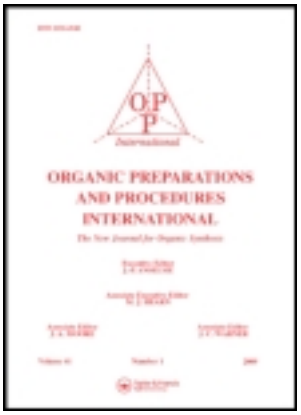



Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

# A Novel and Practical Synthesis of Rimonabant Hydrochloride

Zheng Fang [a] , Zhao Yang [b] , Jia-Feng Xu [a] , Kai Guo [a] & Ping Wei [a]

[a] School of Pharmaceutical Science, Nanjing University of Technology, Nanjing, 210009, P. R. China

[b] College of Pharmacy, China Pharmaceutical University, Nanjing, 210009, P. R. China

Version of record first published: 30 Mar 2012.

To cite this article: Zheng Fang, Zhao Yang, Jia-Feng Xu, Kai Guo & Ping Wei (2012): A Novel and Practical Synthesis of Rimonabant Hydrochloride, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 44:2, 164-168

To link to this article: http://dx.doi.org/10.1080/00304948.2012.657564

*Organic Preparations and Procedures International*, 44:164–168, 2012

ISSN: 0030-4948 print / 1945-5453 online
DOI: 10.1080/00304948.2012.657564



# A Novel and Practical Synthesis of Rimonabant Hydrochloride

Zheng Fang,[1] Zhao Yang,[2] Jia-Feng Xu,[1] Kai Guo,[1] and Ping Wei[1]

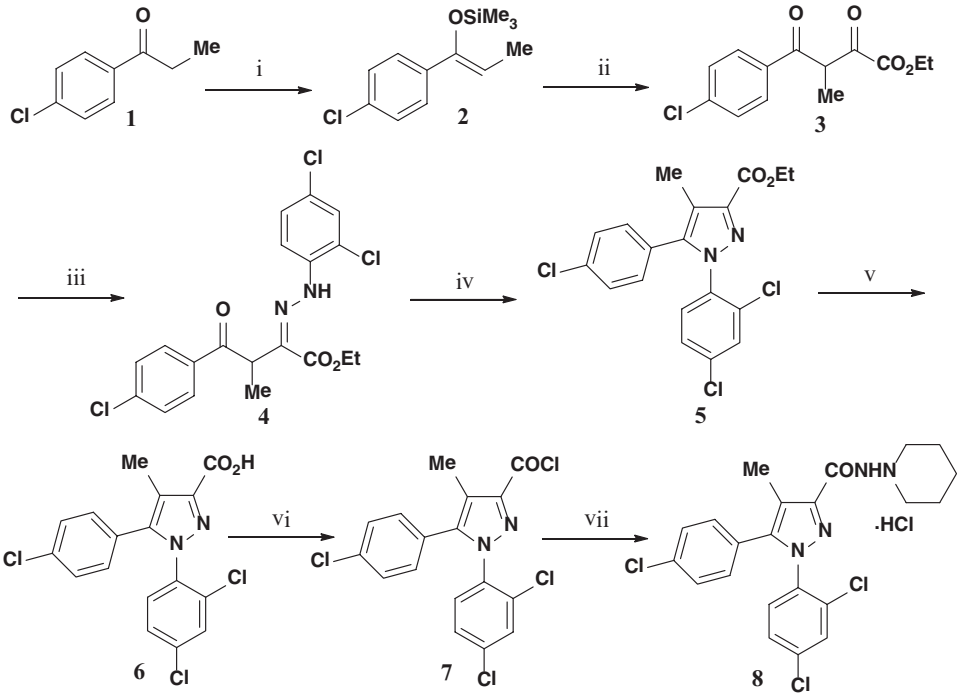
[1]School of Pharmaceutical Science, Nanjing University of Technology, Nanjing, 210009, P. R. China
[2]College of Pharmacy, China Pharmaceutical University, Nanjing, 210009, P. R. China

Rimonabant hydrochloride (**8**) is the first drug in a new class of selective cannabinoid type 1 (CB1) receptor antagonists, which also shows to play a significant role in clinical trials for the treatment of obesity and related metabolic risk factors, as well as tobacco dependence.[1,2]

