5-tetrakis(bromomethyl)benzene **13** using potassium carbonate in the presence of phase-transfer catalyst in acetonitrile at room temperature. Further, the dibromo compound **8** was treated with sodium hydroxymethanesulfinate (rongalite) in the presence of tetrabutylammonium bromide (TBAB) in DMF at 0 °C to generate the key synthon, the sultine derivative **9**, which is a useful precursor for the Diels–Alder reaction[32,33] (Scheme 3). Finally, sultine derivative **9** was treated with various dienophiles (naphthalene-1,4-dione, anthracene-1,4-dione, benzoquinone and 4-phenyl-1,2,4-triazole-3,5-dione) under reflux conditions in toluene to produce the corresponding Diels–Alder adducts (Figure 4).



Scheme 3. Synthesis of sultine, followed by the Diels–Alder reaction

In compounds **19** and **21** we observed Diels–Alder reaction followed by dehydrogenation, however with compound **20** we observed only Diels–Alder product.

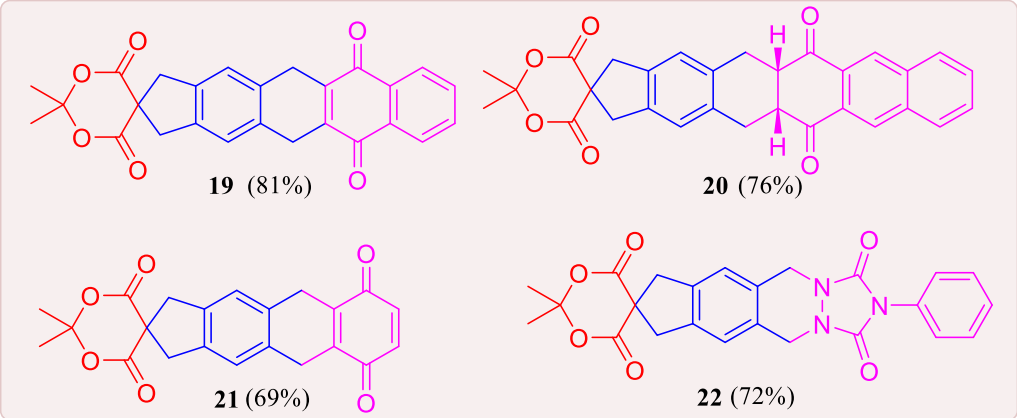
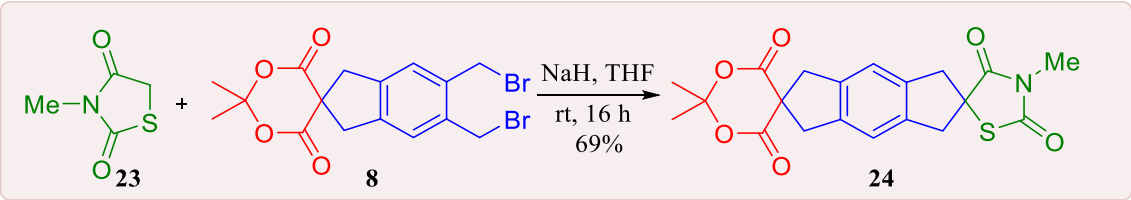


Figure 4. List of Diels–Alder adducts containing Meldrum's acid

To expand the utility of this strategy, the Meldrum's acid derivative **8** was coupled with different heterocycles containing active methylene group like thiazolidine, hydantoin and barbituric acid derivatives. The treatment of dibromo compound **8** with thiazolidine derivative **23** in the presence of sodium hydride (NaH) in THF led to the formation of desired spiro compound **24** in 69% yield (Scheme 4). Unfortunately, we didn't observe the coupling products with *N*,*N*-dimethylhydantoin[34] and *N*,*N*-dimethylbarbituric acid[35] under similar reaction conditions our attempts with different reaction conditions like changing the bases such as K_2CO_3 and Cs_2CO_3 was found to be futile.



Scheme 4. Synthesis of compound **24**

In summary, we developed a new route to spiro Meldrum's acid derivatives via the Diels–Alder reaction. We synthesized various hybrid molecules containing Meldrum's acid unit and the methodology as well as the compound prepared here should find useful applications in medicinal chemistry and also in organic synthesis. Moreover, we provide an alternate route to dibromo compound **8** without using dialkyne derivative **5** and dibromide **7**.

