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Synthesis of celecoxib via 1,3-dipolar cycloaddition

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Abstract—A regioselective 1,3-dipolar cycloaddition reaction between a nitrile imine and an enamine is described for the preparation of celecoxib. Nitrile imines are generated in situ from the corresponding hydrazonoyl benzenesulfonates.

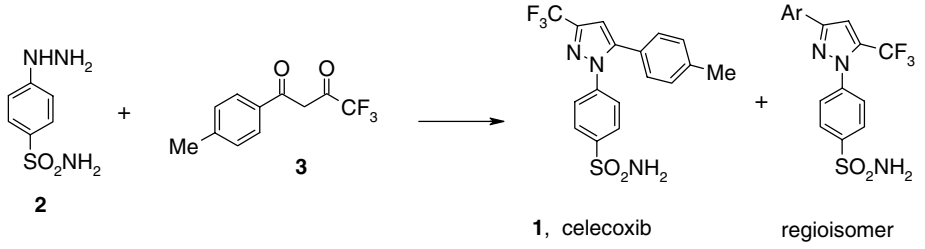
1. Introduction

The 1,3,5-trisubstituted pyrazole structural motif is found in numerous drug targets including the widely prescribed COX-2 inhibitor CELEBREX (celecoxib) **1**. A common approach into these systems, including the commercial process, is to react 4-sulfamidophenylhydrazine **2** with diketone **3** (Scheme 1). However, a regioisomeric mix of both pyrazoles is often produced, requiring the development of a crystallization protocol to obtain a regiopure material.[1] In another strategy, phenyl hydrazines are reacted with trifluoromethyl butynones in a one pot 1,4-conjugate addition/cyclization protocol. Whilst only one regioisomer can be produced, the synthesis of intermediates requires a number of steps (including palladium catalysis), many of which rely on column chromatography to generate a clean material.[2]

1,3,5-Trisubstituted pyrazoles can also be assembled via a 1,3-dipolar cycloaddition between a nitrile imine dipole and a dipolarophile. The appropriate electronic pairing of the dipole precursor and dipolarophile is crucial in ensuring both reactivity and regioselectivity.[3] Herein is described a completely regioselective synthesis of celecoxib via nitrile imine **4** and enamine **5** (Scheme 2).

2. Results and discussion

Nitrile imine dipoles, such as **4**, can be generated in a variety of ways including the oxidation of aldehyde hydrazones,[4] thermolysis of 2,5-disubstituted tetrazoles[5] or oxadiazolin-5-ones[6] and by the photochemical degradation of sydnones.[7] One of the more practical and scalable methods is the dehydrohalogenation of hydrazonoyl halides (via NBS/NCS treatment of the corresponding hydrazones) such as **9**.[8] The dipole is generated in situ using a base such as triethylamine. However, in the case of celecoxib synthesis, the trifluoroacetaldehyde (or its derivatives) required for the formation of hydrazonoyl chloride **9** is expensive and in a limited supply. Previous reports have shown more economical ways around this problem by utilizing



Scheme 1.

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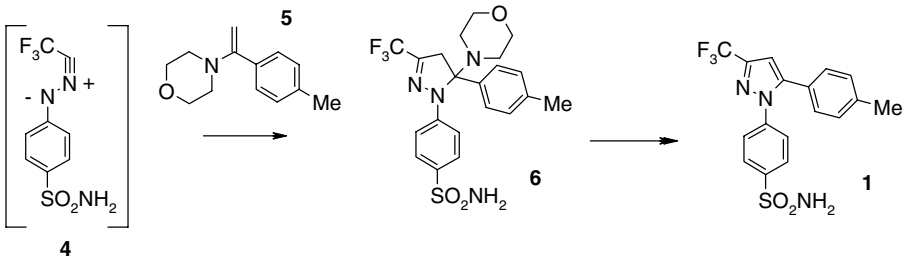


Scheme 2.

trifluoroacetylated hydrazines as intermediates in nitrile imine preparations.[9] The acylation of 4-sulfonamidophenylhydrazine **7** with trifluoroacetic anhydride affords the trifluoroacetylated hydrazine **8**. From **8**, either the hydrazonoyl chloride **9**[9] (an oil) or the hydrazonoyl benzenesulfonate **10** (a crystalline, air and moisture stable solid) can be prepared (Scheme 3). Both precursors were evaluated for their reactivity with potential dipolarophiles.

