SYNTHESIS OF 1,1,2-TRISUBSTITUTED CYCLOPROPANE RING THROUGH CARBON-CARBON BOND NUCLEOPHILE-INTERCEPTED BECKMANN FRAGMENTATION REACTION

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ABSTRACT

The Beckmann fragmentation reaction, considered to be a special type of the Beckmann rearrangement only occurs in particular when α -carbon of the oxime is substituted with alkyl or aryl groups which are capable of stabilizing a carbocation formed when a nitrile group results. In this project, the oxime of dialkyl 2-(3-oxocyclohexyl)malonate are undergone derivatization with *p*-toluenesulfonyl chloride or 2,4-dinitrofluorobenzene. The tosyloxime or oxime ether with no substituents at α -carbon of the oxime derivatives was on treatment with base NaH or CsCO₃ initiates the Beckmann fragmentation, wherein this reaction the carbocation formed on α -carbon atom simultaneously attacked by dialkyl malonate carbon as a nucleophile in the same basic condition and results in the carbon-carbon bond formation as to substituted cyclopropane rings. The strained substituted cyclopropane rings occurred in many complex natural products including terpenoids, steroids, alkaloids pheromones, fatty acid metabolites and unusual amino acids. Some Natural products with cyclopropane motifs not only furnished fascinating structures, but also exhibited versatile biological activities, such as cytotoxic, anti-HIV, antimicrobial, antiviral, and immunosuppressive effects.

Keywords: Oxime, Oxime Ether, Tosyloxime, Cyclopropane, Beckmann Fragmentation etc.

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INTRODUCTION

The intermolecular cyclopropanation reactions were reported by many researchers wherein olefins are treated with activated methylene in presence of heavy metal as catalyst¹. The Beckmann fragmentation through the C-C bond breaking and C-C bond making leads to the intramolecular cyclopropanation with a very good yield to 1,1,2-trisubstituted cyclopropane ring without the use of any heavy metals as a catalyst. The concept of cyclopropanation was an unintended result,²⁻⁵ when we tried to synthesized anti-Bredt's imine compounds as listed in Fig.-1. According to Bredt's rule⁶ in the carbon bicyclic system, carbon-carbon double bonds at the bridgeheads cannot exist for the small ring size.⁷ But, there are reports of anti-Bredt's rule compounds,⁸⁻¹² wherein the bicyclic compound has an unsaturated center at the bridgehead position, although isolation of these compounds was limited.¹³ The examples of bicyclic imines, in which carbon-nitrogen double bond having the similar geometry to its olefinic analog are also reported and these anti-Bredt imine compounds have been isolated including A, B and C¹⁴ (Fig.-1)

Fig.-1: Anti-Bredt Imines¹⁴

The methodology³ for the synthesis of 2,2,5-trisubstituted pyrrolidine was already developed and the same concept was applied to synthesize the anti-Bredt compound **4** (Scheme-1). In this methodology, it was thought that when tosyloxime **3** or oxime ether when treated with base the malonate group can act as

nucleophilic carbon in the basic condition and tosyl group as good leaving group makes nitrogen atom as electrophile leads to ring closure as anticipated anti-Bredt's compound **4** (Scheme 1) but instead of the anti-Bredt compound **4**, the Beckmann fragmentation¹⁵⁻¹⁷ product **5** was obtained in a high yield of 74% (Scheme-2). The malonate nucleophilic carbon attacked on α -carbon atom instead of the nitrogen atom of the tosyl oxime and this resulted in the formation of the Beckmann fragmentation product as a substituted cyclopropane ring. The reaction was repeated; changing the base to anhydrous CsCO_3 in dry CH_2Cl_2 , but gave the same results and no conditions which gave the anti-Bredt product could be identified. The cyclopropane ring is a highly strained system but preferred instead of the five-membered ring system confirmed by the ^1H NMR and mass spectra (Scheme 2). The same Beckmann fragmentation was exploited for various substitutions with changing the active methylene group as dialkyl malonate, ethyl 2-cyanoacetate and ethyl 2-nitroethanoate.

