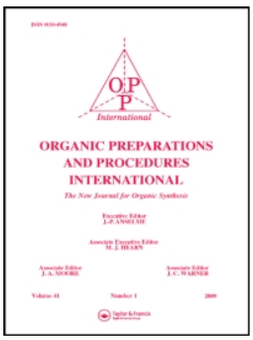

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# OPPI BRIEF

# A Convenient Methanolysis in the Synthesis of Carfentanyl

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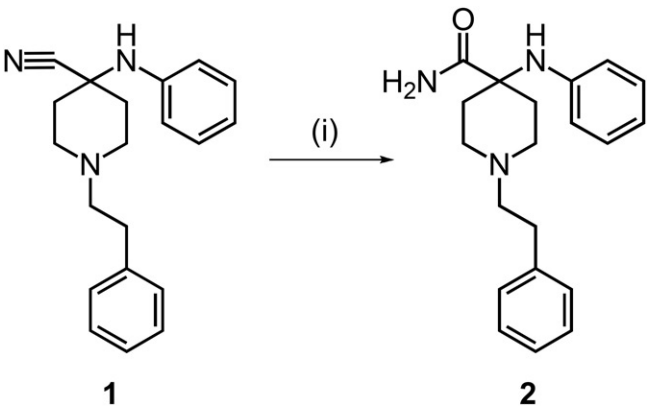
Synthetic opioids, such as remifentanyl, sufentanyl and fentanyl, have found broad applications in medicine for treatment of severe pain.[1–6] One of the most potent of these is carfentanyl, which is approximately ten thousand times more potent than morphine.[4,6–8] In addition, ($^{11}$C)- and ($^{18}$F)-labelled carfentanyl serves as a ligand for μ-opioid receptors in positron emission tomography diagnostics.[9–11]

The main synthetic route to carfentanyl is quite tedious, especially when performed on a large scale. The main reasons for this are difficulties in hydration of the α-substituted nitrile (**1**),[12–13] and the difficulty in working with the corresponding primary amide (**2**) and its subsequent conversions (*Scheme 1*).[6]




**Scheme 1.** Hydration of α-substituted nitrile.

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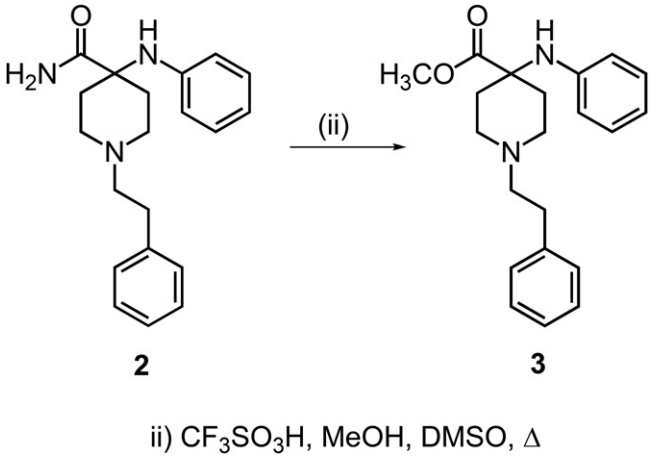
Improvements in the synthetic route have been made by several authors.[13–21] Some have focussed on the conversion of (**2**) to several carboxylate derivates. The first modification included formylation of the aminonitrile followed by subsequent formation and hydrolysis of an imidate to an amide.[14] The second approach proceeded through cyclization of the aminonitrile to 1-phenylspirohydantoin, with subsequent alkaline hydrolysis.[13] The third significant modification in the conversion of the nitrile to the amide was achieved by using dimethyl sulfoxide/hydrogen peroxide in the presence of a base.[15,16] Additionally, application of trimethyloxonium tetrafluoroborate was used for transforming the amide to an imidate, which was then converted to the desired methyl ester.[17] A straightforward *p*-toluenesulfonic acid (TsOH) catalyzed conversion of the amide to the methyl ester in a pressure vessel was reported.[16,18] A combination of trifluororacetic acid and $H_2SO_4$ was applied for preparation of the amide from the nitrile,[19,20] followed by cyclization to a spirodiaza intermediate and $H_2SO_4$ catalyzed methanolysis in a pressure vessel.[20] In addition, two previous approaches of carfentanyl synthesis on small scale included a multicomponent Ugi reaction.[21,22] Despite all the improvements and modifications done, further facilitations are still desirable, especially for an effective multi-gram production of carfentanyl.

We now report a convenient direct conversion of the amide (**2**) to the key intermediate (**3**), which does not require any special equipment. For this transformation we refluxed the amide in a methanolic solution containing approximately 15% (by volume) of trifluorormethanesulfonic acid (TfOH) (*Scheme 2*). Although the $CF_3SO_3H$ mediated formation of a propyl ester is known from the literature,[23] there is no information about application of this acid for amide methanolysis in the synthesis of synthetic opioids.




**Scheme 2.** $CF_3SO_3H$ mediated methanolysis of α-substituted primary amide.

Thus, application of $CF_3SO_3H$ in methanol at elevated temperature allowed us to convert the sterically hindered amide (**2**) to the corresponding methyl ester (**3**) at atmospheric pressure (*Scheme 2*). The reaction times were usually up to 4 days at reflux temperature. After purification the methyl ester (**3**) was obtained in 65% yield. Previously Weltrowska and co-workers accomplished the direct acid-catalyzed methanolysis of a structurally similar amide during the preparation of carba-carfentanyl on milligram scale.[16] The

methanolysis was performed in a glass pressure vessel at 105–110 °C using TsOH in MeOH, and gave the desired methyl ester with relatively low yield after some 4 days.

