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# TMG catalyzed cyclopropanation of cyclopentenone. Illustration by a simple synthesis of bicyclo[3.1.0]hexane-2-one derivatives

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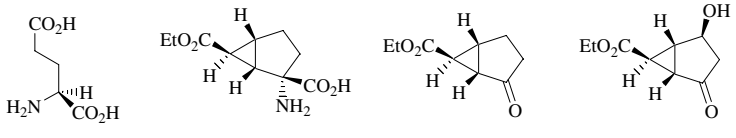
**Abstract**—The catalytic preparation of bicyclo[3.1.0]hexane-2-one-6-carboxylic acid ethyl ester **1** is described by cyclopropanation of cyclopentenone using 1,1,3,3-tetramethylguanidine (TMG) as a catalyst in high yield and high diastereoselectivity. This process has been applied to an efficient synthesis of the important intermediate, β-hydroxyl cyclopentanone **2**.


L-Glutamic acid is a major neurotransmitter at the vast majority of excitatory synapses in the mammalian central nervous system.[1,2] L-Glutamate plays an important role in all major functions of the brain and exerts its effects via two types of excitatory amino acid receptors: ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs). The mGluRs have been distinguished into three groups on the basis of amino acid sequence homology, agonist pharmacology and signal transduction mechanism.[3–7] Recently, a conformationally constrained analog of glutamic acid, LY354740, has been discovered to be a highly potent and selective group 2 metabotropic glutamate receptor (mGluR2) agonist.[8] Bicyclo[3.1.0]hexane-2-one-6-carboxylic acid ethyl ester (**1**) is a key intermediate for the synthesis of LY354740 (Scheme 1). Several methods, including cyclopropanation of cyclopentenone with ethyl dimethylsulfonium acetate bromide, for the preparation of **1** have been developed.[8–11] In the course of our route development for LY354740, a practical and low cost process for the preparation of **1** was desired. Herein we wish to report a practical and cost-effective approach for the synthesis of **1** by a 1,1,3,3-tetramethylguanidine (TMG) catalyzed cyclopropanation of cyclopentenone and its application for the efficient synthesis of the hydroxyl derivative **2**, which is an important intermediate for the mGluRs drug discovery.

Typically, DBU was employed stoichiometrically for the base mediated cyclopropanation of cyclopentenone with (ethoxycarbonylmethyl)dimethylsulfonium bromide for the preparation of **1**.[8] In order to develop a more cost-effective process, we initially screened a variety of less expensive bases for mediation of this transformation, such as triethylamine, pyridine and the inorganic base, $K_2CO_3$ (Table 1). It is believed triethylamine, pyridine, and DMAP are ineffective due to their inferior basicity for generating the ylide from (ethoxycarbonylmethyl)-dimethylsulfonium bromide. No conversion to the desired product was observed with the use of these bases.

Much to our delight, 1,1,3,3-tetramethylguanidine (TMG) was found to be an excellent base for mediation of the cyclopropanation of cyclopentenone. It was found that **1** was obtained in higher yield with a shorter




LY354740 **1** **2**

**Scheme 1.**

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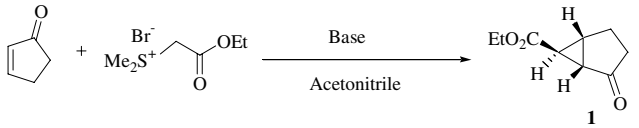
**Table 1.** Cyclopropanation of cyclopentenone with different bases




| Entry | Base[a] | Temperature (°C) | Reaction time (h) | Yield[b] (%) | dr[c] |
|---|---|---|---|---|---|
| 1 | DMAP | 23 | 12 | 0 | / |
| 2 | $NEt_3$ | 23 | 12 | 0 | / |
| 3 | Pyridine | 23 | 12 | 0 | / |
| 4 | $K_2CO_3$ | 23 | 12 | 0 | / |
| 5 | DBU | 23 | 24 | 78 | 99:1 |
| 6 | TMG | 23 | 5 | 89 | 99:1 |

[a] 1.2 equiv of base was used.
[b] Isolated yields after distillation.
[c] The diastereomer ratio was determined by GC.

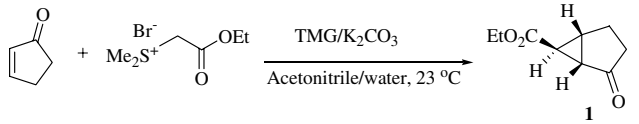
reaction time when 1,1,3,3-tetramethylguanidine (TMG) was used,[12] compared with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[13] Moreover, TMG can be easily recovered for reuse in good yield due to the high crystallinity of its HBr salt. During the production of ylide from (ethoxycarbonylmethyl)dimethylsulfonium bromide, TMG scavenges HBr from the substrate to form a TMG HBr salt which precipitates from the reaction solution. The TMG HBr salt can be separated easily by filtration in quantitative yield and TMG can be recovered in 85% yield after the salt was treated with 50% NaOH.[14,15] For comparison, precipitates were not observed when DBU was used under the same conditions.