EXPERIMENTAL

All the commercially available chemicals were bought from Sigma Aldrich and Spectrochem Company and were used without further purification. Progresses of all reactions were monitored by chromatographic

technique (TLC analysis) with suitable solvent systems (EtOAc/Pet ether) and observation was done under UV light, and immersion in $KMnO_4$ solution. Moisture sensitive (dry/anhydrous) reactions were done with oven-dried glassware under nitrogen/argon atmosphere by using syringe-septum techniques. Column chromatography was done by 100-200 mesh silica gel in all cases with appropriate solvent systems.

All IR samples were recorded with $CHCl_3$ as solvents on Nicolet Impact-400 FTIR spectrometer. Nuclear magnetic resonance (NMR) spectra (^1H and ^{13}C NMR) have been recorded on 400 and 500 MHz spectrometers (Bruker) with $CDCl_3$ solvent and chemical shifts (δ ppm) are reported relative to internal standard such as TMS. The standard abbreviations s, d, t, q and m, refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Coupling constants (*J*) are reported in Hertz. Mass spectra (HRMS) have been recorded under positive ion electrospray ionization (ESI, Q-TOF) mode.

5,6-Bis(bromomethyl)-2',2'-dimethyl-1,3-dihydrospiro[indene-2,5'-[1,3]dioxane]-4',6'-dione (8) : To a solution of Meldrum's acid 500 mg (3.46 mmol), K_2CO_3 (8.67 mmol) and tetrabutylammonium hydrogensulphate (TBAHS) (3.46 mmol) in dry MeCN (30 mL), 1,2,4,5-tetrakis(bromomethyl)benzene (3.46 mmol) was added and reaction mixture was stirred at rt for 6 h. After completion of reaction (TLC monitoring) excess K_2CO_3 was filtered through a sintered funnel and aqueous layer was extracted with EtOAc (3x15 mL). The solvent was removed under reduced pressure and crude product was purified by silica gel column chromatography using appropriate mixture of EtOAc-petroleum ether to give white solid. R_f = 0.35 (1:9 EtOAc-petroleum ether). Yield: 49% (730 mg). **^{1}H NMR (500 MHz, $CDCl_3$):** δ 1.82 (s, 6H), 3.70 (s, 4H), 4.64 (s, 4H), 7.22 (s, 2H). **^{13}C NMR (125 MHz $CDCl_3$):** δ 28.9, 29.9, 45.1, 52.4, 105.3, 126.6, 136.2, 140.5, 170.2 ppm. **IR (neat):** 612, 1030, 1048, 1314, 1736, 2852 cm^{-1} **HRMS (ESI, Q-ToF):** ***m/z*** calculated for $C_{16}H_{16}Br_2NaO_4[M+Na]^+$ 452.9310, found: 452.9308.

2',2'-Dimethyl-6,8-dihydro-1*H*,4*H*-spiro[indeno[5,6-*d*][1,2]oxathiine-7,5'-[1,3]dioxane]-4',6'-dione 3-oxide (9) : To a solution of compound **8** 500 mg (1.15 mmol) in DMF, was added TBAB (1.15 mmol) and rongalite (11.57 mmol) at 0 °C and stirred the reaction mixture for 3 h at 0 °C and rt for another 3 h. After completion of the reaction (TLC monitoring) the compound was extracted with EtOAc (3x15 mL) and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography using appropriate mixture of EtOAc-petroleum ether to give white solid. Yield: 64% (250 mg). ^1H and ^{13}C NMR spectra of compound **16** matched with the literature reports.[20]

General procedure for DA reaction.

The solution of compound **9** 50 mg (1 equiv.) and dienophile (1 equiv.) in toluene was refluxed for 3 h. After completion of reaction (TLC monitoring) the solvent was removed under reduced pressure and the crude products were purified by silica gel column chromatography.

Compound 19. R_f = 0.31 (2:8 EtOAc-petroleum ether). Yield: 81% (51 mg); Yellowish solid, mp 226 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.83 (s, 6H), 3.71 (s, 4H), 3.95 (s, 4H), 7.16 (s, 2H), 7.74 (m, 2H), 8.14, (m, 2H). **^{13}C NMR (100 MHz $CDCl_3$):** δ 28.5, 28.9, 45.1, 52.8, 105.2, 123.7, 126.4, 131.6, 132.1, 133.6, 137.9, 142.4, 170.4, 184.0 ppm. **IR (neat):** 766, 889, 1219, 1732, 1764, 2312, 2916, 3479 cm^{-1}. **HRMS (ESI, Q-ToF): *m/z*** calculated for $C_{26}H_{20}O_6[M+H]^+$ 429.1334, found: 429.1333.