Over the past few years, several synthetic strategies for the preparation of **8** have been reported.[3–12] Potentially the most useful route for the large scale synthesis of **8** is illustrated in *Scheme 1*. Its initial stages involve treatment of 4-chloropropiophenone (**1**), to afford 1-(4-chlorophenyl) -1-trimethylsiloxylpropene (**2**) in the presence of chlorotrimethylsilane and upon addition of ethyl chlorooxoacetate produced ethyl 4-(4-chlorophenyl)-3-methyl-2,4-dioxobutanoate (**3**).[3] An alternate approach to **3** entails the acylation of the enolate of **1** (from LiHMDS) to yield the lithium salt of **3**.[3,4] Condensation of **3** with 2,4-chlorophenylhydrazine to give phenylhydrazone intermediate **4** which was cyclized to ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-*1H*-pyrazole-3-carboxylate (**5**); hydrolysis of **5** gave 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-*1H*-pyrazole-3-carboxylic acid (**6**) which was subsequently converted to **8** (*Scheme 1*).

Although this method appears to be a viable approach because the reagents are inexpensive and easily obtained, it was irreproducible in our laboratory. In numerous attempts, it was difficult to replicate the result and the yield fluctuated considerably.[3] The major problem is the difficulty in removing impurities (and unreacted **1**) formed during conversion of **1** to **2**. Utilization of the crude mixture of product **2** and starting material **1** led to more impurities in further steps. These crude intermediates were not easily purified since they were all oils. Even though **6** is a solid and was isolated, it still required several recrystallizations to give the pure product. Additionally, it has been reported that the synthesis of **4** also leads phenylhydrazone isomer **9**, thus inevitably form by-product **10**.[5]

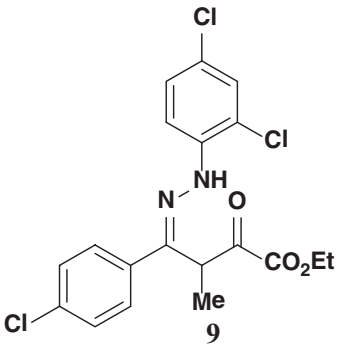
Submitted July 28, 2011.
Address correspondence to Zheng Fang, School of Pharmaceutical Science, Nanjing University of Technology, Nanjing, 210009, P. R. China. E-mail: fzcpu@163.com

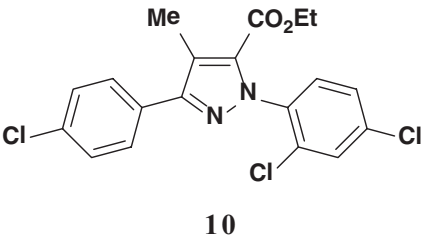


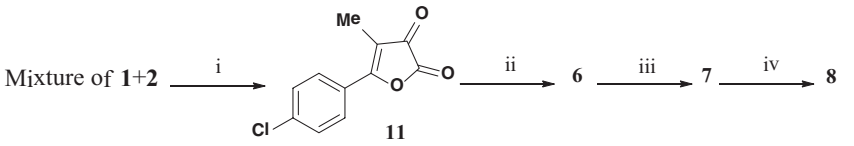

Reagents: (i) Chlorotrimethylsilane, KI, $NEt_3$; (ii) Ethyl chlorooxoacetate, $ZnCl_2$; (iii) 2,4-Dichlorophenylhydrazine hydrochloride, $NEt_3$; (iv) *p*-Toluenesulfonic acid; (v) KOH, $H_2O$, MeOH; (vi) Thionyl chloride; (vii) N-aminopiperidine, $NEt_3$, HCl

**Scheme 1**

All these problems lead to complicated operations and lesser control over the whole synthetic procedure. The reported overall yield of rimonabant hydrochloride (**8**) was only 26% (the yield before salt formation was 28%).[3,4] We now report a novel and practical methodology for synthesis of **8** using a four-step reaction sequence.






Reagents: (i) Oxalyl chloride in THF; (ii) 2,4-Dichlorophenylhydrazine hydrochloride, $NEt_3$, p-toluenesulfonic acid; (iii) Oxalyl chloride; (iv) N-Amino piperidine, $NEt_3$, HCl

**Scheme 2**

A solution of oxalyl chloride in THF was added directly to the crude product mixture of **2** and **1** to afford 5-(4-chlorophenyl)-4-methylfuran-2,3-dione (**11**).[13,14] Because of the difference in solubility between **2** and **11** in THF, pure **11** easily precipitated and separated while **2** remained in solution. Referring to the method reported in the literature,[3,4,12] condensation of **11** and 2,4-dichlorophenylhydrazine gave **6**, and eliminated the ester hydrolysis step and avoided production of by-product isomer **9**, thus facilitating the purification of **6**. It is noteworthy that rimonabant did not require purification and its salt **8** could be formed in solution with HCl gas (*Scheme 2*). Thus, pure **8** was easily obtained by recrystallization.

