A novel method for synthesis of flutamide on the bench-scale

Mohammad Ghaffarzadeh* and Sahar Rahbar

Chemistry & Chemical Engineering Research Center of Iran, PO Box 14335-186, Tehran, Iran

Flutamide has been synthesised conveniently in high yields and by an economically beneficial method. Benzotrifluoride was first nitrated and the product was reduced and acylated in one pot in the presence of iron powder and isobutyric acid to produce 3-trifluoroisobutyranilide. Finally, flutamide was produced by further nitration.

Keywords: flutamide, prostate anticancer, reductive acylation, iron powder, nitro compounds, benzotrifluoride, isobutyric acid

Flutamide, 4-nitro-3-trifluoromethylisobutyranilide, is one of the most important anti-androgenic drugs without any hormonal activity for the treatment of prostate cancer. There are several methods for the synthesis of flutamide.[1–3] In most of the reported methods, activated acylating reagents, such as isobutyryl chloride or isobutyric anhydride, have been used for acylation of 3-trifluoromethylaniline. Another procedure reports the replacement of activated acylating agents, but 3-trifluoromethylaniline has still been used.[4] The preparation and storage of aniline compounds are difficult. The preparation from nitro compounds is usually using hydrogenation, which on the large scale needs special high pressure equipment and expensive catalysts. Other inexpensive methods for the synthesis of aniline compounds, such as metals in acid, produce impurities and large amounts of waste. It follows that eliminating the aniline producing step in the preparation of anilides can be very useful and have economic benefits.

Results and discussion

Nowadays, chemical process simplification, especially by diminishing the number of process steps and replacing expensive reagents by inexpensive ones, is an important development in the pharmaceutical industry. We report here a simplified process for flutamide preparation. In our methodology we eliminate the 3-trifluoromethyl aniline synthesis step and also replace the expensive acylating agents by iron powder in isobutyric acid (IBA). Our methodology is shown in Scheme 1;

The reductive acylation of nitro compounds to the corresponding *N*-acylated amines by iron powder in carboxylic acids was reported in 1977.[5] We have developed this method for the synthesis of flutamide using novel methodology and on the bench scale.

In order to achieve optimal conditions for the reaction, the second step was investigated thoroughly. The first step and third step were performed by known methods[4,6,7] with slight modification. In the second step, the reaction conditions such as time of reaction, temperature and molar ratios of reactants were optimised. Our investigations showed that the reaction temperature was the crucial parameter. At lower temperatures, the reaction did not proceed to completion; at room temperature and a long reaction time (10 h) only reduction of 3-trifluoronitrobenzene (3-TFNB) to the corresponding aniline without any acylation was detected. In a boiling water bath 37% of acylated product was obtained after 10 hours. So the boiling point of the isobutyric acid (IBA) was selected as the best reaction temperature. Optimisation of molar ratios of reactants and of the time of reaction are summarised in Tables 1 and 2.

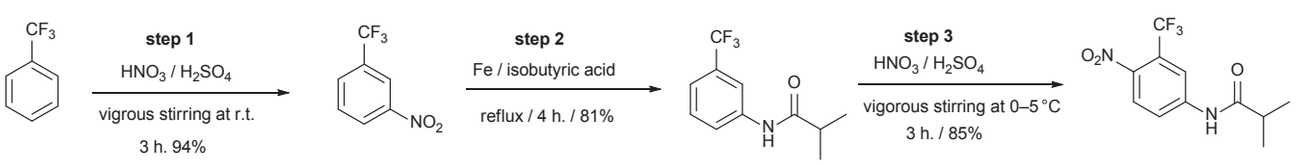
As shown in Tables 1 and 2, the optimum reaction time for preparing 3-trifluoroisobutyranilide is 4 h and the best molar ratio of 3-trifluoronitrobenzene: iron powder: isobutyric acid is 1 : 3 : 7 which is in good agreement with stoichiometry. To obtain

Table 1 Optimisation of molar ratios of reactants for 4 h reaction time

GC Run	3-TFNB : Fe : IBA/mol ratio	Yield/%
1	1 : 1 : 1	Trace
2	1 : 1 : 2	Trace
3	1 : 2 : 2	18
4	1 : 3 : 2	25
5	1 : 3 : 3	27
6	1 : 3 : 4	33
7	1 : 4 : 4	33
8	1 : 3 : 5	42
9	1 : 4 : 5	43
10	1 : 3 : 6	62
11	1 : 4 : 6	62
12	1 : 3 : 7	81
13	1 : 3 : 8	81
14	1 : 4 : 8	81

Table 2 Optimisation of reaction time with 1 : 3 : 7 molar ratios of reactants (3-TFNB: Fe: IBA)

GC Run	Time/min	Yield/%
1	10	0
2	30	0
3	60	0
4	90	15
5	120	36
6	150	63
7	180	72
8	210	80
9	240	81
10	270	81



Scheme 1 Synthesis of flutamide from benzotrifluoride.

* Correspondent. E-mail: mghaffarzadeh@ccerci.ac.ir

reproducible results usually slight excesses of iron powder and of isobutyric acid were used. The yields of optimisation reactions were determined by gas chromatography with purified samples as references.

In conclusion, our method is superior to other methods because 3-trifluoronitrobenzene is converted to the corresponding amide by inexpensive isobutyric acid and iron powder without any aniline intermediate and without converting the carboxylic acid into an acyl chloride or anhydride.

Experimental

^{1}H NMR spectra were recorded on Bruker AC 80 MHz using DMSO-d_6 as a solvent. IR (KBr) spectra were recorded on a Shimadzu-IR460 FTIR spectrometer. Melting points were determined by a Buchi B-545 apparatus and the GC analyses were recorded on a VARIAN CP-3800 gas chromatograph.

