

Synthesis of RWJ 68354: A Potent Inhibitor of the MAP Kinase p38

James R. Henry* and John H. Dodd

The R.W. Johnson Pharmaceutical Research Institute, Route 202 PO Box 300 Raritan, NJ 08869

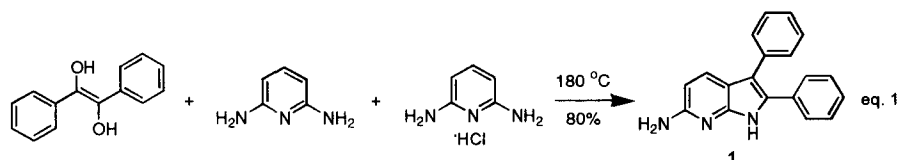
Received 29 July 1998; revised 11 September 1998; accepted 18 September 1998

Abstract: The regiospecific synthesis of RWJ 68354, a potent inhibitor of the p38 MAP kinase, via a variation of the Bischler-Möhlau indole synthesis is reported. © 1998 Elsevier Science Ltd. All rights reserved.

The MAP kinase p38 has been established as a key player in the intracellular signal transduction cascade required for the biosynthesis of the inflammatory cytokines IL-1 and TNF- α .¹ As such, p38 has recently attracted much interest as a potential target for anti-inflammatory drugs. These drugs would possess a novel mode of action which would attack the disease state of disorders like rheumatoid arthritis, rather than merely treat their symptoms. RWJ 68354 has proven to be a highly selective inhibitor of p38, orally active, and extremely potent in vitro (6 nM) and in vivo. Because of these attributes it has been selected for further biological study requiring large amounts of compound. We wish to report its novel and straightforward preparation.

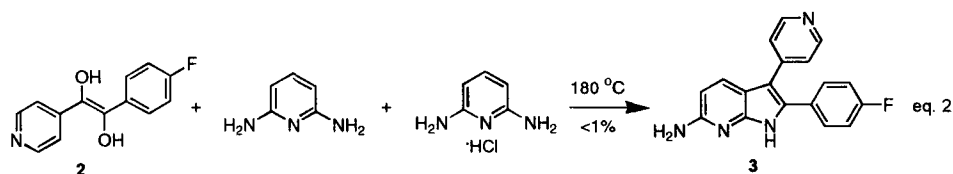


In the late 1940's, Bernstein et al.² reported the synthesis of pyrrolopyridine **1** via the condensation of benzoin, 2,6-diaminopyridine, and the latter's HCl salt under melt conditions (180 °C) to give the product in 80% yield (eq. 1).



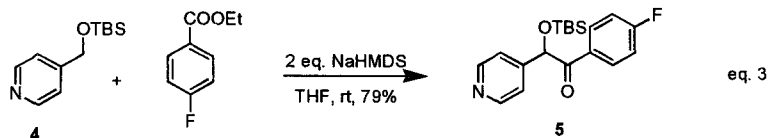
This reaction was repeated by Herbert and Wibberley³ with 4,4'-dimethoxybenzoin with similar results, however the reaction was reported to not be general.

We began our work by preparing the simple analog of RWJ 68354, compound **3**. Our initial attempts were to repeat the work of Bernstein, but treatment of unsymmetrical benzoin **2**⁴ with 2,6-diaminopyridine under melt conditions led to only trace amounts of product (eq. 2).



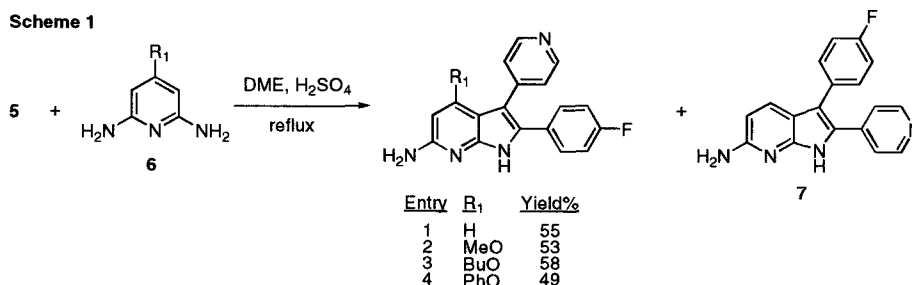
Fearing the instability of **2** was the reason for the poor yields, we prepared the protected benzoin **5**⁵ using a modified literature procedure. Dropwise addition of 2 equivalents of a 1.0 M solution of NaHMDS to siloxy picoline **4** and ethyl 4-fluorobenzoate in