For optimization of the $CF_3SO_3H$ mediated amide methanolysis, we studied the effects of different concentrations of trifluoromethanesulfonic acid on the reaction time and conversion of the starting material to product. We started at 20% TfOH in MeOH and minimized the acid concentration to 2.5%. The results of those experiments are outlined in *Table 1*. The optimum content of $CF_3SO_3H$ was 15%.

**Table 1**
Optimization of $CF_3SO_3H$ Content in MeOH

| Entry | Content of $CF_3SO_3H$ (by volume) in MeOH, %[a] | Reaction time, days | Conversion % (HPLC) |
|---|---|---|---|
| 1 | 20 | 4 | 90 |
| 2 | 15 | 4 | 90 |
| 3 | 10 | 5 | 60 |
| 4 | 5 | 12 | 50 |
| 5 | 2.5 | 12 | < 30 |

[a]All experiments were made in the presence of a small amount DMSO (0.035 ml DMSO in 1ml MeOH).

We have also noticed that if methanolysis were performed with non-recrystallized amide (**2**) prepared by using $H_2O_2$/DMSO in the presence of a base,[15,16] containing some DMSO from the previous nitrile hydration step, the crude product contained only minor impurities. At the same time, if recrystallized and DMSO-free primary amide (**2**) was used in the methanolysis step, the amount of the impurities increased significantly. Due to this fortuitous observation, we decided to add DMSO to the reaction mixture (approx. 0.035 ml of DMSO per 1ml of $CH_3OH$) and obtained good results.

The crude product was purified by column chromatography on silica gel (DCM:EtOAc:iPrOH 6:2:1) and gave methyl ester (**3**) in 65% yield and purity of greater than 96% (HPLC).

In conclusion, we developed a convenient procedure for the direct preparation of a key intermediate in the synthesis of carfentanyl, suitable for multi-gram production.

## Experimental Section

All solvents and reagents were purchased from Merck, Sigma-Aldrich or TCI. Melting points were determined on electrothermal melting point apparatus (Mel-Temp®) and were corrected. Reactions were monitored by TLC (silica gel, Fluka, $F_{254}$, DCM:MeOH 8:1) and HPLC (Agilent HPLC system, 1260 series; column: C18, Gemini-NX, ACN:0.1% TFA, 35:65, 1ml/min). Flash chromatography was performed with silica gel (particle size 63-200 $\mu$m, DCM:EtOAc:iPrOH 6:2:1). $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker 700 MHz spectrometer in $CDCl_3$ as solvent with tetramethylsilane (TMS) as the internal reference.

*Safety Note*: *Since trifluorormethanesulfonic acid is volatile and extremely corrosive, the procedure should be performed in an efficient hood. Since mixing of trifluoromethanesulfonic acid with methanol is very exothermic, efficient cooling is required*

*during this step. Workers should wear protective equipment, including appropriate gloves and eye protection.*

***Methyl 4-(phenylamino)-1-(2-phenylethyl)-4-piperidinecarboxylate (3)***

Methanol (65 ml) was poured into a 250 ml round bottom flask and cooled to 0 °C in an ice bath. Trifluorormethanesulfonic acid (11.5 ml) was added dropwise to the MeOH with intensive stirring and cooling (***Caution***: Very corrosive vapors and liquid! Greatly exothermic process!). After the addition of $CF_3SO_3H$ was complete, the ice bath was removed and 2.2 ml DMSO was added, followed by the addition of 3.16 g amide (**2**). The reaction mixture was refluxed and monitored by TLC (DCM:MeOH, 8:1) until the starting material was mostly consumed (after about 4 days of refluxing), about 90% conversion. The reaction mixture was cooled down to room temperature and slowly poured into 300 ml of 10% aqueous $K_2CO_3$. The mixture was transferred to a separatory funnel and the product was extracted with 6 x 50 ml EtOAc. Combined extracts were washed with 2 x 50 ml aq. $NaHCO_3$ solution, followed by drying over anhydrous $Na_2SO_4$ and removal of the volatiles under reduced pressure. The obtained crude product was purified by flash chromatography on silica gel with DCM:EtOAc:iPrOH 6:2:1.

Methyl 4-(phenylamino)-1-(2-phenylethyl)-4-piperidinecarboxylate (2.09 g) was obtained in 65% yield as a creamy white solid, mp. 92-94 °C, lit.[6] mp. 94.9 °C; Rf =0.5; $^1$H NMR (700 MHz, $CDCl_3$) $\delta$: 2.08 (d, $J$ = 14.0 Hz, 2H, $CH_2$), 2.30 (t, $J$ = 10.5 Hz, Ph-$CH_2$-$CH_2$-N, 2H), 2.54 (t, $J$ = 10.5 Hz, Ph-$CH_2$-$CH_2$-N, 2H), 2.64 - 2.66 (m, 2H, $CH_2$), 2.73 (s, $CH_2$, 2H), 2.81–2.83 (m, $CH_2$, 2H), 3.69 (s, $COOCH_3$, 3H), 3.87 (s, NH, 1H), 6.58 (d, $J$= 8.4 Hz, Ar(H), 2H), 6.76 (t, $J$= 7.7 Hz, Ar(H), 1H), 7.14 - 7.16 (m, Ar(H), 2H), 7.19 - 7.21 (m, Ar(H), 3H), 7.25 - 7.29 (m, Ar(H), 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 32.86, 33.56, 48.99, 52.36, 58.17, 60.30, 115.51, 118.87, 126.16, 128.45, 128.69, 129.17, 139.99, 144.85, 175.68.

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