Typical dipolarophiles in a 1,3-dipolar cycloaddition are substituted alkynes or olefins.[3,10,11] Since this is a LUMO-dipole, HOMO-dipolarophile controlled reaction, a number of electron-rich olefins (which raise the HOMO)[3b] such as TMS enol ether **11**, 1,1-disubstituted enamine **5**[10] and 1,2-disubstituted enamine **12**[12] were prepared. The commercially available 4-methylphenylacetylene **13** was also screened as a dipolarophile (Fig. 1). Hydrazonoyl chloride **9** proved to be an unreactive partner with all the dipolarophiles screened, requiring extended reactions times and affording low yields. In the same manner, potential dipolarophiles such as TMS enol ether **11** and 4-methylphenylacetylene **13** produced very little of pyrazole product even at elevated temperatures with either hydrazonoyl chloride **9** or benzenesulfonate **10** as the dipole precursor.

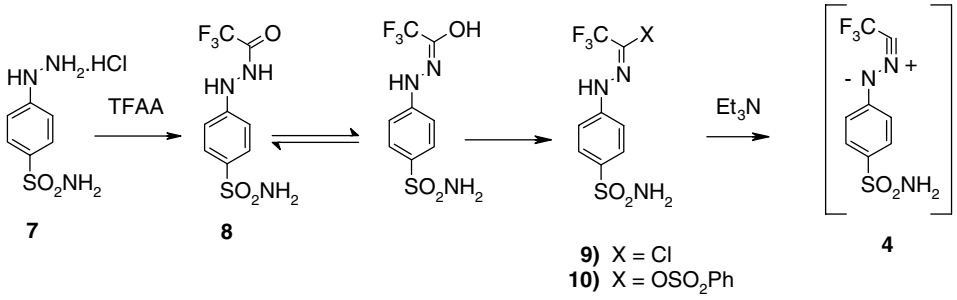
On the other hand, when benzenesulfonate **10** is utilized in conjunction with 1,1-disubstituted enamine **5**, a fast and clean reaction ensued to generate the 1,3,5-pyrazole, celecoxib, with 100% regioselectivity. In order to confirm the regiochemistry, 1,2-disubstituted enamine **12** was employed as the dipolarophile producing *only* 1,3,4-pyrazole isomer **14**, albeit in a more sluggish, low yielding reaction (Scheme 4). None of the 1,3,5-regioisomer was detected by LC, thus indicating that regiocontrol during the cycloaddition is governed entirely by the enamine substitution and that the reactivity of 1,2-disubstituted enamines is less than the corresponding 1,1-disubstituted version.[11]

In conclusion, the preparation of celecoxib was accomplished via a 1,3-dipolar cycloaddition with complete regioselectivity, between a nitrile imine dipole, generated in situ from hydrazonoyl benzenesulfonate **10**, and 1,1-disubstituted enamine **5**. The protocol is simple and practical, employing economical and readily available reagents. In the three steps, the overall yield from 4-sulfonamidophenylhydrazine **2** is 52%.

3. Experimental

3.1. 4-[2-(Trifluoroacetyl)hydrazino]benzenesulfonamide (8)

Sulfonamidophenylhydrazine hydrochloride (25 g, 0.11 mol) is slurried in acetonitrile (125 mL) and cooled to 5–10 °C. Trifluoroacetic acid anhydride (17.3 mL, 0.12 mol) is added dropwise and the reaction mixture



Scheme 3.

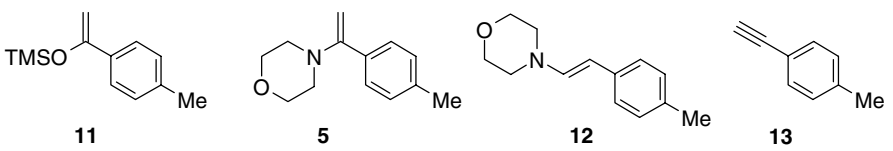
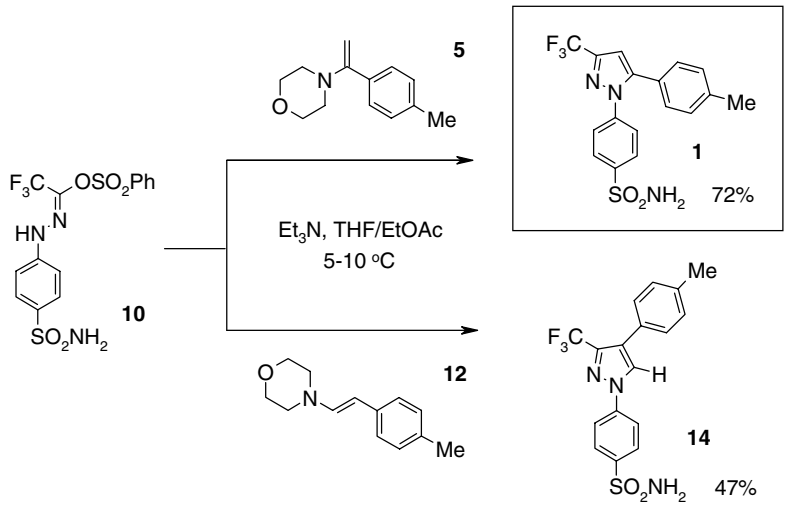


Figure 1.