In comparison to the reported method, this new synthetic strategy not only decreased the number of skips, but also simplified the work-up processes. The overall yield of rimonabant from **1** increased to 40% and the operation is suitable for large scale industrial production by a simple, convenient and efficient synthetic protocol.

## Experimental Section

All reagents were purchased from commercial sources and used as supplied. The melting points were determined on YRT-3 melting point apparatus and are uncorrected. $^1$H NMR data were recorded on a Bruker AV-500 spectrometer in $CDCl_3$ or DMSO-$d_6$ using TMS as an internal standard. Mass spectra was measured with Aglilent 1100 LC/MS. The elemental analyse were performed on an Elementa Vario EL III instrument.

### *1-(4-Chlorophenyl)-1-trimethylsiloxylpropene (2)*

To a 5L reaction flask were added 4-chloropropiophenone (**1**, 168.6 g, 1.0 mol), triethylamine (202.4 g, 2.0 mol), methyl iodide (180.0 g, 1.21 mol) and anhydrous acetonitrile (1.2 L), followed by the dropwise addition of trimethylchlorosilane (217.2 g, 2.0 mol) under nitrogen at room temperature. The mixture was stirred at 45°C for 24 h before being concentrated at 40°C under reduced pressure. The residue was dissolved in toluene (1.5 L), and the solution was washed with ice water (800 mL × 2), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting brown oil (249.6 g) was used in the next step directly without further purification.

### *5-(4-Chlorophenyl)-4-methylfuran-2,3-dione (11)*

Oxalyl chloride (126.9 g, 1.0 mol) was added dropwise to a solution of the above crude product mixture in THF (1.8 L) at 10–15°C. After being stirred at room temperature for

5 h, the reaction mixture was cooled to 5°C and the precipitated solid was collected. The solid obtained was washed with 200 mL of cold THF to afford the title compound as a light yellow-green solid (141.2 g), mp. 163–163.5°C. The combined filtrate and wash liquid was concentrated to about 800 mL to afford an additional 36.5 g of product, mp. 162.5–163.5°C. The overall weight of the combined products was 177.7 g (80%) from **1**. ESI-MS: $m/z = 223.0[M+H]^+$. $^1$H NMR($CDCl_3$):$\delta$ 2.14 (s, 3H), 7.57 (d, $J =$ 6.9 Hz, 2H), 7.87 (d, $J = 6.9$ Hz, 2H).

*Anal*. Calcd for $C_{11}H_7ClO_3$: C, 59.35; H, 3.17. Found: C, 59.63; H, 3.01.



***5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic Acid (6)***

Triethylamine (51 g, 0.5 mol) was added dropwise to a solution of **11** (111.3 g, 0.5 mol) and 2,4- chlorophenylhydrazine hydrochloride (106.8 g, 0.5 mol) in toluene (2 L). The reaction mixture was stirred at 20°C for 12 h followed by filtration of $Et_3N$.HCl and concentration *in vacuo*. The residue was dissolved in toluene (1 L), to which was added *p*-toluenesulfonic acid (8.6 g, 0.05 mol) and the mixture was refluxed for 12 h. After cooling to room temperature, an NaOH solution (5%, 1 L) was added and the mixture was stirred vigorously for 0.5 h. After separation of the layers, the pH of the aqueous phase was adjusted to 2 by the addition of conc. HCl. The resulting precipitate was collected, dried and recrystallized from 80% aqueous acetic acid to give 145.5 g (76%) of a white solid, mp. 215.8–217.0°C (*lit*.[3] mp. 210°C).

$^1$H NMR(DMSO-$d_6$):$\delta$ 2.23(s, 3H), 7.23(d, $J = 8.4$ Hz, 2H), 7.45(d, $J = 8.4$ Hz, 2H), 7.57(dd, $J_1 = 8.5$ Hz, $J_2 = 2.2$ Hz, 1H), 7.70(d, $J = 8.5$ Hz, 1H), 7.77(d, $J = 2.2$ Hz, 1H), 12.91(br, 1H).

*Anal*. Calcd for $C_{17}H_{11}Cl_3N_2O_2$: C, 53.50; H, 2.91; N, 7.34. Found: C, 53.61; H, 2.79; N, 7.32.

