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Technical Notes

An Improved and Scalable Process for Celecoxib: A Selective Cyclooxygenase-2 Inhibitor§

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Abstract:

An improved, scalable and commercially viable process is developed for an active pharmaceutical ingredient, celecoxib.

Introduction

Pyrazoles have been widely described as pharmaceutical therapeutic agents, including antiinflammatories and antidiabetics. Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl] benzene sulfonamide, Figure 1) was the first cyclooxygenase-2 (COX-2) inhibitor approved for the treatment of rheumatism and osteoarthritis.[1,2] This drug was devoid of the usual adverse effects associated with conventional nonsteroidal antiinflammatory agents.[3] Celecoxib was developed by GD Searle, currently available in the market under the brand name of Celebrex.

The preparation of pyrazoles from the condensation of diketones with hydrazines is well documented[4] in the literature. The first reported synthetic method[5−7] for the preparation of celecoxib involved condensation of diketone **2** with phenyl hydrazine hydrochloride **3** in refluxing ethanol, and this reaction yielded celecoxib **1** along with regioisomer **4** in the ratio of 99.5:0.5 with a yield of around 46% (Scheme 1). O'Shea and co-workers[8] described a two-step process for the preparation of celecoxib from a similar condensation of a diketone **2** and phenyl hydrazine hydrochloride **3** in an amide solvent. The celecoxib was obtained as a solvate of the amide solvent and was subsequently isolated and recrystallised from isopropanol and water to produce an unsolvated celecoxib. Usage of multisolvent system and repeated crystallizations made this process less attractive. Zhi and co-workers[9] synthesized celecoxib by reacting diketone **2** with phenyl hydrazine hydrochloride **3** in a mixture of 90% ethanol and methyl *tert*-butyl ether

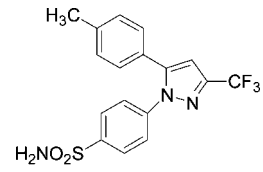

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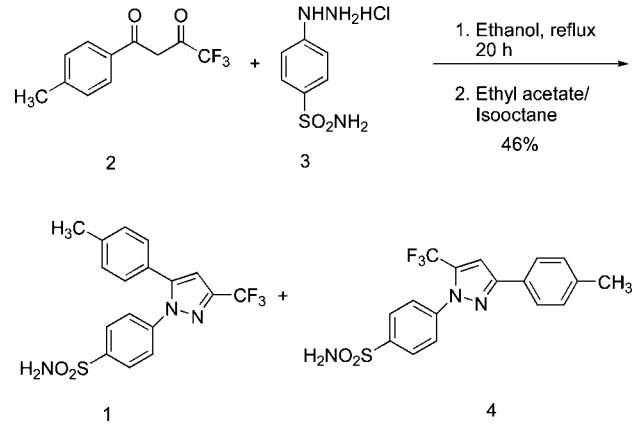
Figure 1. **Chemical structure of celecoxib.**

Scheme 1. **Synthetic scheme of celecoxib**



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(MTBE). Concentration of the reaction mass followed by dilution with water provided celecoxib in 73% yield.

In an alternative process,[10] the condensation was performed in the presence of trifluoroacetic acid (0.5−1.5 equiv) in isopropyl alcohol. The yield and quality were good, but the work-up process was laborious, involving repeated pH adjustment and 12−14 h maintenance for isolation. Furthermore, as the isopropyl alcohol is miscible in water, it can not be recovered through normal distillation.

Thus, the reported processes suffer from several disadvantages such as (a) lengthy reaction time (20 h), (b) purification using a mixture of solvents, (c) a relatively higher content of regioisomer impurity (0.5%), and (d) usage of a multisolvent system, making the processes less viable for commercial production. Herein we describe an improved, economic, simple and scalable process for the preparation of celecoxib that meets the regulatory quality requirements.[11] Our process involves condensation of diketone **2**[6,12] and phenyl hydrazine hydrochloride **3**[12,13] in a mixture of ethyl acetate and water to provide celecoxib in a yield of 84% after recrystallisation from toluene.

Results and Discussion

Condensation of 4,4,4-trifluoro-1-[4-(methyl)phenyl]-butane-1,3-dione (**2**) and 4-sulfonamidophenyl hydrazine hydrochloride (**3**) in a mixture of ethyl acetate and water, followed by usual work-up furnished crude celecoxib containing <0.5% of 4-[3-(4-methylphenyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (**4**), a regioisomer of celecoxib (specification limit is not more than 0.15%). Recrystallisation of this crude material from toluene afforded celecoxib in 84% yield with more than 99.97% purity and ≤0.03% of regioisomer **4**.

Different solvent media such as methanol, ethanol, isopropanol, ethyl acetate, toluene, water, a mixture of water and toluene, and a mixture of water and ethyl acetate were explored to obtain celecoxib in high yields from the condensation of diketone **2** and phenyl hydrazine derivative **3**. A mixture of water and ethyl acetate was found to be the best solvent system in terms of yield of **1** (Table 1). When reaction was conducted in simple aqueous medium, the yield of the resulting celecoxib was comparable to that obtained from aqueous ethyl acetate, but regioisomer **4** was formed at a slightly higher level; hence, a mixture of water and ethyl acetate medium was selected for further optimization. By increasing the ethyl acetate ratio in the solvent mixture, the yield of celecoxib was decreased because of its high solubility in ethyl acetate. On the other hand, increasing the water content in the solvent mixture led to a higher amount of regioisomer **4** in the product. The 1:1 ratio of the mixture of water and ethyl acetate was found to be suitable to obtain celecoxib in quantitative yield with good purity (Table 2).