EXPERIMENTAL

General Procedure for the Preparation of Michael Adduct

The 7.50 mmol of cyclohex-2-enone (0.72 ml) was added drop-wise to a well-stirred mixture of 6.25 mmol Diethyl malonate (0.95 ml) and 9.37 mmol of anhydrous K_2CO_3 (1.29 g) in dry CH_2Cl_2 20ml and the mixture was stirred for 15 hr at r.t. or till completion of the reaction by TLC¹⁸. Water and EtOAc were added sequentially and the organic layers were separated, washed with 1 M HCl, water, brine and dried over Na_2SO_4 . The concentration of the organic layer gave the crude product, which was purified by flash column chromatography (eluting with EtOAc : petrol) to afford the Michael adduct product **1**.

General Procedure for Preparation Oxime of Michael Adduct

To the solution of 3.90 mmol Michael adduct ketone **1** (1g) in 20 ml EtOH has added 7.81 mmol of $\text{NH}_2\text{OH}\cdot\text{HCl}$ (531mg) and 9.75 mmol of Et_3N (984mg) and the reaction mixture was heated to reflux for 2 hr. The progress of the reaction was monitored by TLC and on completion of the reaction mixture was allowed to cool to room temperature¹⁹. EtOH was removed under reduced pressure and the residue was dissolved in EtOAc and H_2O added. The organic layer was separated, washed with brine and dried over Na_2SO_4 . The concentration of the organic layer gave the crude product, which was purified by flash column chromatography (eluting with EtOAc : petrol) to afford the oxime product **2**.

General Procedure for Preparation Tosyl Oxime From Oxime

The stirring solution 3.69 mmol of **2** oxime (1g) in dry 20 ml CH_2Cl_2 at 0 $^\circ\text{C}$ was treated with 7.38 mmol of Et_3N or pyridine (745mg or 583mg) followed by slow addition 5.53 mmol of *p*-toluenesulphonyl

chloride (1.05g). The reaction was further stirred for 2 hr and progress was monitored by TLC and after completion of the reaction, (1 M) HCl was added and the product was extracted by CH₂Cl₂ and the extracts were washed with saturated NaHCO₃ and dried over Na₂SO₄¹⁹. The concentration of CH₂Cl₂ gave the crude product which was purified by flash column chromatography (eluting with EtOAc : petrol) to afford the tosyl oxime product **3**.

General Procedure for Cyclopropanation through Beckmann Fragmentation²⁰

To the solution, 2.35 mmol of compound **3** tosyl oxime (1g) in dry THF at room temperature, 7.05 mmol of NaH (169 mg, 60% dispersion in mineral oil) was added and heated to reflux for 30 min to 1 hr and the progress of the reaction was monitored by TLC²⁰. After completion of the reaction, saturated NH₄Cl was added and the Beckmann fragmentation product as substituted cyclopropane was extracted by EtOAc. The extracts were dried over Na₂SO₄, the concentration of reaction mixture gave the crude product which was purified by flash column chromatography (eluting with EtOAc: petrol) to afford 1,1,2-trisubstituted cyclopropane ring as products **4**.