***Rimonabant Hydrochloride (8)***

To a suspension of **6** (38.2 g, 0.1 mol) in dichloromethane (250 mL) containing DMF (1 mL) in an ice bath was added a solution of oxalyl chloride (10 mL, 0.11 mol) in dichloromethane (20 mL). After the addition, the reaction mixture was stirred for 2 h at room temperature before being added to a solution of N-aminopiperidine (12.0 g, 0.12 mol) and triethylamine (17 mL, 0.12 mol) in dichloromethane (200 mL); the addition was carried out slowly so as to keep temperature at 10–15°C; then the reaction mixture was stirred at room temperature for another 1 h and then washed with water (200 mL × 2), and dried over anhydrous sodium sulfate. After filtration, the pH of the solution was adjusted to 1 by passing HCl gas. The white solid obtained was recrystallized from a mixture of methanol and ether (1:3) to give the pure product (33.0 g, 66%) as a white solid, mp. 229–235°C (dec.). [*lit*.[3] mp. 224°C (dec.)].

ESI-MS: $m/z = 463.1[M\text{-}Cl]^+$; $^1$H NMR(DMSO-$d_6$):$\delta$ 1.46∼1.59 (m, 2H), 1.80∼1.82 (m, 4H), 2.33 (s, 3H), 3.34∼3.39 (m, 4H), 7.24 (d, $J = 7.8$ Hz, 2H), 7.46 (d, $J = 7.8$ Hz, 2H), 7.58∼7.79 (m, 3H), 8.59 (br, 1H); 11.09 (s, 1H).

*Anal*. Calcd for $C_{22}H_{22}Cl_4N_4O$: C, 52.82; H, 4.43; N, 11.20. Found: C, 52.73; H, 4.44; N, 11.12.

## References


1. L. F. VanGaal, A. M. Rissanen, A. J. Scheen, O. Ziegler and S. Rossner, *Lancet*, **365**, 1387 (2005).
2. B. Poirier, J. P. Bidouard, C. Cadrouvele, X. Marniquet, B. Staels, S. E. O'Connor, P. Janiak and J. M. Herbert, *Diabets. Obes. Metab.*, **7**, 65 (2005).
3. F. R. Barth, P. Casellas, C. Congy, S. Martinez, M. Rinaldi and G. Ann-Archard, EP 656354, 1994; *Chem. Abstr.*, **123**, 286006 (1994).
4. K. K. Vijay, S. Sashikanth, M. R. Jambula, P. R. Chitneni, B. Vijaybhaskar, B. Apurba and B. Rakeshwar, *Org. Process Res. Dev.*, **11**, 910 (2007).
5. S. R. Donohue, C. Halldin and V. W. Pike, *Tetrahedron. Lett*, **49**, 2789 (2008).
6. K. D. Aloke, S. Howard, R. William, K. R. Raj, R. C. David and R. M. Billy, *Med. Chem. Res.*, **5**, 54 (1995).
7. M. Daumas and P. Vayron, PCT Int. Appl. WO 2005115989, 2005; *Chem. Abstr.*, **143**, 460145 (2005).
8. P. Vayron, M. Daumas, R. Sole and A. Dlubala, FR 2873372, 2008; *Chem. Abstr.*, **144**, 170983 (2006).
9. R. P. Padi, V. Bolugoddu, V. K. Kotagiri, S. Suthrapu, S. Vecha, S. R. S. Peri, N. R. Challa and P. Cherukupally, PCT Int. Appl. WO 2007121466, 2007; *Chem. Abstr.*, **147**, 469334 (2007).
10. P. J. Mas and A. Torrens-Jover, EP 1947090, 2008; *Chem. Abstr.*, **149**, 176329 (2008).
11. A. Sandoz, S. Nerdinger, PCT Int. Appl. WO 2008101860, 2008; *Chem. Abstr.*, **149**, 307838 (2008).
12. C. H. Wu, M. S. Huang, J. S. Song, T. K. Yeh, M. C. Chou, C. M. Chu, J. J. Jan, M T. Hsieh, S. L. Tseng, C. P. Chang, W. P. Hsieh, Y. C. Lin, Y. N. Yeh, W. L. Chung, C. W. Kuo, C. Y. Lin, H. S. Shy, Y. S. Chao and K. S. Shia, *J. Med. Chem.*, **52**, 4496 (2009).
13. S. Toshiaki, O. Taichi, S. Kiyomi, N. Yosihiro, H. Mitsuru, H. Yoshie, T. Jun and S. Takehiro, *Chem. Pharm. Bull.*, **44**, 956 (1996).
14. V. V. Zalesov and A. P. Kozlov, *Russ. J. Org. Chem.*, **38**, 1491 (2002).