Scheme 4.

is allowed to warm up to room temperature over 4 h. The slurry is concentrated in vacuo to approximately 1/3 of the original volume and tbme–heptane (60:60 mL) is added to precipitate the product out. The slurry is cooled to 0–5 °C, held for 1 h, filtered and washed with heptanes. The cake is collected and dried in vacuo at 50 °C. Yield = 26.5 g (90%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.56 (1H, s), 8.80 (1H, br s), 7.66 (2H, d, $J = 8.0$ Hz), 7.12 (2H, br s), 6.81 (2H, d, $J = 8.0$ Hz).

3.2. *N*-[4-(Aminosulfonyl)phenyl]-2,2,2-trifluoroethanehydrazonoyl benzenesulfonate (10)

Trifluoroacetylated hydrazine **8** (11.0 g, 41.4 mmol) is slurried in ethyl acetate (88 mL) and cooled to 5–10 °C in an ice bath. Benzenesulfonyl chloride (6.4 mL, 49.6 mmol) is added, followed by dropwise addition of *N*-methylmorpholine (4.8 mL, 43.3 mmol). The reaction mixture is held for 1 h at 5–10 °C after which water (44 mL) is added and the mixture is stirred for 0.5 h. The organic layer is separated from the aqueous layer and washed with brine (44 mL). After a phase cut, the organic layer is dried over $MgSO_4$ and concentrated to approximately 45 mL. Heptane (45 mL) is added at room temperature to triturate out the product which is dried in a vacuum oven at 50 °C. Yield = 14.1 g (80.6%).

^{1}H NMR (400 MHz, DMSO-d_6) 10.97 (1H, s), 8.13 (2H, d, $J = 4.0$ Hz), 7.86 (1H, t, $J = 8.0$ Hz), 7.73 (4H, m), 7.22 (4H, m).

3.3. 4-[1-(4-Methylphenyl)vinyl]morpholine[13] (5)

Morpholine (40 mL, 450.0 mmol) is added to a slurry of toluene (80 mL) and sodium sulfate (50 g) at 5 °C. Titanium tetrachloride (8.2 mL, 74.4 mmol) is added dropwise to form a light green slurry (Ti–morpholine complex). Diisopropylethylamine (28.0 mL, 370.0 mmol) is added, followed by 4-methylacetophenone (10 g, 74.4 mmol). The reaction is heated to 70 °C for 3 h. Once the reaction is deemed complete (approximately 2–3 h), it is cooled to 5–10 °C and filtered. The cake is washed with toluene, which is added to the filtrate. The combined filtrates are concentrated until morpholine is <10 mol % (via GC) with respect to **5**. THF (40 mL) is added to the crude morpholine enamine **5** followed by triethylamine (13.5 mL, 96.7 mmol) and stored cold until further use.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (2H, d, $J = 8.0$ Hz), 7.16 (2H, d, $J = 8.0$ Hz), 4.32 (1H, s), 4.17 (1H, s), 3.78 (4H, t, $J = 8.0$ Hz), 2.85 (4H, t, $J = 8.0$ Hz), 2.38 (3H, s).

3.4. Celecoxib (1)

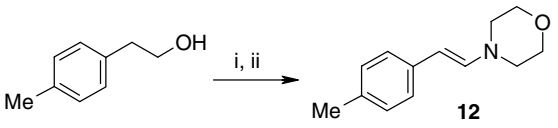
Hydrazonoyl benzenesulfonate **10** (12.1 g, 28.6 mmol) is dissolved in 60 mL THF and cooled to 5–10 °C. The solution of morpholine enamine **3** solution (33 g of the THF/Et_3N solution, 30.0 mmol) is added dropwise over 10 min. The reaction is complete once the addition is finished. HCl (20 mL, 4 N) is added and stirred for 0.5–1 h after which ethyl acetate (60 mL) is added and a phase cut is performed. The organic layer is washed with water (60 mL) and dried over $MgSO_4$. After concentrating to 25 mL, heptanes (50 mL) are added and the resulting slurry is filtered to produce 10.9 g of crude celecoxib. The crude product is recrystallized in a mixture of hot isopropanol–water (60:60 mL) to generate an off-white solid. Yield = 8.7 g (72%). DSC = 159.7–162.2 °C, $\Delta H_f = 92.03$ J/g (ramp 10 °C/min).