Compound 20. R_f = 0.36 (2:8 EtOAc-petroleum ether). Yield: 76% (54 mg); Yellow solid, mp 256-258 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80 (s, 6H), 2.99 (dd, J_1 = 17.46, J_2 = 4.84 Hz, 2H), 3.33 (dd, J_1 = 17.14, J_2 = 6.05 Hz, 2H), 3.30 (t, J = 4.59 Hz, 2H), 3.65 (d, J = 7.02 Hz, 4H), 6.98 (s, 2H), 7.70 (m, 2H), 8.08 (m, 2H), 8.61 (s, 2H). **^{13}C NMR (100 MHz $CDCl_3$):** δ 28.6, 28.9, 45.1, 47.1, 52.6, 105.1, 124.4, 128.9, 129.4, 130.0, 130.0, 132.4, 135.3, 137.3, 170.5, 197.6 ppm. **IR (neat):** 664, 959, 1297, 1742, 1768, 2355, 2926 cm^{-1} **HRMS (ESI, Q-ToF): *m/z*** calculated for $C_{30}H_{24}NaO_6[M+Na]^+$ 503.1464, found: 503.1465.

Compound 21. R_f = 0.31 (2:8 EtOAc-petroleum ether). Yield: 69% (39 mg); brown solid, mp 241-243 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.82 (s, 6H), 3.69 (s, 4H), 3.78 (s, 4H), 6.79 (s, 2H), 7.11 (s, 2H). **^{13}C NMR (100 MHz $CDCl_3$):** δ 27.9, 28.9, 45.1, 52.7, 105.2, 123.8, 131.3, 136.3, 137.9, 140.1, 170.4, 186.4 ppm. **IR (neat):** 758, 955, 1212, 1296, 1668, 1736, 1765, 2329, 2926 cm^{-1}. **HRMS (ESI, Q-ToF): *m/z*** calculated for $C_{22}H_{18}O_6[M+H]^+$ 379.1175, found: 379.1176.

Compound 22. R_f = 0.29 (4:6 EtOAc-petroleum ether).Yield: 72% (48 mg); white solid, mp 220-222 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.83 (s, 6H), 3.73 (s, 4H), 4.80 (s, 4H), 7.12 (s, 2H), 7.54 (m, 5H). **^{13}C NMR (100 MHz $CDCl_3$):** δ 28.9, 45.0, 46.0, 52.7, 105.4, 122.3, 125.5, 128.1, 128.3, 129.2, 131.0, 139.1, 152.9, 170.2 ppm. **IR (neat):** 667, 959, 1115, 1303, 1715, 1760, 2336, 2797 cm^{-1}. **HRMS (ESI, Q-ToF): *m/z*** calculated for $C_{24}H_{21}N_3NaO_6[M+Na]^+$ 470.1324, found: 470.1323 .

2'',2'',3-Trimethyl-5',7'-dihydro-1'*H*,3'*H*-dispiro[thiazolidine-5,2'-*s*-indacene-6',5''-[1,3]dioxane]-2, 4,4'',6''-tetraone (24): To a suspension of sodium hydride (1.90 mmol) in dry THF (15 mL), the compound *N*-methylthiazolidine (100 mg, 0.76 mmol) was added and the reaction mixture was stirred at

rt for 30 min. Later, the dibromo compound **8** (329 mg, 0.76 mmol) was added and the stirring was continued at the same temperature for 24 h. After completion of the starting material (TLC monitoring), the reaction mixture was quenched with water an aqueous layer was extracted with EtOAc (3x10 mL) and crude compound were purified by column chromatography. R_f = 0.41 (2:8 EtOAc-petroleum ether). Yield: 69% (210 mg), white solid, mp 212-214 ^oC. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 1.81 (s, 6H), 3.18 (s, 4H), 3.32 (s, 1H), 3.36 (s, 1H), 3.68 (s, 3H), 3.84 (s, 1H), 3.88 (s, 1H), 7.07 (s, 2H). **^{13}C NMR (100 MHz $CDCl_3$):** δ 28.1, 28.9, 45.0, 46.8, 52.8, 64.7, 105.2, 120.0, 125.0, 138.7, 170.4, 171.1, 176.7 ppm. **IR (neat):** 758, 955, 1296, 1424, 1678, 1735, 2329, 2926 cm^{-1}. **HRMS (ESI, Q-ToF): *m/z*** calculated for $C_{20}H_{19}KNO_6S[M+K]^+$ 440.0562, found: 440.0565.