With this finding, we thought that the catalytic version of this cyclopropanation could be realized if the TMG HBr salt was neutralized in situ with inexpensive inorganic bases. We are pleased to find that a catalytic amount of TMG can be utilized for this process without loss of productivity in the presence of saturated $K_2CO_3$ (Table 2).

As we expected, saturated $K_2CO_3$ alone was not effective to carry out the reaction (entry 1). Less than 10% yield of the product was observed after the reaction mixture was allowed to stir at ambient temperature for 24 h without TMG. When 5 mol % of TMG was added to the reaction mixture, 65% of the product was isolated (entry 2). The result with 20 mol % of TMG (entry 5) is equivalent to that of the reaction mediated with stoichiometric TMG (entry 6).[16] It seems to indicate that a soluble, strong base such as TMG in a moderately catalytic amount (20 mol %) is required to sustain a reasonable reaction rate (entry 5). Thus, we have discovered a catalytic version of the cyclopropanation of cyclopentenone which proceeds in high yield and excellent diastereoselectivity.[17]

The successful catalytic cyclopropanation of cyclopentenone encouraged us to apply this new method toward the development of an efficient synthesis of the hydroxyl

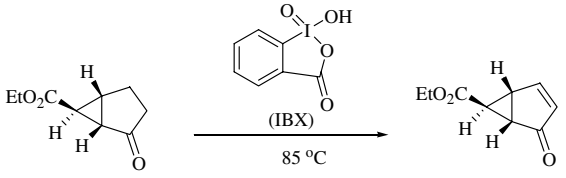
**Table 2.** Catalytic cyclopropanation of cyclopentenone with TMG[a]



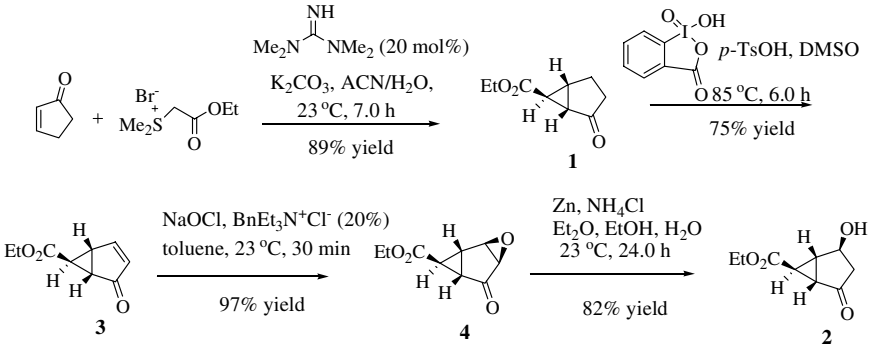

| Entry | TMG (equiv) | Reaction time (h) | Yield[b] (%) | dr[c] |
|---|---|---|---|---|
| 1 | 0 | 24 | <10 | 95:1 |
| 2 | 0.05 | 24 | 65 | 99:1 |
| 3 | 0.10 | 12 | 72 | 99:1 |
| 4 | 0.15 | 12 | 81 | 99:1 |
| 5 | 0.20 | 7 | 89 | 99:1 |
| 6 | 1.00 | 5 | 89 | 99:1 |

[a] 2.0 equiv of $K_2CO_3$ was used.
[b] Isolated yields after distillation.
[c] The diastereomer ratio was determined by GC.

**Table 3.** Direct oxidation of ketone **1** to enone **3**




| Solvent | IBX (equiv) | *p*-TsOH (equiv) | Reaction time (h) | Isolated yield (%) |
|---|---|---|---|---|
| DMSO/toluene | 4.0 | 0 | 72 | 35 |
| DMSO | 4.0 | 0 | 72 | 58 |
| DMSO | 2.5 | 0.3 | 10 | 67 |
| DMSO | 2.0 | 1.0 | 6 | 75 |




**Scheme 2.**

derivative **2**, which is an important intermediate for the mGluR drug discovery effort.[18] Recently, Nicolaou[19] reported an effective method to prepare enones from ketones with IBX. After several trials, we succeeded in the direct oxidation of ketone **1** to enone **3** with IBX in 75% yield (Table 3). It was found that *p*-toluenesulfonic acid significantly accelerated this oxidation.

Using a phase-transfer catalyzed epoxidation,[20] enone **3** was converted to epoxide **4** in near quantitative yield. Reduction of epoxide **4** with zinc and ammonium chloride afforded the desired hydroxy ketone **2**.[21] Therefore, an efficient synthesis of **2** has been developed in 51% overall yield over four steps without purification by chromatography (Scheme 2).

In conclusion, the catalytic cyclopropanation of cyclopentenone using TMG as a catalyst has been developed for the preparation of bicyclo[3.1.0]hexane-2-one-6-carboxylic acid ethyl ester (**1**). This practical and cost-effective process has also been exemplified for the efficient synthesis of important derivatives for mGluR drug discovery effort.