(±)Diethyl 2-(3-oxocyclohexyl)malonate, **1**

Following the general procedure, 23.4 mmol of cyclohex-2-enone (2.26ml) was added to a solution 19.5 mmol of diethyl malonate (2.97ml) and 29.3 mmol of anhydrous K₂CO₃ (3.92g) in dry CH₂Cl₂ (30mL) and the mixture was stirred at r.t. to give crude product which was purified by flash column chromatography to afford adduct **2** (4.10g, 82%) as a colourless oil²¹; *R_f* = 0.53 (EtOAc : petrol, 4:6); *v*_{max}(film)/cm⁻¹ 2982, 1731, 1448, 1423, 1297, 1229, 1156, 1061, 965; *δ*_H(400 MHz; CDCl₃; Me₄Si) 1.23 (6H, t, *J* 7.1 Hz, 2 × OCH₂CH₃), 1.47, 1.65 (2H, m, COCH₂CH₂CH₂), 1.90 (2H, m, COCH₂CH₂CH₂), 2.23 (2H, m, COCH₂CH₂CH₂), 2.39 (2H, m, COCH₂CH), 2.49 (1H, m, COCH₂CH), 3.26 (1H, d, *J* 7.9 Hz CH(COOEt)₂), 4.17 (4H, q, *J* 7.1 Hz, 2 × OCH₂CH₃); *δ*_C(100 MHz; CDCl₃; Me₄Si) 13.5 (OCH₂CH₃), 23.9 (COCH₂CH₂CH₂), 26.2 (COCH₂CH₂CH₂), 37.4 (COCH₂CH), 40.4 (COCH₂CH₂CH₂), 44.5 (COCH₂CH), 56.3 (CH(COOEt)₂), 60.9 (OCH₂CH₃), 167.2, 167.3 (2 x COO), 209.1 (CO); *m/z* (ESI⁺) 535 ([2M+Na]⁺, 85%), 279 ([M+Na]⁺, 60%), 255 ([M-H]⁻, 100%), HRMS (ESI⁺) C₁₃H₂₀NaO₅⁺ ([M+Na]⁺) requires 279.1203; found 279.1199.

(±)Diethyl 2-(3-(hydroxyimino)cyclohexyl)malonate, **2**

Following the general procedure, to the solution 14.9 mmol of adduct **1** (3.82g) in EtOH (40ml), 22.4 mmol of NH₂OH.HCl (1.54g) and 29.8 mmol of Et₃N (3.01g) was added and heated to reflux for 1 hr to give crude product which was purified by flash column chromatography to afford oxime **2** (3.82 g, 94%) as a colourless oil; *R_f* = 0.45, 0.37 (EtOAc : petrol, 4:6); *v*_{max}(film)/cm⁻¹ 3240, 2938, 1731, 1448, 1369, 1233, 1156, 1096, 966, 862; (major isomer) *δ*_H(400 MHz; CDCl₃; Me₄Si) 1.17 (6H, t, *J* 7.1 Hz, 2 × OCH₂CH₃), 1.34 (2H, m, CCH₂CH₂CH₂), 1.70 (2H, m, CCH₂CH₂CH₂), 1.93 (2H, m, CCH₂CH₂CH₂), 2.26 (2H, m, CCH₂CH), 3.11 (1H, m, CCH₂CH), 3.19 (1H, d, *J* 8.3 Hz CH(COOEt)₂), 4.11 (4H, q, *J* 7.1 Hz, 2 × OCH₂CH₃), 9.40 (1H, bs, OH); *δ*_C(100 MHz; CDCl₃; Me₄Si) 14.0 (OCH₂CH₃), 23.7, 23.8 (CCH₂CH₂CH₂), 25.1, 27.8 (CCH₂CH₂CH₂), 29.4, 29.5 (CCH₂CH₂CH₂), 31.6, 35.5 (CCH₂CH), 36.7, 37.7

(CCH₂CH), 56.9, 57.0 (CH(COOEt)₂), 61.3, 61.4 (OCH₂CH₃), 158.4, 158.7 (C=NOH), 168.0, 168.1, 168.2 (2 x COO); m/z (ESI⁺) 565 ([2M+Na]⁺, 100%), 294 ([M+Na]⁺, 50%), 270 ([M-H]⁻, 100%), HRMS (ESI⁺) C₁₃H₂₁NNaO₅⁺ ([M+Na]⁺) requires 294.1312; found 294.1310.