Table 1. **Optimization of solvent in the condensation reaction of compounds 2 and 3**

entry	solvent	celecoxib **1** (%)	regioisomer **4** (%)	yield (%)[b]
1	methanol	97.0	3.0	80
2	ethanol	98.0	2.0	77
3	isopropanol	98.2	1.8	85
4	ethyl acetate[a]	–	–	–
5	toluene[a]	–	–	–
6	water	96.7	3.3	97
7	water and toluene	97.0	3.0	87
8	water and ethyl acetate	98.5	1.5	95

[a] Reaction was not initiated. [b] Isolated yield.

Table 2. **Optimization of solvent mixture in the condensation reaction of compounds 2 & 3**

entry	water:EA[a] ratio	celecoxib **1** (%)	regioisomer **4** (%)	yield (%)[c]
1	0:1[b]	–	–	–
2	1:0	96.76	3.10	97
3	1:1	98.56	1.36	95
4	1:2	99.46	0.41	79
5	1:3	99.83	0.12	71

[a] Ethyl acetate. [b] Reaction was not initiated. [c] Isolated yield.

Table 3. **Impact of reaction temperature on the yield of celecoxib**

entry	temperature (°C)	reaction time (h)	celecoxib **1** (%)	regioisomer **4** (%)	yield (%)[c]
1	reflux (75−85)	2	99.31	0.5	95
2	55−65	7[a]	99.26	0.7	88
3	25−35	14[b]	98.46	1.5	66

[a] 90% reaction was completed. [b] 70% reaction was completed. [c] Isolated yield.

To study the impact of reaction temperature on reaction time and content of regiosiomer, experiments were conducted at different temperatures. The results clearly indicated that the reaction temperature plays a major role. While the reaction was completed within 2 h at reflux temperature, the reaction got slowed down, and the regioisomer content increased by decreasing the reaction temperature (Table 3).

Enhanced formation of regioisomer **4** at lower reaction temperatures may be attributed to the formation of diketone hydrate **5** resulting from the attack of nucleophile (H_2O) at the more electropositive carbonyl carbon. Subsequent reaction of hydrazine function at the aroyl carbonyl leads to regioisomer **4** (Scheme 2).[10]

Celecoxib was isolated through a simple work-up process by cooling the reaction mixture to 0−5 °C and subsequent filtration after 1−1.5 h stirring. Isolation temperature and time did not have any significant impact on the quality and yield of the product.

The crude clecoxib containing <0.5% of regioisomer was subjected to further purification to meet the regulatory requirements.[11] The reported purification process for celecoxib involved a mixture of isopropanol and water,[4h] a mixture of ethyl acetate and isooctane/[5,6]dichloromethane and hexane.[7] We have explored the methanol, isopropanol, toluene, and ethyl acetate to use a single solvent for the recrystallisation process. Yield and quality were excellent when celecoxib was recrystallised from

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Scheme 2. **Pathway for the formation of diketone hydrate 5**

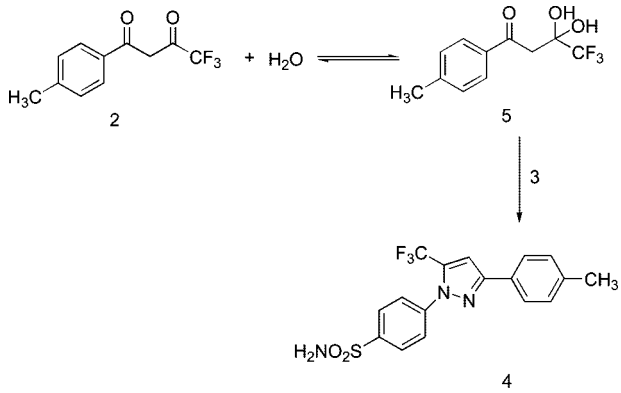

Table 4. **Optimization of solvents for recrystallisation of celecoxib**

entry	solvent	celecoxib **1** (%)	regioisomer **4** (%)	yield (%)[a]
1	methanol	99.80	0.12	50
2	isopropyl alcohol	99.95	0.05	72
3	toluene	99.92	0.06	92
4	ethyl acetate	99.70	0.27	28

[a] Isolated yield.

Table 5. **Experimental results of different isolation temperatures**

entry	temperature (°C)	celecoxib **1** (%)	regioisomer **4** (%)	yield (%)[a]
1	0−5	99.89	0.06	95
2	10−15	99.88	0.07	95
3	25−35	99.91	0.04	90
4	40−45	99.94	0.03	84

[a] Isolated yield.

