Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: B. Narsaiah , A. Sivaprasad & R. V. Venkataratnam (1991) A Novel Synthesis of 3,4-Discubstituted-1H-pyrazolo[3,4-b]quinolines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:15-16, 1611-1617, DOI: 10.1080/00397919108021060

To link to this article: http://dx.doi.org/10.1080/00397919108021060

SYNTHETIC COMMUNICATIONS, 21(15&16), 1611-1617 (1991)

A NOVEL SYNTHESIS OF 3,4-DISUBSTITUTED-1H-PYRAZOLO[3,4-b] QUINOLINES

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ABSTRACT: A simple and efficient synthesis of pyrazolo[3,4-b] quinolines is described. The synthesis involves reaction of 2-amino-3-cyanoquinoline-4-carboxylates(**1**)with hydrazine hydrate to give regioselectively only pyrazolo[3,4-b]quinolines (**2**). No formation of pyridazino quinolines (**3**) is observed.

Pyrazole fused heterocyclic ring systems are of chemical and biological interest. A synthesis based on hydrazine hydrate as the reagent requires ortho substituted reactive groups on the substrate. Such a structural feature is available in o-amino nitriles, and studies on the action of hydrazine on them have been very few[1]. We have choosen the amino nitrile substrate (**1**) which contains an alkoxy carbonyl group ortho to the nitrile, so that the regioselectivity of the ring formation may be studied. It is found that the pyrazole ring formation takes place almost quantitatively when 2-amino-3-cyano-4-carboxylates[2] are reacted with

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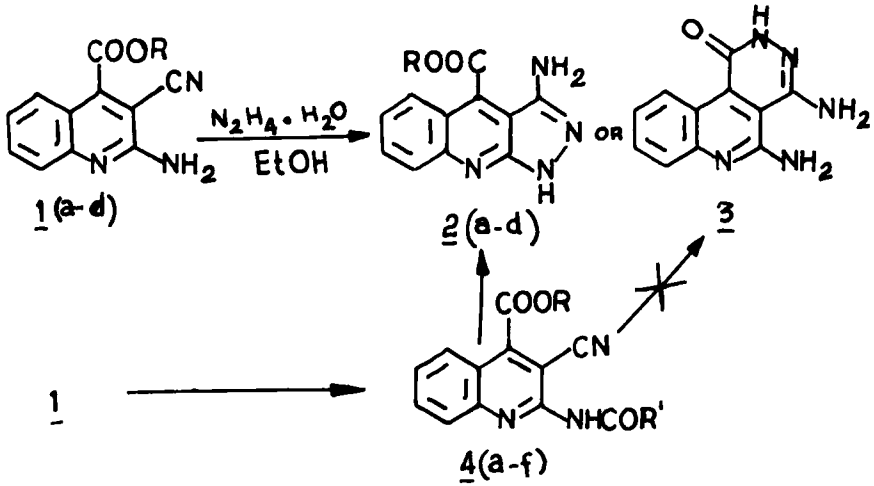
IICT Communication No.2814

hydrazine hydrate. There is no formation of even slight amount of the pyridazine alternative (3). The regioselectivity is preserved even if the amino group of (1) is acylated as in 4a-f.

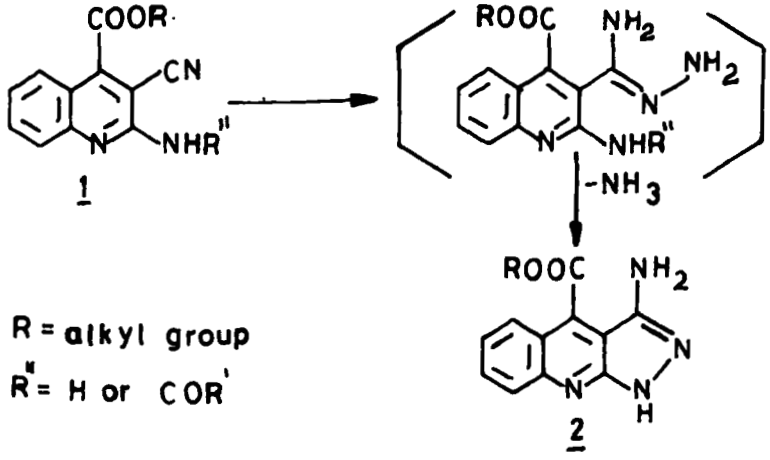


1a R = $-CH_3$
b R = $-CH_2CH_3$
c R = $-(CH_2)_2CH_3$
d R = $-(CH_2)_3CH_3$

4a R = $-CH_3$, R'= $-CH_3$
b R = $-C_2H_5$, R'=CH_3
c R = $-(CH_2)_2CH_3$, R'=CH_3
d R = $-(CH_2)_3CH_3$, R'=CH_3
e R = $-CH_3$, R'=Ph
f R = $-C_2H_5$, R'= Ph