(±)Diethyl 2-(3-(tosyloxyimino)cyclohexyl)malonate, 3

Following the general procedure, to the solution 5.09 mmol of oxime **2** (1.38g) in dry CH₂Cl₂ (25 ml) was added 10.2 mmol of Et₃N (1.02g) at 0°C followed by 7.63 mmol *p*-toluenesulphonyl chloride (1.45g) and the mixture stirred for 2 hr at r.t. to give crude product which was purified by column chromatography to afford tosyl oxime **3** (1.82 g, 84%) as colourless a oil; R_f = 0.59 (EtOAc : petrol, 4:6); *v*_{max}(film)/cm⁻¹ 2938, 1730, 1447, 1369, 1155, 1032, 817, 732; (major isomer) δ_H(400 MHz; CDCl₃; Me₄Si) 1.23 (6H, t, *J* 7.1 Hz, 2 x OCH₂CH₃), 1.47 (2H, m, CCH₂CH₂CH₂), 1.86 (2H, m, CCH₂CH₂CH₂), 2.03 (2H, m, CCH₂CH₂CH₂), 2.28 (2H, m, CCH₂CH), 2.39 (3H, s, ArCH₃), 2.49 (1H, m, CCH₂CH), 3.26 (1H, d, *J* 7.9 Hz CH(COOEt)₂), 4.16 (4H, q, *J* 7.1 Hz, 2 x OCH₂CH₃), 7.29 (2H, d, *J* 8.1 Hz, ArH), 7.79 (2H, d, *J* 8.1 Hz, ArH); δ_C(100 MHz; CDCl₃; Me₄Si) 13.5 (OCH₂CH₃), 21.1 (ArCH₃), 23.9 (CCH₂CH₂CH₂), 28.2 (CCH₂CH₂CH₂), 37.4 (CCH₂CH), 40.4 (CCH₂CH₂CH₂), 44.5 (CCH₂CH), 56.3 (CH(COOEt)₂), 60.9 (OCH₂CH₃), 128.1, 128.9, 132.1, 144.2 (ArC), 167.1 (C=NOTs), 167.3, 167.5 (2 x COO); m/z (ESI⁺) 873 ([2M+Na]⁺, 100%), 448 ([M+Na]⁺, 80%), HRMS (ESI⁺) C₂₀H₂₇NNaO₇S⁺ ([M+Na]⁺) requires 448.1400; found 448.1400.

(±)Diethyl 2-(3-cyanopropyl)cyclopropane-1,1-dicarboxylate, 5

Following the general procedure, to the solution 0.60 mmol of tosyl oxime **3** (256mg) in dry THF (10 ml) was added 1.80 mmol of NaH (43 mg, 60% dispersion in mineral oil) and heated to reflux for 30 min, instead ring closure pyrroline as bicyclic anti-Bredt's compound, we have isolated Beckman fragmentation product which was purified by flash column chromatography to afford substituted cyclopropane **5** (113 mg, 74%) as a colourless oil; R_f = 0.49 (EtOAc : petrol, 4:6)^{22,23}; *v*_{max}(film)/cm⁻¹ 2938, 2256, 1731, 1431, 1447, 1369, 1156, 1096, 1030, 967, 916, 862; δ_H(400 MHz; CDCl₃; Me₄Si) 1.24, 1.27 (6H, t, *J* 7.1 Hz, 2 x OCH₂CH₃), 1.33 (2H, m, NCCH₂CH₂CH₂), 1.39 (1H, m, CHCHHC), 1.55 (1H, m, CHCH₂C), 1.74 (1H, m, CHCHHC), 1.82 (2H, m, NCCH₂CH₂CH₂), 2.33 (2H, t, *J* 7.1 Hz NCCH₂CH₂CH₂), 4.11, 4.21 (4H, q, *J* 7.1 Hz, 2 x OCH₂CH₃); δ_C(100 MHz; CDCl₃; Me₄Si) 13.8 (OCH₂CH₃), 16.5 (NCCH₂CH₂CH₂), 20.3 (CHCH₂C), 24.5 (NCCH₂CH₂CH₂), 26.4 (CHCH₂C), 27.3 (NCCH₂CH₂CH₂), 33.8 (C(COOEt)₂), 61.3 (OCH₂CH₃), 118.9 (CN), 167.6, 169.8 (2 x COO); m/z (ESI⁺) 276 ([M+Na]⁺, 100%), HRMS (ESI⁺) C₁₃H₁₉NNaO₄⁺ ([M+Na]⁺) requires 276.1206; found 276.1207.

