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A High-Yield and Cost-Effective Synthesis of Spirotetramat

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Abstract—*cis*-8-Methoxy-1,3-diazaspiro[4.5]decane-2,4-dione, the key intermediate in the synthesis of spirotetramat, was synthesized by catalytic hydrogenation, oxidation, and Bucherer–Bergs reaction with 4-methoxycyclohexan-1-one as raw material. Spirotetramat was obtained in an overall yield of 20.4% by a multi-step reaction sequence including hydrolysis, esterification, acylation, intramolecular condensation, and O-acylation. The advantages of the proposed method are mild conditions, simple operation, and good to excellent yields in each step.

Keywords: *cis*-8-methoxy-1,3-diazaspiro[4.5]decane-2,4-dione, spirotetramat, synthesis

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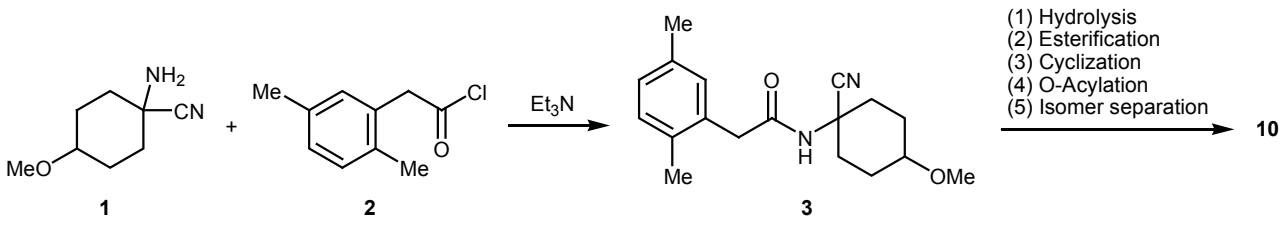
INTRODUCTION

Spirotetramat, *cis*-3-(2,5-dimethylphenyl)-8-methoxy-2-oxo-1-azaspiro[4.5]dec-3-en-4-yl ethyl carbonate (**10**), is a second-generation insecticide developed by Bayer CropScience (Germany) under the brand name Movento [1]. Spirotetramat has a good efficacy and safety for crops. Its unique two-way internal absorption and transport properties enable spirotetramat to be transported to any part of the plant, which can effectively prevent egg hatching and larval development of pests on roots and leaves. In addition, spirotetramat exhibits a long-lasting efficacy, and it can effectively control pests for as long as two months [2]. Furthermore, the characteristics of spirotetramat such as high activity, low dosage, broad-spectrum insecticidal efficacy, and environmental safety meet China's pesticide requirements [3]. Therefore, spirotetramat has prominent applications and market prospects. In this work, we intended to improve the procedure for the synthesis of spirotetramat by optimizing the conditions and reducing the synthetic cost.