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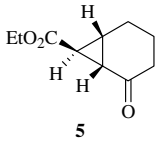
12. *Preparation of* **1** *using stoichiometric TMG:* A 500 mL of flask was charged with (ethoxycarbonylmethyl)dimethylsulfonium bromide (55.5 g, 0.24 mol) and 150 mL of acetonitrile. The resulting suspension was treated with 1,1,3,3-tetramethylguanidine (30.1 mL, 0.24 mol) at ambient temperature. The mixture became a clear solution after stirring for 2 min, and then a white precipitate formed. After stirring at ambient temperature for 10 min, a solution of 2-cyclopenten-1-one (16.4 g, 0.20 mol) in 40 mL of acetonitrile was added at once. This resulting pale yellow mixture was stirred at ambient temperature for 5 h, and poured into 1200 mL of MTBE. The white solid (TMG HBr salt) was collected by filtration and was washed with MTBE (47.0 g, 100% recovery). The filtrate was washed with 200 mL of water and 100 mL of brine, dried over sodium sulfate and evaporated. The yellow residue was distilled at reduced pressure to collect the desired product (31.2 g, 85–90 °C/0.3 mm Hg) as a colorless liquid, which was dissolved in 80 mL of hot hexanes and crystallized at ambient temperature to afford 29.9 g of the pure desired product **1** (89% yield). $^1$H NMR ($CDCl_3$) $\delta$ 4.18 (q, 2H, $J = 7.1$ Hz), 2.55 (q, 1H, $J = 4.9$ Hz), 2.29–2.00 (m, 6H), 1.26 (t, 3H, $J = 7.1$ Hz). $^{13}$C NMR ($CDCl_3$) $\delta$ 212.2, 170.9, 61.6, 32.4, 29.6, 26.9, 23.0, 14.7.
13. The price of TMG ($3.80/mol) is lower than DBU ($4.20/mol) in ton quantity.
14. *Recovery of TMG*: 23.5 g of white solid (TMG HBr salt) in a 500 mL of separation funnel was treated with 100 mL of 50% NaOH aqueous solution. The generated TMG was extracted with methylene chloride ($3 \times 200$ mL). The combined methylene chloride solutions were dried over sodium sulfate and evaporated to provide 11.7 g (85% recovery) of 1,1,3,3-tetramethylguanidine (TMG).
15. TMG can also be recovered by extraction with toluene (75% recovery) and isopropyl acetate (71% recovery).
16. *Preparation of* **1** *using catalytic TMG*: A 500 mL of flask was charged with (ethoxycarbonylmethyl)dimethylsulfonium bromide (41.6 g, 0.18 mol) and 110 mL of acetonitrile. The resulting suspension was treated with 1,1,3,3-tetramethylguanidine (4.5 mL, 0.036 mol) at ambient temperature for 15 min. A solution of 2-cyclopenten-1-one (12.3 g, 0.15 mol) in 20 mL of acetonitrile, and a solution of saturated $K_2CO_3$ (30 mL) were added. This resulting mixture was stirred at ambient temperature for 7 h. The reaction was quenched by the addition of 200 mL of water and extracted with MTBE ($2 \times 300$ mL). The combined MTBE solutions were washed with sat. $NH_4Cl$ aqueous solution and brine. After evaporation, the yellow residue was distilled at reduced pressure to collect the desired product (22.4 g) as a colorless liquid which solidified after standing at ambient temperature. 89% yield. $^1$H NMR ($CDCl_3$) $\delta$ 4.18 (q, 2H, $J = 7.1$ Hz), 2.55 (q, 1H, $J = 4.9$ Hz), 2.29–2.00 (m, 6H), 1.26 (t, 3H, $J = 7.1$ Hz). $^{13}$C NMR ($CDCl_3$) $\delta$ 212.2, 170. 9, 61.6, 32.4, 29.6, 26.9, 23.0, 14.7.
17. Cyclopropanation of 2-cyclohexen-1-one was carried out under the same condition to give the bicyclo[4.1.0] adduct **5** in 59% yield and 99% dr.




**5**

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21. Compound **2**: $^1$H NMR ($CD_3OD$) $\delta$ 4.60 (d, 1H, $J = 5.5$ Hz), 4.15 (q, 2H, $J = 7.5$ Hz), 2.56 (m, 1H), 2.48 (d, 1H, $J = 5.5$ Hz), 2.44 (dd, 1H, $J = 6.0$ and 0.5 Hz), 2.24 (m, 1H), 2.16 (dd, 1H, $J = 3.5$ and 2.5 Hz), 1.88 (d, 1H, $J = 19$ Hz), 1.26 (t, 3H, $J = 7.5$ Hz). $^{13}$C NMR ($CDCl_3$) $\delta$ 209.9, 169.7, 68.4, 61.9, 42.9, 36.5, 34.5, 25.7, 14.3.