(±)1-ethyl 1-methyl 2-(3-cyanopropyl)cyclopropane-1,1-dicarboxylate, 9

Following the general procedure, to the solution 0.29 mmol of tosyl oxime **8** (120 mg) in dry THF (5ml) was added 0.87 mmol of NaH (21mg, 60% dispersion in mineral oil) and heated to reflux for 30 min, cyclopropanation product was isolated as competing Beckman fragmentation reaction which was purified by flash column chromatography to afford substituted cyclopropane **9** (47 mg, 69%) as a colourless oil; R_f

= 0.48 (EtOAc : petrol, 4:6); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2939, 2255, 1730, 1732, 1431, 1448, 1369, 1180, 1159. $\delta_{\text{H}}(400 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$ 1.25 (3H, t, J 7.1 Hz, OCH_2CH_3), 1.33 (2H, m, $\text{NCCH}_2\text{CH}_2\text{CH}_2$), 1.38 (1H, m, CHCHHC), 1.57 (1H, m, CHCH_2C), 1.75 (1H, m, CHCHHC), 1.82 (2H, m, $\text{NCCH}_2\text{CH}_2\text{CH}_2$), 2.33 (2H, t, J 7.0 Hz $\text{NCCH}_2\text{CH}_2\text{CH}_2$), 4.20 (2H, q, J 7.1 Hz, OCH_2CH_3); 4.09 (3H, OCH_3) $\delta_{\text{C}}(100 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$ 13.9 (OCH_2CH_3), 16.5 ($\text{NCCH}_2\text{CH}_2\text{CH}_2$), 20.6 (CHCH_2C), 24.2 ($\text{NCCH}_2\text{CH}_2\text{CH}_2$), 26.4 (CHCH_2C), 27.3 ($\text{NCCH}_2\text{CH}_2\text{CH}_2$), 33.9 ($\text{C}(\text{COOR})_2$), 60.1 (OCH_3), 61.3 (OCH_2CH_3), 118.9 (CN), 167.5, 169.9 (2 x COO); m/z (ESI^+) 262 ($[\text{M}+\text{Na}]^+$, 100%), HRMS (ESI^+) $\text{C}_{12}\text{H}_{17}\text{NNaO}_4^+$ ($[\text{M}+\text{Na}]^+$) requires 262.1055; found 262.1109.