Table 6. **Experimental results of celecoxib by using recovered ethyl acetate**

entry	ethyl acetate	celecoxib **1** (%)	regioisomer **4** (%)	yield (%)[a]
1	fresh	99.3	0.7	95
2	recovered	99.2	0.8	93

[a] Isolated yield.

toluene (Table 4). Hence, further optimization was carried out by using toluene.

In the recrystallisation of crude celecoxib, isolation temperature was impacting the yield of the product. Thus, no significant change was observed by isolating the celecoxib at 0−5 °C and 10−15 °C, but further increases in the temperature led to lower yields due to the enhanced solubility of the product in ethyl acetate at the higher temperatures (Table 5).

Solvents used for the condensation reaction and recrystallisation were recovered (65% of ethyl acetate and 85% of toluene) by simple distillation and were reused in the preparation of celecoxib (Tables 6 and 7).

In the recovered ethyl acetate ~25% of ethanol and ~5% of acetic acid were observed. Experiments were conducted with

Table 7. **Experimental results of celecoxib recrystallisation from recovered toluene**

entry	toluene	celecoxib **1** (%)	regioisomer **4** (%)	yield (%)[a]
1	fresh	99.9	0.1	95
2	recovered	99.9	0.1	95

[a] Isolated yield.

Table 8. **Experimental results of final optimized process**

entry	celecoxib **1** (%)	regioisomer **4** (%)	yield (%)[a]
1	99.97	0.03	84
2	99.98	0.02	83
3	99.97	0.03	84

[a] Isolated yield.

recovered ethyl acetate, and no significant impact was observed on the yield and quality of celecoxib.

The quality of recovered toluene matches that of fresh solvent.

In the final optimized process, celecoxib was obtained with consistent quality with a yield of around 84% (Table 8).

Conclusion

In conclusion, we have developed an improved, scalable, and commercially viable manufacturing process for the preparation of celecoxib with a yield of around 84%, and this active pharmaceutical ingredient is substantially free of impurities and meets the regulatory requirements.

Experimental Section

A liquid chromatograph equipped with a variable wavelength UV detector and integrator was used in recording HPLC. Mass spectra were obtained using a 4000-Q-trap LC/MS/MS mass spectrometer. ^{1}H NMR and ^{13}C NMR were recorded in DMSO-d_6 at 400 and 100 MHz, respectively, on a Mercury Plus (Varian 400 MHz) FT NMR spectrometer; the chemical shifts are reported in δ ppm relative to TMS (δ 0.00 ppm) and DMSO-d_6 (δ 39.5 ppm) as internal standards, respectively.

4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (Celecoxib). A mixture of 4,4,4-trifluoro-1-[4-(methyl) phenyl]-butane-1,3-dione (17.0 kg, 73.91 mol), 4-sulfonamidophenyl hydrazine hydrochloride (17.85 kg, 79.86 mol), water (85 L, 1.15 L/mol) and ethyl acetate (85 L, 1.15 L/mol) was heated to reflux for 2 h. The reaction mixture was cooled to 0−5 °C and stirred for 1−1.5 h. The obtained solid was filtered under reduced pressure and washed with water (34 L, 0.46 L/mol). Wet material was taken into toluene (375 L, 5.07 L/mol) and heated to 80−85 °C, and the aqueous layer was separated. The organic layer was cooled to 10−15 °C and stirred for 1−1.5 h. The isolated solid was filtered, washed with toluene (25 L, 0.34 L/mol), and dried at 75−85 °C for 6−8 h under reduced pressure to give the title compound. Yield 23.7 kg (84%); purity by HPLC 99.97%; regioisomer 0.03%; DSC 162.14 °C; Heavy metals <10 ppm; M/S *m/z* 382 $M^+ + H$; IR (KBr) cm^{-1} 3341, 3235 (N−H); ^{1}H NMR, (DMSO-d_6) δ 7.89 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H); 7.52 (s, NH_2);

7.22 (m, 4H); 7.17 (s, 1H); 2.32 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 20.7, 37.4, 106.1, 121.5, 125.3, 125.9, 126.8, 128.7, 129.4, 139.1, 141.1, 142.2, 144.0, 145.2, 267.4; Anal. Calcd for $C_{17}H_{14}F_3N_3O_2S$: C 53.53, H 3.69, N 11.01, S 8.39. Found: C 53.50, H 3.70, N 11.01, S 8.44.

HPLC Conditions: Column: Kromasil 100 C18, 250 mm $\times$ 4.6 mm $\times$ 5 μm

Wavelength: 258 nm

Flow: 0.8 mL/min

Temperature: 25 °C

Injection load: 10 μL

Run time: 60 min

Mobile phase A: buffer (1.36 g potassium dihydrogen phosphate and 0.22 g octane-1-sulfonic acid sodium salt in 1 L of milli-Q water. pH adjusted to 3.3 with dilute H_3PO_4)

Mobile phase B: acetonitrile and water in the ratio of 7:3

Gradient program: time (min): 0 8 20 30 42 45 60

% of mobile phase A: 50 50 10 5 5 50 50

% of mobile phase B: 50 50 90 95 95 50 50

Retention time of celecoxib: ~29.2 min

Retention time of regioisomer: ~30.9 min

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