ACKNOWLEDGEMENT

S. K. thanks Dr. P. N. Pandey, Penam Laboratories Ltd. New Delhi for the financial support and V. B. G. thanks IIT Bombay for the award of a research fellowship.

REFERENCES

1. K. Byun and J. Y. Gao, *J. Am. Chem. Soc*., 2001, **123**, 3974.
2. E. M. Arnett and J. A. Harrelson, *J. Am. Chem. Soc.*, 1987, **109**, 809.
3. A. S. Ivanov, *Chem. Soc. Rev*., 2008, **37**, 789.
4. J. Gerencser, G. Dorman, and F. Darvas, *QSAR Comb. Sci*., 2006, **25**, 439.
5. A. M. Gaber, *Synthesis*, 2001, 2059.
6. N. Katagiri, H. Nochi, A. Kurimoto, H. Sato, and C. Kaneko, *Chem. Pharm. Bull*., 1994, **42**, 1251.
7. Y. Morita, R. Kamakura, M. Takeda, and Y. Yamamoto, *Chem. Commun*., 1997, 359.
8. M. M. Gillena, M. R. Alexandre, D. M. Henrique, M. S. Diniz, T. C. Paulo, R. F. Ricardo, and E. S. Luiz, *EXCLI J*., 2014, **13**, 1022.
9. Y. Oikawa, K. Sugano, and O. Yonemitsu, *J. Org. Chem*., 1978, **43**, 2087.
10. N. Pemberton, L. Jakobsson, and F. Almqvist, *Org. Lett*., 2006, **8**, 935.
11. R. Bloch, *Synthesis*, 1978, 140.
12. S. Perreault and C. Spino, *Org. Lett*., 2006, **8**, 4385.
13. N. Katagiri, Y. Morishita, and C. Kaneko, *Heterocycles*, 1997, **46**, 503.
14. R. L. Danheiser, A. R. Renslo, D. T. Amos, and G. T. Wright, *Org. Synth*., 2003, **80**, 133.
15. M. Zia-Ebrahimi and G. W. Huffman, *Synthesis*, 1996, 215.
16. S. Danishefsky and R. K. Singh, *Org. Synth*., 1990*,* **7**, 411.
17. S. Danishefsky, *Acc. Chem. Res*., 1979, **12**, 66.
18. S. Danishefsky and R. K. Singh, *J. Org. Chem*., 1975, **40**, 3807.

19. S. Kotha and G. Sreevani, *Tetrahedron Lett*., 2015, **56**, 5903.
20. S. Kotha and G. Sreevani, *Synthesis*, 2018, **50**, 4883.
21. S. Kotha and N. Sreenivasachary, *Bioorg. Med. Chem. Lett*., 2000, **10**, 1413.
22. S. Kotha and E. Bramhachary, *Bioorg. Med. Chem*., 2002, **10**, 2291.
23. (a) S. Kotha, M. Behera, and V. R. Shah, *Synlett*, 2005, 1877; (b) S. Kotha, K. Mandal, A. C. Deb, and S. Banerjee, *Tetrahedron Lett.*, 2004, **45**, 9603.
24. H. F. Mohssen, N. M. Ali, and H. A. Ali, *J. Chem. Pharm. Res*., 2017, **9**, 20.
25. S. Kotha and A. K. Ghosh, *Tetrahedron*, 2004, **60**, 10833.
26. S. Kotha, *Acc. Chem. Res*., 2003, **36**, 342.
27. (a) S. Kotha and P. Khedkar, *Chem. Rev*., 2012, **112**, 1650; (b) S. Kotha, P. Khedekar, and Y. Dammaraju, *Tetrahedron Lett*., 2019, **60**, 631.
28. S. Kotha and G. T. Waghule, *J. Org. Chem*., 2012, **77**, 6314.
29. S. Kotha, D. Goyal, N. Thota, and V. Srinivas, *Eur. J. Org. Chem*., 2012, 1843.
30. S. Kotha and R. Ali, *Tetrahedron*, 2015, **71**, 6944.
31. F. C. Raps, V. C. Faseke, D. Haussinger, and C. Sparr, *Angew. Chem. Int. Ed*., 2020, **59**, 18390.
32. S. Kotha, E. Bramhachary, and N. Sreenivasachary, *Tetrahedron Lett.*, 1998, **39**, 4095.
33. S. Kotha, A. S. Chavan, and D. Goyal, *ACS. Comb. Sci.*, 2017, **17**, 253.
34. S. Kotha and G. Sreevani, *Tetrahedron Lett.*, 2018, **59**, 1996.
35. S. Kotha and R. Ali, *Heterocycles*, 2014, **88**, 789.