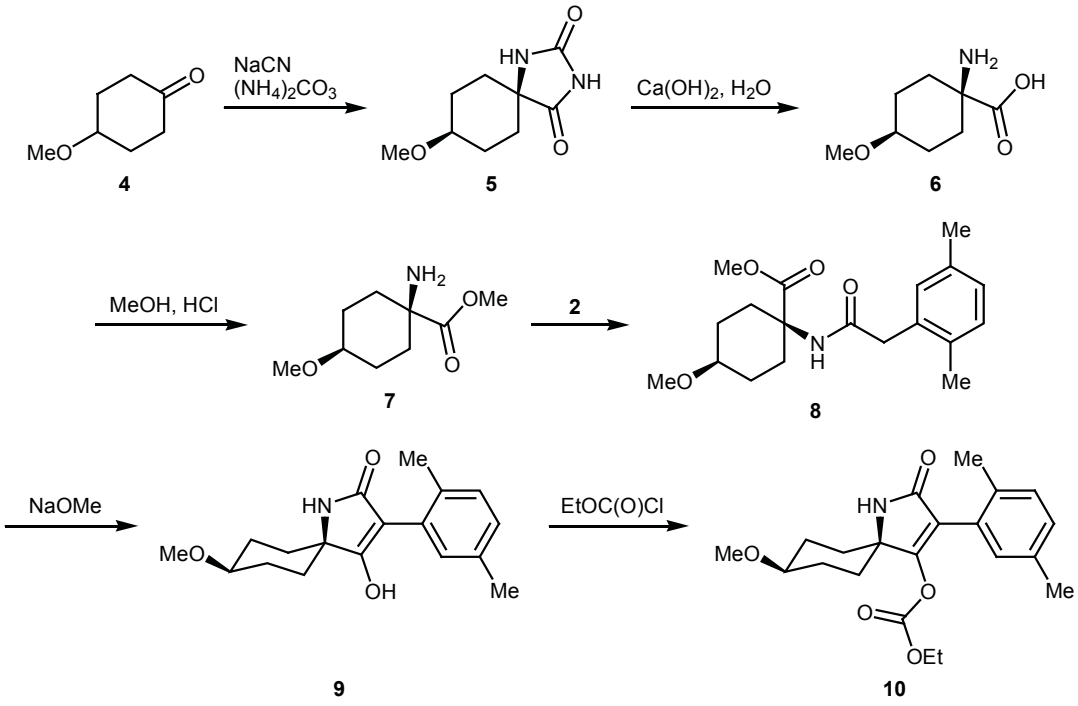
Two main synthetic routes of spirotetramat have been reported (Scheme 1). In the first route, 1-amino-4-methoxycyclohexane-1-carbonitrile (**1**) and 2,5-dimethylphenylacetyl chloride (**2**) were used as starting materials. The target compound was obtained by N-acylation, cyano hydrolysis, esterification, intramolecular cyclization, and final O-acylation with ethyl chloroformate [4–11]. However, spirotetramat obtained by this method is a racemic mixture that needs to be separated, which reduces the yield and increases the cost. In the second method, spirotetramat can be obtained via esterification, acylation, cyclization, and nucleophilic substitution reaction from *cis*-1-amino-4-methoxycyclohexane-1-carboxylic acid (**6**) [12–17]. This method could avoid isomer separation of isomers, but the disadvantage is that the raw material is more expensive.

In terms of yield and necessity of isomer separation, the second method is advantageous over the first, so we chose to optimize the process based on the second technique. In our new route, the basic chemical raw material was used as the starting material to synthesize

Scheme 1.



Scheme 2.



the key compound, *cis*-1-amino-4-methoxycyclohexane-1-carboxylic acid, and spirotetramat was then obtained by a multistep reaction (Scheme 2). This route is both economical and practical, reducing costs, and increasing the yield.

RESULTS AND DISCUSSION

Using 4-methoxycyclohexan-1-one [18] (**1**) as the raw material, *cis*-1-amino-4-methoxycyclohexanecarboxylic acid (**6**) was obtained by the Bucherer–Bergs reaction, followed by hydrolysis. The key intermediate (compound **8**) was synthesized from **6** by esterification and acylation. The target compound (**10**) was obtained by intramolecular condensation, followed by O-acylation with ethyl chloroformate.

The key step in this route is the classical Bucherer–Bergs reaction used to synthesize spiro hydantoin **5**. The product also contained the corresponding *trans* isomer, which can be effectively removed by recrystallization. We found that temperature was critical when cooling the reaction mixture after the reaction had ended. Lower temperature led to a higher content of the *trans* isomer, which affected the product quality. However, higher temperature would reduce the yield. Finally, we chose 25–30°C as the best cooling temperature, because there was almost no *trans* isomer (the concentration of *cis* isomer **5** was 99% or more).

Calcium hydroxide was used as catalyst instead of traditional NaOH or KOH for the hydrolysis of **5**. In the post-treatment, the calcium salt can be effectively removed by sulfuric acid, which could reduce the presence of inorganic salts in the product and improve the quality of **6**. Furthermore, removal of moisture from the filtrate with toluene made the precipitated compound **6** easier to separate by filtration and dry.

Compound **9** was synthesized by the Dieckmann condensation using sodium methoxide to provide alkaline medium. The product was precipitated by slowly adding hydrochloric acid to adjust the pH value. Otherwise, the impurities could immediately be entrapped in the product, and hard blocks could be formed in the reactor, thus affecting filtration and quality of compound **9**.