Synthesis of 1-nitro-3-trifluoromethylbenzene

This step was performed by modification of two literature methods.[6,7] A pre-cooled mixture of 98% sulfuric acid (190 mL, 3.5 mol) and 65% nitric acid (80 mL, 1.15 mol) ***(CAUTION**: strong acids)* was added dropwise to benzotrifluoride (73 g, 0.5 mol) with vigorous stirring and external cooling to room temperature. The mixture was stirred for 3 h and then poured onto crushed ice (700 g). Dichloromethane (250 mL) was added and organic phase was separated and dried with anhydrous sodium sulfate. After evaporating solvent and residual crude product under reduced pressure on a boiling water bath, 1-nitro-3-trifluoromethylbenzene (89.8 g, 0.47 mol) was obtained as a yellow oil (94% based on benzotrifluoride). It was enough pure for the next step.

Synthesis of 3-trifluoromethylisobutyranilide

Iron powder (60 g, 1.07 mol) was added gradually to a mixture of 1-nitro-3-trifluoromethyl benzene (63.5 g, 0.33 mol) and isobutyric acid (220 mL, 2.42 mol) under reflux conditions in a nitrogen atmosphere was added over about 15 min. Heating and mixing was continued for 4 h, and then the mixture was poured into a mixture of concentrated hydrochloric acid (200 mL) and crushed ice (500 g) and agitated for 15 minutes. The reaction mixture was extracted with ethyl acetate (2 × 500 mL). After evaporating to dryness, the crude product was dissolved in methanol (1000 mL) and after adding charcoal (10 g), the mixture was boiled for 10 minutes and filtered while it was hot. Water (2500 mL) was added to the solution obtained with stirring and cooling to 0–5 °C. The mixture was kept at 0–5 °C for 2 h. Flaky cream crystals were obtained. 3-Trifluoromethylisobutyranilide (62 g, 0.268 mol) was filtered under suction (81% based on the starting material). M.p. 117–118 °C (lit.[4] 115–120 °C). IR(KBr) ν = 663, 892, 1069, 1107, 1252, 1275, 1388, 1165, 2979, 3253. ^{1}H NMR (80 MHz, DMSO-d_6) δ = 1.05 (d, 6H, $(CH_3)_2$), δ 2.48 (m, 1H, CH), δ7.31 (m, 2H, ArH), δ 7.72 (d, 1H, ArH), δ7.95 (m, 1H, ArH), δ 8.08 (s, 1H, ArH), 10.10 (bs, 1H, NH).

Synthesis of flutamide

Flutamide was synthesised and purified by modification of a literature procedure.[4] 3-Trifluoromethylisobutyranilide (58 g, 0.25 mol) was dissolved in concentrated sulfuric acid (200 mL, 2.2 mol) at 0–5 °C with efficient agitation ***(CAUTION**: strong acid)*. A pre-cooled mixture of 98% sulfuric acid (20 mL, 0.22 mol) and 65% nitric acid (20 mL, 0.29 mol) ***(CAUTION**: strong acids)* was added drop-wise to the above solution while the temperature was controlled at 0–5 °C. Stirring was continued for 3 h, and the mixture was poured onto crushed ice (500 g) mixed efficiently with a mechanical stirrer in a 2 L beaker. The crude product was filtered under suction. The precipitate obtained was dissolved in 96% ethanol (350 mL) under reflux and decolourised with charcoal (10 g) by 15 minutes heating and filtered. The filtrate was cooled and precipitated with drop-wise addition of distilled water (1.5 L). After 60 min in an ice-cooled bath the yellow precipitate was filtered off and dried in a good ventilating hood. The impure product (50 g, 0.18 mol) was twice re-crystallised from toluene (150 mL) for further purification. The pale yellow needle-shaped crystals (41 g, 0.15 mol) of flutamide were obtained after gentle drying under reduced pressure (60% based on the starting material, 3-trifluoroisobutyranilde). The overall yield of three steps was 45% based on benzotrifluoride. M.p. 111.5–112 °C (lit.[4,1] 111.5–112 °C and 110–111 °C). IR(KBr) ν = 3360 (N–H, stretching), 3100–3000 (C–H aromatic), 1717 (C=O), 1543 (N–H, bending), 1517 and 1347 (N–O), 1243 (C–F). ^{1}H NMR (80 MHz, DMSO-d_6) δ = 1.02 (d, 6H, $(CH_3)_2$), 2.57 (m, 1H, $CH(CH_3)_2$), 7.75 (d, 2H, ArH), 8.20 (s, 1H, ArH), 10.27 (bs, 1H, N–H).

Received 11 December 2013; accepted 1 February 2014
Paper 1302330 doi: 10.3184/174751914X13929219796481
Published online: 2 April 2014

References

1 J.W. Baker, G.L. Bachman, I. Schumacher, D.P. Roman and A.L. Tharp, *J. Med. Chem.,* 1967, **10**, 93.
2 R.O. Neri and J.G. Topliss, US Patent 4144270, 1979.
3 L. Peer and J. Maye, US Patent 4302599 1981.
4 B.P. Bandgar and S.S. Sawant, *Synth. Commun.*, 2006, **36**, 859.
5 D.C. Owsley and J.J. Bloomfield, *Synthesis*, 1977, 118.
6 G.C. Finger, N.H. Nachtrieb and F.H. Reed, *Illinois State Acad. Sci. Trans.,* 1939, **31**, 132.
7 J.F. Lamendola, D. Vashi and R.G. Tyson, US Patent 4831193, 1989.
8 R.G. Stabile and A.P. Dicks, *J. Chem. Educ.*, 2003, **80**, 1442.