(±)1-*tert*-Butyl 1-ethyl 2-(3-cyanopropyl)cyclopropane-1,1-dicarboxylate, 13

Following the general procedure, to the solution 0.30 mmol of tosyl oxime **12** (136 mg) in dry THF (5ml) was added 0.90 mmol of NaH (21 mg, 60% dispersion in mineral oil) and heated to reflux for 30 min, cyclopropanation product was isolated as competing Beckman fragmentation reaction which was purified by flash column chromatography to afford substituted cyclopropane **13** (49mg, 58%) as a colourless oil; R_f = 0.50 (EtOAc : petrol, 4:6); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2935, 2250, 1735, 1739, 1432, 1449, 1369, 1194, 1158. $\delta_{\text{H}}(400 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$ 1.1 (9H, s, $t\text{Bu}$), 1.27 (3H, t, J 7.0 Hz, OCH_2CH_3), 1.33 (2H, m, $\text{NCCH}_2\text{CH}_2\text{CH}_2$), 1.33 (1H, m, CHCHHC), 1.59 (1H, m, CHCH_2C), 1.75 (1H, m, CHCHHC), 1.82 (2H, m, $\text{NCCH}_2\text{CH}_2\text{CH}_2$), 2.33 (2H, t, J 7.0 Hz $\text{NCCH}_2\text{CH}_2\text{CH}_2$), 4.20 (2H, q, J 7.0 Hz, OCH_2CH_3); $\delta_{\text{C}}(100 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$ 13.1 ($t\text{Bu}$), 13.7 (OCH_2CH_3), 16.5 ($\text{NCCH}_2\text{CH}_2\text{CH}_2$), 20.6 (CHCH_2C), 24.11 ($\text{NCCH}_2\text{CH}_2\text{CH}_2$), 26.3 (CHCH_2C), 27.3 ($\text{NCCH}_2\text{CH}_2\text{CH}_2$), 34.0 ($\text{C}(\text{COOR})_2$), 60.0 (OCH_2CH_3), 63.5 ($\text{OC}(\text{CH}_3)_3$), 118.9 (CN), 167.9, 173.3 (2 x COO); m/z (ESI^+) 304 ($[\text{M}+\text{Na}]^+$, 100%), HRMS (ESI^+) $\text{C}_{15}\text{H}_{23}\text{NNaO}_4^+$ ($[\text{M}+\text{Na}]^+$) requires 304.1525; found 304.1208.

(±) 1-Benzyl 1-ethyl 2-(3-cyanopropyl)cyclopropane-1,1-dicarboxylate, 17

Following the general procedure, to the solution 0.32 mmol of tosyl oxime **16** (160 mg) in dry THF (5ml) was added 0.98 mmol of NaH (23 mg, 60% dispersion in mineral oil) and heated to reflux for 30 min, cyclopropanation product was isolated as competing Beckman fragmentation reaction which was purified by flash column chromatography to afford substituted cyclopropane **17** (69 mg, 67%) as a colourless oil; R_f = 0.51 (EtOAc : petrol, 4:6); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 3078, 2939, 2252, 1731, 1735, 1432, 1438, 1359, 1172, 1157. $\delta_{\text{H}}(400 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$ 1.23 (3H, t, J 7.0 Hz, OCH_2CH_3), 1.31 (2H, m, $\text{NCCH}_2\text{CH}_2\text{CH}_2$), 1.38 (1H, m, CHCHHC), 1.55 (1H, m, CHCH_2C), 1.78 (1H, m, CHCHHC), 1.82 (2H, m, $\text{NCCH}_2\text{CH}_2\text{CH}_2$), 2.34 (2H, t, J 7.0 Hz $\text{NCCH}_2\text{CH}_2\text{CH}_2$), 4.21 (2H, q, J 7.0 Hz, OCH_2CH_3); 4.38 (2H, OCH_2Ph), 7.2-7.5 (5H, m, ArH) $\delta_{\text{C}}(100 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$ 13.9 (OCH_2CH_3), 16.5 ($\text{NCCH}_2\text{CH}_2\text{CH}_2$), 20.76 (CHCH_2C), 24.4 ($\text{NCCH}_2\text{CH}_2\text{CH}_2$), 26.5 (CHCH_2C), 27.4 ($\text{NCCH}_2\text{CH}_2\text{CH}_2$), 33.8 ($\text{C}(\text{COOR})_2$), 61.3 (OCH_2CH_3), 60.9 (OCH_2Ph), 118.9 (CN), 123, 125, 127, 149, (ArC), 167.7, 173.2 (2 x COO); m/z (ESI^+) 338 ($[\text{M}+\text{Na}]^+$, 100%), HRMS (ESI^+) $\text{C}_{18}\text{H}_{21}\text{NNaO}_4^+$ ($[\text{M}+\text{Na}]^+$) requires 338.1368; found 338.1203.