EXPERIMENTAL

The reagents and solvents were purchased from commercial vendors and were used as received without further purification. The reaction progress was monitored using thin-layer chromatography (TLC). Melting points were determined with a YuHua X-3 melting point apparatus and are uncorrected. All NMR spectra were recorded on a Bruker spectrometer at 400 or 600 MHz for ^{1}H and at 100 MHz for ^{13}C in DMSO-d_6 or $CDCl_3$ solutions.

***cis*-8-Methoxy-1,3-diazaspiro[4.5]decane-2,4-dione (5).** Ammonium carbonate, 95 g (1 mol), and sodium cyanide, 60 g (1.2 mol), were added to 1500 mL of water under stirring. Compound **4**, (128 g, 1 mol), was then added, and the mixture was stirred for 15 h at 50°C. After completion of the reaction (TLC), the mixture was cooled down to 25°C and stirred for 2 h. The mixture was filtered, and the filter cake was washed with cold methanol and dried to get compound **5** (53 g, 44.6%) as white powder, mp 180–182°C [12]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.37–1.47 m (2H, CH_2), 1.57-1.67 m (4H, CH_2), 1.91–1.95 m (2H, CH_2), 3.13–3.19 m (1H, CH), 3.23 s (3H, OCH_3), 8.44 s (1H, NH), 10.61 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 26.35, 31.34, 54.86, 61.32, 76.52, 156.27, 178.36.

***cis*-1-Amino-4-methoxycyclohexane-1-carboxylic acid (6).** Calcium hydroxide (220 g, 3.0 mol) was added to 800 mL of water under stirring at 40°C. Compound **5** (100 g, 0.5 mol) was then added, and the mixture was stirred for 45 h at 95°C. The reaction was assumed to be complete when the concentration of **5** was less than 3% (HPLC). The mixture was cooled to 60°C, and the pH value was adjusted to pH 3 with 50% sulfuric acid. After adding 150 g of water and 25 g of active carbon, the mixture was stirred for 1 h at 80°C and filtered while hot. The filtrate was concentrated, and water was removed by refluxing with toluene (400 g). The residue was cooled to 30°C and filtered to obtain insoluble compound **6** (92%) as gray powder, mp 166–170°C [12]. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.12 t (1H, CH, J = 8.0 Hz), 1.34–1.43 m (2H, CH_2), 1.60–1.65 m (2H, CH_2), 1.80–1.90 m (4H, CH_2), 3.15 s (1H, CH), 3.21 s (3H, OCH_3), 7.49 s (2H, NH_2).

Methyl *cis*-1-amino-4-methoxycyclohexane-1-carboxylate (7). Compound **6** (86 g, 0.5 mol) was dissolved in 320 mL of methanol under stirring, the solution was heated to 60°C, and thionyl chloride (70 g, 0.6 mol) was slowly added over a period of 2–3 h. The mixture was refluxed for 10 h until it contained less than 1% of **6** (HPLC), methanol was removed under reduced pressure, and cyclohexane (400 mL) was added to the residue. Methanol was taken away by a water divider, the mixture was cooled down to 30°C, and compound **7** (92%) was filtered off. Gray powder, mp 171–173°C [12]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.90–1.95 m (4H, CH_2), 2.02–2.09 m (2H, CH_2), 2.26–2.32 m (2H, CH_2), 3.31 m (4H, CH_2), 3.81 s (3H, OCH_3), 8.92 s (2H, NH_2). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 29.23, 29.59, 53.33, 55.61, 59.62, 75.63, 171.00.

Methyl *cis*-1-[2-(2,5-dimethylphenyl)acetamido]-4-methoxycyclohexane-1-carboxylate (8). A Saturated aqueous solution of potassium carbonate (200 g, 1.5 mol) was added slowly to a solution of compound **7** (190 g, 1 mol) in ethyl acetate. (2,5-Dimethylphenyl)-acetyl chloride (**2**) [19] (200 g, 1.1 mol) was added slowly to the mixture at 0–5°C, and the mixture was stirred for 2 h at 25°C. The reaction was assumed to be complete when less than 2% of **7** remained in the reaction mixture (HPLC). The mixture was added to 650 g of water and stirred for 1 h at 30°C, and the organic phase was separated and concentrated under reduced pressure. Petroleum ether (820 g) was added to the residue, the mixture was refluxed for 0.5 h, and the precipitate was filtered off and dried to obtain compound **8** (90%) as white powder, mp 235–237°C [13]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.11–1.19 m (2H, CH_2), 1.71 s (1H, CH), 1.77–1.90 m (4H, CH_2), 2.03 d (2H, CH_2, J = 16.0 Hz), 2.27 s (3H, CH_3), 2.32 s (3H, CH_3), 3.11–3.18 m (1H, CH), 3.31 s (3H, OCH_3), 3.53 s (2H, CH_2), 3.70 s (3H, OCH_3), 5.44 s (1H, CH), 7.03 d (2H, H_{arom}, J = 8.0 Hz), 7.11 d (1H, NH, J = 8.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 18.93, 20.92, 26.68, 30.03, 41.88, 52.41, 55.80, 57.86, 128.66, 130.75, 131.10, 132.96, 133.99, 170.60, 173.98.