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.88 (2H, dt, $J = 8.7$, 2.4 Hz), 7.54 (dt, 2H, $J = 8.7$, 2.4 Hz), 7.52 (s, 2H), 7.29–7.13 (5H, m), 2.32 (3H, s).

References and notes

1. Letendre, L.; McGhee, W. D.; Snoddy, C.; Klemm, G.; Gaud, H. T. WO 03/09974 A1.
2. Reddy, M.; Ramana, V.; Bell, S. C. WO 03/024400 A2.
3. (a) Bianchi, G.; DeMicheli, C.; Gandolfi, R. 1,3-Dipolar Cycloadditions Involving X = Y Groups. In *The Chemistry of Double Bonded Functional Groups*; Patai, S., Ed.; Interscience: London, 1977; pp 369–532; (b) Carruthers,

W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: New York, 1990.
4. (a) Rai, K. M. L.; Hassner, A. *Synth. Commun.* **1989**, *19*, 2799; (b) Rai, K. M. L.; Linganna, N. *Synth. Commun.* **1997**, *27*, 3737; (c) Chen, D. W.; Chen, Z. C. *Synth. Commun.* **1995**, *25*, 1617; (d) Bishop, J. E.; Flaxman, K. A.; Orlek, B. S.; Sammes, P. G.; Weller, D. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2551; (e) Gladstone, W. A. F.; Aylward, J. B.; Norman, K. O. C. *J. Chem. Soc.* **1969**, 2587.
5. (a) Clovis, H. S.; Eckell, A.; Huisgen, R.; Sustmann, R. *Chem. Ber.* **1967**, *100*, 60; (b) Huisgen, R. *Angew. Chem.* **1960**, *72*, 359; (c) Butler, R. N. *Adv. Heterocycl. Chem.* **1977**, *21*, 323.
6. (a) Sauer, J.; Mayer, K. K. *Tetrahedron Lett.* **1968**, *9*, 325; (b) Marky, M.; Meier, J.; Wunderli, A.; Heimgartner, H.; Schmid, H.; Hansen, H. J. *Helv. Chim. Acta* **1978**, *61*, 1477.
7. (a) Ollis, W. D.; Ramsden, C. A. *Adv. Heterocycl. Chem.* **1976**, *19*, 1; (b) Gotthard, H.; Reiter, F. *Tetrahedron Lett.* **1971**, *12*, 2749; (c) Pfoetner, K. H.; Foricher, J. *Helv. Chim. Acta* **1980**, *63*, 653.
8. (a) Tanaka, K.; Maeno, S.; Mitsuhashi, K. *J. Heterocyl. Chem.* **1985**, *22*, 565; (b) Tanaka, K.; Maeno, S.; Mitsuhashi, K. *Chem. Lett.* **1982**, *4*, 543; (c) Shawali, A. S.; Párkányi, C. *J. Heterocyl. Chem.* **1980**, *17*, 833; (d) Sharp, J. T. Nitrile Ylides and Nitrile Imines. In *1,3-Dipolar Cycloadditions*; Padwa, A., Pearson, W. H., Eds.; Interscience: New York, 2002; pp 376–378.
9. (a) Zhou, J.; Oh, L. M.; Confalone, P.; Li, H. Y.; Ma, P. U.S. Patent 6,329,527 B1; (b) Zhou, J.; Oh, L. M.; Ma, P.; Li, H. Y. WO 03/049681.
10. Enamines have been used previously with nitrile imines to enhance the reactivity. See: (a) Nomura, Y.; Takeuchi, Y.; Tomoda, S.; Ito, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 261; (b) Meilahn, M.; Cox, B.; Munk, M. *J. Org. Chem.* **1975**, *40*, 819.
11. For studies on the relative reactivity of olefins as dipolarophiles, including the effects of 1,1- versus 1,2-substitution, see: Jäger, V.; Colinas, P. A. Nitrile Oxides. In *1,3-Dipolar Cycloadditions*; Padwa, A., Pearson, W. H., Eds.; Interscience: New York, 2002; pp 376–378.
12. Preparation of morpholine enamine **12** from 4-methylphenethylalcohol. Reagents and conditions: (i) SO_3·pyr, CH_2Cl_2, 0 °C; (ii) morpholine 5 equiv, THF, 20 °C.



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13. Modified procedure of Carlson, R.; Nilsson, Å.; Strömquist, M. *Acta Chem. Scand.* **1983**, *B37*, 7.