Pergamon

Tetrahedron Letters 39 (1998) 5133–5134

TETRAHEDRON LETTERS

An Unusual Product in a Doebner–von Miller Quinoline Synthesis

Z.P. Zhang, L.M.V. Tillekeratne, and Richard A. Hudson*

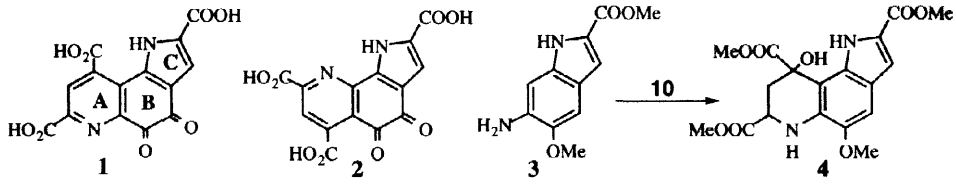
Department of Medicinal and Biological Chemistry, College of Pharmacy, and Department of Chemistry, College of Arts and Sciences, University of Toledo, Toledo, Ohio 43606-3390, USA.

Received 9 April 1998; revised 8 May 1998; accepted 11 May 1998

Abstract: In an attempt to synthesize an aza pyrroloquinolinequinone isomer, Doebner–von Miller quinoline synthesis from an aminoindole resulted in an unexpected product, formed by reaction at an electron-rich benzenoid carbon with the unsaturated carbon atom β to the ketone of dimethyl *trans*-2-oxoglutaconate. This observation suggests an alternative mechanistic possibility for Doebner–von Miller reaction with some electron-rich aromatic amines.

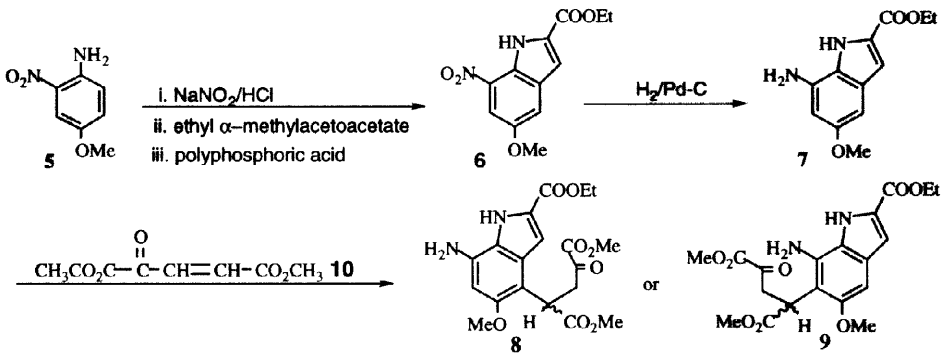
Keywords: quinolines; Doebner–von Miller reaction.

In the synthesis of the novel coenzyme pyrroloquinolinequinone (PQQ) **1**, Corey and Tramontano adopted a B → ABC approach involving two annulation steps for synthesis of the fused tricyclic system.[1] The addition of ring A was accomplished by a Doebner–von Miller type annulation. It was suggested, based on characterization of the piperidinol **4**,[1] that this reaction proceeds by conjugate addition of the amino group of indole **3** to the carbon ß to the ketone of dimethyl *trans*-2-oxoglutaconate **10**, followed by cyclization.



In our synthesis of several aza isomers of pyrroloquinolinequinone,[2] Corey's PQQ synthesis proved to be versatile and generally applicable. However, our early attempts to synthesize isomer **2** from indole **7** proved problematic at the Doebner–von Miller annulation stage and resulted in an unexpected compound as the major product. This suggested that, with some electron-rich aromatic amines, the reaction may take an alternative mechanistic course. We transformed 4-methoxy-2-nitroaniline **5** conveniently into aminoindole **7** through the sequence of reactions shown below.[3] Attempted Doebner–von Miller cyclization with **10** gave an unexpected product consistent with either structure **8** or **9** based on ^{1}H and ^{13}C NMR spectra.[4] The isolated compound failed to undergo Schiff's base formation and aromatization under a variety of forcing conditions, so it was assigned structure **8**. This assignment was confirmed by 2D-NMR spectroscopy (NOESY) when an NOE was observed between the aromatic proton at C-6 and the primary amine group at C-7.

0040-4039/98/$19.00
PII: S0040-4039(98)01008-9



The Doebner–von Miller reaction with dimethyl 2-oxoglutaconate is thought normally to proceed via initial conjugate 1,4-addition of the primary aromatic amine group to the carbon atom β to the ketonic function of the ester, followed by cyclization to a piperidinol. Dehydration and aromatization of this piperidinol leads to a quinoline product. However, in our case the product **8** appears to have formed by addition of the benzenoid carbon atom *para* to the primary amine group of the electron-rich aromatic ring to the double bond of dimethyl 2-oxoglutaconate. If reaction had instead occurred by addition of the carbon atom *ortho* to the primary amine group, the resulting product **9** could have undergone Schiff's base formation and subsequent aromatization to generate the desired quinoline intermediate. Hence, this may represent an alternative mechanistic possibility for the Doebner–von Miller reaction. Our experience also suggests that the scope of the reaction may be limited in some systems in which the aromatic ring bearing the primary amine function is electron rich and the position *ortho* to the amine is sterically hindered, as in the case of indole **7**. Indeed, when the methoxy group in indole **7** is moved to the position *para* to the amine, the expected Doebner–von Miller reaction proceeds smoothly.[2]

REFERENCES AND NOTES

1. Corey, E.J.; Tramontano, A. *J. Am. Chem. Soc.* **1981**, 103, 5599-5600.
2. Zhang, Z.P., Tillekeratne, L.M.V., Hudson, R.A. *Synthesis.* **1996**, 377-382.
3. Julia, M., Nickel, P. *Chem. Abstr.* **1967**, 66, 85664e.
4. Physical and spectral properties of **8**: yellow crystals, mp 141–142°C; Anal.: Calcd. for $C_{19}H_{22}N_2O_8$: C, 56.15, H, 5.46, N, 6.89; found: C, 56.42, H, 5.53, N, 7.01. IR (KBr): 3435, 3410, 1710, 1690,1320 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.44 (t, 3H), 2.89 (dd, 1H, J_1 = 20.2 Hz, J_2 = 5.1 Hz), 3.64 (s, 3H), 3.80 (s, 3H), 3.87 (s, 3H), 4.03 (dd, 1H, J_1 = 20.2 Hz, J_2 = 10.7 Hz), 4.26 (brs, 2H, exchangeable), 4.39 (q, 2H), 4.79 (dd, 1H, J_1 = 10.7 Hz, J_2 = 5.1 Hz), 6.40 (s, 1H), 7.20 (d, 1H, J = 2.2 Hz), 9.93 (br, 1H); ^{13}C NMR ($CDCl_3$): δ 14.34, 38.63, 40.90, 52.42, 53.00, 57.17, 61.45, 98.01, 107.08, 107.85, 123.86, 127.68, 127.73, 132.53, 151.96, 161.10, 163.00, 174.28, 192.47. TLC: R_f = 0.41 (2% MeOH in CH_2Cl_2).