The pyrazolo[3,4-b]quinolines (2a-d) have been characterised on the basis of PMR, IR and Mass spectral data. The PMR spectra show >NH broad singlet at δ6.41 and $-NH_2$ singlet at δ7.53 in DMSO-d_6, readily undergoing deuterium exchange. The alkyl and aromatic protons appeared in the expected regions (see experimental for spectral data).

The mode of formation of pyrazolo products is obviously through the addition of hydrazine to the nitrile, followed by nucleophilic displacement of the amino group or its derivatives. The carbonyl of the carboxyl group is not susceptible for nucleophilic attack and is intact in the product.



All the products give similar mass spectra with the typical loss of the alkyl group, the mechanism of which is under investigation and will be reported elsewhere.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded using Perkin-Elmer 810 model. ^{1}H NMR spectra were measured with a varian (80 MHz) spectrometer. Chemical shifts are reported in ppm., internal standard was tetramethylsilane (δ scale). Mass spectra were recorded on VG micromass-7070 H.

Preparation of 1a-d:

General Procedure - The following is a modified method to that given in the literature[2]: 1-Acetyl-3-(dicyanomethylene)-1,3-dihydro-2H-indol-2-one (1.3 g, 0.005 mole) is taken in an appropriate anhydrous alcohol (30 ml) and benzylamine (1.6 g, 0.015 mole) is added. Immediately exothermicity of the reaction observed and the reaction mixture has become dark homogeneous solution. On stirring further for two hours at room temperature a light yellow solid separated. This is filtered off, washed with n-hexane, dried and used for further work without crystallisation.

1a: Yield 82% yellow crystals, m.p. 206-208°C. - ^{1}H NMR ($CDCl_3$): δ = 4.1 (s, 3H, CH_3), 7.25-7.87 (m, 4H, aromatic H), 5.43 (br. s, 2H, NH_2),(2H, NH_2 readily exchanged with D_2O.)- IR: $\tilde{\nu}$ = 3450 and 3150 cm^{-1} (NH_2), 2250 (CN), 1730 (CO), $M^{+\cdot}$ 227.

1b: Yield 55%, m.p. 168-172°C (Lit.[2] 165-166°C) - ^{1}H NMR ($CDCl_3$): δ = 1.37-1.56 (t, 3H, CH_3), 4.45-4.68 (q, 2H, CH_2), 7.2-8.0 (m, 4H, aromatic H), 5.5 (br. s, 2H, NH_2) (2H, NH_2 exchanged with D_2O) - IR: = 3450 and 3150 cm^{-1}, (NH_2), 2250 (CN), 1730 (CO), $M^{+\cdot}$ 241.

1c: Yield 87%, m.p. 181°C. ^{1}H NMR ($CDCl_3$): δ = 1.12 (t, 3H, CH_3), 1.75-2.0 (m, 2H, CH_2), 4.35-4.5 (t, 2H, CH_2), 7.2-8.0 (m, 4H, aromatic H), 5.4 (br. s, 2H, NH_2) (2H, NH_2 exchanged with D_2O) - IR: 3450 and 3150 cm^{-1} (NH_2), 2210 (CN), 1725 (CO). M^+. 255.

1d: Yield: 85%, m.p. 186°C - ^{1}H NMR ($CDCl_3$): δ = 0.93 (t, 3H, CH_3), 1.25-2.06(m, 4H, CH_2-CH_2), 4.47 (t, 2H, CH_2), 7.18-7.90 (m, 4H,

aromatic H), 5.37 (br, s, 2H, NH_2) (2H, NH_2 exchanged with D_2O). M^+ 269.

Preparation of 2a-d:

General Procedure - **1** (1 mmole) is dissolved in absolute ethanol (15 ml) and hydrazine hydrate (3 ml) is added to it. Refluxed for three hours, and cooled to room temperature. As a result yellow solid (**2**) is separated. Filtered and washed with cold water and dried.