THF gives the enolate of **5** as a stable yellow precipitate which can be collected by filtration. Protonation with a solution of NH_4Cl gives **5** in 79% yield (eq. 3). Using **5** under the same melt conditions however, resulted in only marginal increases in yield.



Discouraged by these results we began to explore alternative methods for the preparation of **3**. After testing several sets of reaction conditions, we found that reaction of **5** with 2,6-diaminopyridine in DME in the presence of 5 equivalents of H_2SO_4 gave **3** (Scheme 1, entry 1) in 69% HPLC yield (55% isolated) as the only regioisomer. On scaleup (20–30g scale), 2–3% of the regioisomer **7** (Scheme 1) could be isolated from the mother liquor following trituration with ethyl acetate (see experimental).

Scheme 1



In a similar fashion RWJ 68354 (Scheme 1, entry 2) could be prepared in 53% yield by treating **5** with aminopyridine **6** ($\text{R}_1 = \text{MeO}$).⁶ In the case of RWJ 68354 the corresponding regioisomer was not detected even in large scale runs.^{7,8}

Thus we have prepared the potent p38 inhibitor RWJ 68354 via a novel regiospecific variation of the Bischler-Möhlau indole synthesis utilizing an unsymmetrical benzoin as starting material. This reaction appears to be quite general, and various analogs will be reported along with their biological data elsewhere.

References

- Badger, A.M.; Bradbeer, J.N.; Votta, B.; Lee, J.C.; Adams, J.L.; Griswold, D.E. *J. Pharmacol. Exp. Ther.* **1996**, *27*, 1453 and references therein.
- Bernstein, J.; Stearns, B.; Shaw, E. Lott, W.A. *J. Amer. Chem. Soc.* **1947**, *69*, 1151.
- Herbert, R.; Wibberley, D.G. *J. Chem. Soc. (C)* **1969**, 1505.
- Senderoff, S.G.; Heys, J.R.; Blackburn, D.W. *J. Labelled Compd. Radiopharm.* **1987**, *24*, 971.
- Gallagher, T.F.; Fier-Thompson, S.M.; Garigipati, R.S.; Sorenson, M.E.; Smietana, J.M.; Lee, D.; Bender, P.E.; Lee, J.C.; Laydon, J.T.; Griswold, D.E.; Chabot-Fletcher, M.C.; Breton, J.J.; Adams, J.L. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1171.
- Markees, D.G.; Dewey, V.C.; Kidder, G.W. *J. Med. Chem.* **1968**, *11*, 126.
- Experimental:** Aminopyridine **6** ($\text{R} = \text{MeO}$) (9.5 g, 0.068 mol) and ketone **5** (35.3 g, 0.10 mol) were dissolved in 250 mL of DME and conc. H_2SO_4 (19 mL) was added. The mixture was then refluxed for 4 h, cooled to rt, poured into 1L of water and neutralized with solid K_2CO_3 . The aqueous phase was extracted with ethyl acetate (3x300 mL). The organics were dried with sodium sulfate and concentrated. Trituration with 300 mL of ethyl acetate gave RWJ 68354 (12 g, 53 %) as an off white solid. ^1H NMR (300 MHz, d_6 DMSO) δ 11.5 (s, 1H), 8.4 (d, 2H, $J=7.7$ Hz), 7.3–7.1 (m, 6H), 5.8 (s, 1H), 5.8 (bs, 2H), 3.7 (s, 3H). MP 279–280 °C.
- It was initially thought that the observed regioselectivity was a direct result of the desymmetrization of the alcohols of benzoin.
- However, HPLC studies of the reaction seem to indicate that the silyl group of **5** comes off before the reaction begins to give the H_2SO_4 salt of **2**. Studies are currently underway to determine the origin of selectivity and mechanism of this reaction.