***cis*-3-(2,5-Dimethylphenyl)-4-hydroxy-8-methoxy-1-azaspiro[4.5]dec-3-en-2-one (9).** A solution of compound **8** (250 g, 0.75 mol) in DMF (450 mL) was added dropwise to a solution of sodium methoxide (60 g, 1.1 mol) in DMF (150 mL) under nitrogen atmosphere at 20–30°C, and the mixture was stirred for 2 h. The reaction was assumed to be complete when less than 2% of **8** remained in the mixture (HPLC). The mixture was concentrated to a viscous liquid under reduced pressure and cooled to 40°C. Water (100 mL) was added slowly in portions, and the mixture was stirred for 15 min. A 6% aqueous solution of sodium hydroxide (500 mL) was added slowly, the mixture was stirred for 20 min, the aqueous phase was acidified to pH 3 with hydrochloric acid, the mixture was stirred for 30 min, and the precipitate was filtered off. Yield 273 g (91.1%), white powder, mp 251–255°C [14]. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.17 s (1H, CH), 1.39–1.55 m (4H, CH_2), 1.87–1.98 m (4H, CH_2), 2.08 s (3H, CH_3), 2.25 s (3H, CH_3), 3.08–3.15 m (1H, CH), 3.36 s (1H, CH), 6.88 s (1H, CH), 6.98 d (1H, CH, J = 8.0 Hz), 7.07 d (1H, CH, J = 8.0 Hz), 8.15 s (1H, NH), 10.66 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 19.15, 20.49, 27.51, 32.11, 54.89, 59.08, 77.58, 104.61, 127.53, 129.32, 130.68, 131.52, 133.60, 134.21, 171.64, 172.62.

***cis*-3-(2,5-Dimethylphenyl)-8-methoxy-2-oxo-1-azaspiro[4.5]dec-3-en-4-yl ethyl carbonate (10).** Compound **9** (300 g, 1 mol) was added to 1500 mL of dichloromethane, and the mixture was stirred for 10 min. Triethylamine (120 g, 1.2 mol) was then added slowly at 20–25°C, ethyl chloroformate (135 g, 1.2 mol) was added over a period of 0.5–1 h, and the mixture was stirred at 20–30°C until the conversion of **9** was more than 99% (HPLC). The mixture was treated with water (650 g) and concentrated hydrochloric acid (40 g) and stirred for 20 min. The organic phase was separated and evaporated under atmospheric pressure at 75°C. Petroleum ether (1000 mL) was added to the residue, the mixture was refluxed for 30 min, cooled down to 30°C at a rate of 15–20 deg per hour, and the precipitate was filtered off to obtain compound **10** (320 g, 85%) as white powder, mp 287–290°C [15]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.10 t (3H, CH_3, J = 4.0 Hz), 1.36–1.47 m (2H, CH_2), 1.75 d (2H, CH_2, J = 12.0 Hz), 1.93 t (2H, CH_2, J = 12.0 Hz), 2.21–2.25 m (3H, CH_3), 2.26 d (2H, CH_2, J = 4.4 Hz), 2.29 s (3H, CH_3), 3.21–3.28 m (1H, CH), 3.21–3.28 m (1H, CH), 3.39 s (3H, CH_3), 4.02 d.d (2H, CH_2, J = 4.0, 8.0 Hz), 6.75 s (1H, CH), 6.99 s (1H, CH), 7.04 d (1H, CH, J = 12.0 Hz), 7.11 d (1H, CH, J = 4.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.72, 19.21, 20.89, 28.40, 31.65, 55.85, 60.25, 65.74, 121.43, 127.79, 129.48, 129.91, 130.20, 133.96, 134.98, 149.87, 164.76, 170.01.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIALS

Supplementary materials are available for this article at https://doi.org/10.1134/S1070428020100176 and are accessible for authorized users.