(±) Ethyl 1-cyano-2-(3-cyanopropyl)cyclopropanecarboxylate, 25

Following the general procedure, to the solution 0.24 mmol of tosyl oxime **24** (89 mg) in dry THF (5 ml) was added 0.70 mmol of NaH (16 mg, 60% dispersion in mineral oil) and heated to reflux for 30 min, cyclopropanation product was isolated as competing Beckman fragmentation reaction which was purified

by flash column chromatography to afford substituted cyclopropane **25** (17 mg, 36%) as a colourless oil; $R_f = 0.39$ (EtOAc : petrol, 4:6); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2937, 2254, 2210, 1733, 1433, 1436, 1357, 1157. $\delta_{\text{H}}(400 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$ 1.22 (3H, t, J 7.0 Hz, OCH_2CH_3), 1.31 (2H, m, $\text{NCCH}_2\text{CH}_2\text{CH}_2$), 1.43 (1H, m, CHCHHC), 1.55 (1H, m, CHCH_2C), 1.79 (1H, m, CHCHHC), 1.88 (2H, m, $\text{NCCH}_2\text{CH}_2\text{CH}_2$), 2.35 (2H, t, J 7.0 Hz $\text{NCCH}_2\text{CH}_2\text{CH}_2$), 4.20 (2H, q, J 7.0 Hz, OCH_2CH_3); $\delta_{\text{C}}(100 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$ 13.8 (OCH_2CH_3), 16.6 ($\text{NCCH}_2\text{CH}_2\text{CH}_2$), 20.84 (CHCH_2C), 24.4 ($\text{NCCH}_2\text{CH}_2\text{CH}_2$), 26.6 (CHCH_2C), 27.4 ($\text{NCCH}_2\text{CH}_2\text{CH}_2$), 34.7 ($\text{C}(\text{COOR})$), 61.3 (OCH_2CH_3) 118.9, 120.2 (CN), 173.2 (COO); m/z (ESI^+) 229 ($[\text{M}+\text{Na}]^+$, 100%), HRMS (ESI^+) $\text{C}_{11}\text{H}_{14}\text{N}_2\text{NaO}_2^+$ ($[\text{M}+\text{Na}]^+$) requires 229.0953; found 229.1117.

The instruments used for the data analysis are NMR instruments with models are AVG400/AVF400/AVB400 and IR-Spectrometer used FTS6000/FTS7000 and for mass spectra, we used LC-MS LCT.

RESULTS AND DISCUSSION

The diethyl malonate was reacted with cyclohex-2-enone, in the presence of anhydrous K_2CO_3 , in dry CH_2Cl_2 heated to reflux for 5 hr and afforded the Michael adduct **1**²⁴⁻²⁸ in a very high yield of 82%. This Michael adduct was then readily converted into the corresponding oxime, by using standard conditions ($\text{NH}_2\text{OH} \cdot \text{HCl}$ and base Et_3N in EtOH, heated to reflux for 1 hr) and gave oxime **2** again in a very high yield of 94%. The resultant oxime was easily converted into the tosyl oxime (*p*-toluenesulfonyl chloride and base Et_3N in dry CH_2Cl_2) stirred at r.t. for 2 hr and afforded the tosyl oxime **3** in a high yield of 84% (Scheme 3). The tosyl oxime **3** was treated with base (NaH , in dry THF or anhydrous CsCO_3 in dry CH_2Cl_2 heated to reflux for 30 min) and gave the Beckmann fragmentation product as the substituted cyclopropane ring. The Beckmann fragmentation reaction was repeated with ethyl methyl malonate, *tert*-butyl ethyl malonate, benzyl ethyl malonate and cyclohex-2-enone in the same sequence as the first Michael addition reaction of dialkyl malonate and cyclohex-2-enone in presence of a mild base as anhydrous K_2CO_3 results in adducts in good yield. The same adducts subsequently converted into oximes ($\text{NH}_2\text{OH} \cdot \text{HCl}$ and base Et_3N in EtOH, heated to reflux for 1 hr) in good yield and further oximes were derivatized with *p*-toluenesulfonyl chloride or 2,4-dinitrofluorobenzene² to tosyloximes or oxime ethers in good yield²⁹⁻³⁴. The tosyloximes or oxime ether on treatment with NaH , in dry THF or anhydrous CsCO_3 in dry CH_2Cl_2 heated to reflux for 30 min gave good yield of Beckmann fragmentation products as 1,1,2-trisubstituted cyclopropanes. (Schemes 4). It was observed that the bulk of the ester group suppressed the attack of nucleophilic carbon leads to the lowering of the yield which was observed in the case of compounds 13 and 17 *t*-butyl ester and benzyl ester respectively. Hence compound 5 and compound 9 as diethyl or ethyl methyl ester have moderately high and same yield.