REFERENCES

1. Lieb, F., Fischer, R., Bretschneider, T., Ruther, M., Graff, A., Schneider, U., Erdelen, C., Wachendorff-Neumann, U., Andersch, W., and Turberg, A., US Patent no. 6114374.
2. Yang, L., Ke, S., and Zhang, M., *Agrochemicals*., 2013, vol. 52, p. 306.
3. Jhornto, J., *Pure Appl. Chem*., 2001, vol. 73, p. 1231. https://doi.org/10.1351/pac200173081231
4. Tsukiyama, T., Kajino, H., Tsukamoto, Y., Nakagawa, H., Yanai, T., Sato, K., Yokoi, S., Ichinose, R., and Tanaka, K., *J. Antibiot*., 2004, vol. 57, p. 446. https://doi.org/10.7164/antibiotics.57.446
5. Buijs, W., Comba, P., Corneli, D., and Pritzkow, H., *J. Organomet. Chem*., 2002, vol. 641, p. 71. https://doi.org/10.1016/S0022-328X(01)01291-8
6. Bretschneider, T., Benet-Buchholz, J. and Nauen, R., *Chimia*, 2003, vol. 57, p. 697. https://doi.org/10.2533/000942903777678588
7. Ke, S.Y., Zhang, Z.Q., and Zhang, Y.N., *Res. Chem. Intermed*., 2012, vol. 38, p. 1827. https://doi.org/10.1007/s11164-012-0506-0
8. Klempner, A., *Bayer CropSci. J*., 2008, vol. 61, p. 203.
9. Shi, W., Liao, D., Yang, F., Shao, L., and Meng, D., *Agrochemicals*, 2010, vol. 49, p. 250. https://doi.org/10.3969/j.issn.1006-0413.2010.04.004
10. Kaiho, T., Sannohe, K., Kajiya, S., Suzuki, T., Otsuka, K., Ito, T., Kamiya, J., and Maruyama, M., *J. Med. Chem*., 1989, vol. 32, p. 351. https://doi.org/10.1021/jm00122a012
11. Lee, C.K., Lee, I.H., and Noland, W.E., *Heterocycles*, 2007, vol. 71, p. 419. https://doi.org/10.3987/COM-06-10933
12. Ito, M., Okui, H., Nakagawa, H., Mio, Sh., Kinoshita, A., Obayashi, T., Miura, T., Nagai, J., Yokoi, Sh., Ichinose, R., Tanaka, K., Kodama, S., Iwasaki, T., Miyake, T., Takashio, M., and Iwabuchi, J., *Biosci., Biotechnol., Biochem*., 2003, vol. 67, p. 230. https://doi.org/10.1271/bbb.67.1230
13. Accinel, L., Mencarelli, C., and Balogh, M.,, *Crop Prot*., 2015, vol. 43, p. 243. https://doi.org/10.1016/j.cropro.2014.10.028
14. Calvayrac, C.F., Laurent, M., and Faveaux, A., *Pest Manage. Sci*., 2012, vol. 68, p. 340. https://doi.org/10.1002/ps.2263
15. Zhao, Q.Q., Li, Y.Q., Xiong, L.X., and Wang, Q.M., *J. Agric. Food Chem*., 2010, vol. 58, p. 4992. https://doi.org/10.1021/jf1001793
16. Graus, S., Casabona, D., Uriel, S., Cativiela, C., and Serrano, J.L., *Cryst. Eng. Commun*., 2010, vol. 12, p. 3132. https://doi.org/10.1039/c001232g
17. Ayres, F.D., Khan, S.I., Chapman, O.L., and Kaganove, S.N., *Tetrahedron Lett*., 1994, vol. 35, p. 7151. https://doi.org/10.1016/0040-4039(94)85347-9
18. Kayser, M.M. and Clouthier, C.M., *J. Org. Chem*., 2006, vol. 45, p. 562. https://doi.org/10.1021/jo061349t
19. Himmler, T., Int. Patent Appl. Pub. no. WO 25075401.