Reagents and conditions (a) anhydrous K_2CO_3 , CH_2Cl_2 , reflux; (b) $\text{NH}_2\text{OH} \cdot \text{HCl}$, Et_3N ; (c) *p*TsCl, Et_3N , CH_2Cl_2 , rt; (d) i) NaH , dry THF, reflux, 30 min; ii) anhydrous CsCO_3 , CH_2Cl_2 , reflux.

Scheme-3: Synthesis of Oxime Derivatives

The cyclopropanation^{35,36} through the Beckmann fragmentation reaction was also tested with ethyl 2-cyanoacetate, ethyl 2-nitroacetate and cyclohex-2-enone. The Michael addition reaction of ethyl 2-cyanoacetate, ethyl 2-nitroacetate and cyclohex-2-enone in presence of mild base as anhydrous K_2CO_3 gave good yields. The same adducts then converted into oximes ($\text{NH}_2\text{OH} \cdot \text{HCl}$ and base Et_3N in EtOH,

heated to reflux for 1 hr) in good yield and further oximes were derivatised with *p*-toluenesulfonyl chloride or 2,4-dinitrofluorobenzene² to tosyloximes or oxime ethers in good yield. The tosyloximes **24** or oxime ether on treatment with NaH, in dry THF or anhydrous CsCO₃ in dry CH₂Cl₂ heated to reflux for 30 min gave various results as ethyl 2-cyano-2-(3-((tosyloxy)imino)cyclohexyl)acetate **24** undergoes Beckmann fragmentation reaction and gave yield 36% of **25** as ethyl 1-cyano-2-(3-cyanopropyl)cyclopropanecarboxylate (1,1,2-trisubstituted cyclopropane) whereas the **20** tosyloxime (ethyl 2-nitro-2-(3-((tosyloxy)imino) cyclohexyl) acetate) on treatment with NaH, in dry THF or anhydrous CsCO₃ in dry CH₂Cl₂ heated to reflux did not undergoes Beckmann fragmentation as well as the Beckmann rearrangement reaction and end up with uncharacterized yellow mass. (Schemes-5 and 6).

Scheme-4: Synthesis of Substituted Cyclopropane Rings

Scheme-5: Oxime Derivatives of Nitro, Cyano Adducts

Reagents and conditions (d) i) NaH, dry THF, reflux, 30 min; ii) anhydrous CsCO₃, CH₂Cl₂, reflux.

Scheme-6: Cyclopropanation

CONCLUSION

In summary unexpected results were obtained while the synthesis of planned anti-Bredt's compounds, when the unknown compounds were characterized and confirmed by NMR and Mass spectroscopy as cyclopropanation through Beckmann Fragmentation as 1,1,2-trisubstituted cyclopropane ring. This methodology was then developed with various substitution patterns as different substituted ester groups and cyano group whereas to incorporate the nitro group using ethyl 2-nitroacetate fails. The methodology developed will be very useful to get quick access to synthesize 1,1,2-trisubstituted cyclopropane ring which is a part of many natural products of high importance.

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