Same products (**2a-d**) are also obtained when compounds (**4a-f**) are refluxed in hydrazine hydrate for one hour.

2a: Yield 88%, m.p. 327°C - ^1H NMR (DMSO-d_6), δ = 4.86 (s, 3H, CH_3), 9.1 (d, C_5-H, 1H), 8.5(d, C_8-H, 1H), 7.3-7.8 (m, C_6-H and C_7-H, 2H), 7.57 (s, 2H, NH_2), 6.41 (s, 1H, NH) - IR (KBr): 3400-3200 cm^{-1} (NH_2, NH), 1730 (CO), Mass: m/e 242.

2b: Yield 96%, m.p. 303°C - ^1H NMR (DMSO-d_6), δ = 1.52 (t, 3H, CH_3), 4.46 (q, 2H, CH_2), 9.0 (d, C_5-H, 1H), 8.3 (d, C_8-H, 1H), 7.25 - 7.76 (m, C_6-H and C_7-H, 2H), 7.10(s, 2H, NH_2), 6.90 (s, 1H, NH) - IR (KBr): $\bar{\nu}$ 3400-3250 cm^{-1} (NH_2, NH),1730 (CO), Mass: m/e 256.

2c: Yield 87%, m.p. 221°C - ^1H NMR (DMSO-d_6). δ = 1.21 (t, 3H, CH_3), 2.12 (sextet, 2H, CH_2), 4.86 (t, 2H, CH_2), 7.56 (s, 2H, NH_2), 6.43 (s, 1H, NH), 10.12(d, C_5-H, 1H), 9.55 (d, C_8-H, 1H), 8.03-8.65 (m, C_6-H, C_7-H, 2H). IR (KBr): $\bar{\nu}$ 3450-3250 cm^{-1} (NH_2, NH), 1728 (CO), Mass: m/e 270.

2d: Yield 82%, m.p. 216°C - ^{1}H NMR (DMSO-d_6): δ = 0.93 (t, 3H, CH_3), 1.25-2.06 (m, 4H, CH_2-CH_2), 4.5 (t, 2H, CH_2), 10.23 (d, C_5-H, 1H), 9.62 (d, C_8-H, 1H), 8.2-8.83 (m, C_6-H and C_7-H, 2H), 7.63 (s, 2H, NH_2), 6.37 (s, 1H, NH)- IR(KBr): $\bar{\nu}$ 3400-3200 cm^{-1} (NH_2, NH), 1728 (CO), Mass: m/e 284.

Preparation of 4a-d:

General Procedure - **1** (1 mmole) is dissolved in anhydrous toluene (15 ml) and acetic anhydride (5 ml) is added to it. Refluxed for one hour. During one hour, the progress of the reaction was checked with TLC (chloroform: methanol, 95:5). Reaction mixture was cooled to room temperature and was concentrated to remove toluene and excess acetic anhydride. To the residue ice cold water (5 ml) was added and neutralised with aqueous ammonia solution. Extracted thrice with chloroform. Combined extracts dried over anhydrous sodium sulphate and concentrated over rotavapor. Residue is washed with n-hexane. As a result, white solid separated. Filtered and washed with water and dried.

4a: Yield 93%, m.p. 144°C - ^{1}H NMR ($CDCl_3$): δ = 4.19 (s, 3H, OCH_3), 2.5 (s, 3H, $COCH_3$), 7.5-8.1 (m, 4H, aromatic H), 11.07 (br, s, 1H, NH) - IR (KBr): $\bar{\nu}$ 2210 cm^{-1} (CN), 1720 cm^{-1} (CO), 3300 cm^{-1} (NH). Mass m/e 269.

4b: Yield 88%, m.p. 176% - ^{1}H NMR ($CDCl_3$): δ = 1.5 (t, 3H, CH_3), 4.56 (q, 2H, CH_2), 2.5 (s, 3H, $COCH_3$), 7.5-8.2(m, 4H, aromatic H), 11.04 (br, s, 1H, NH) - IR (KBr) : $\bar{\nu}$ 2210 cm^{-1} (CN), 1720 cm^{-1} (CO), 3250 cm^{-1} (NH),Mass: m/e 283.

4c: Yield 95%, m.p. 124°C - ^{1}H NMR ($CDCl_3$): δ = 1.13 (t, 3H, CH_3), 1.91 (sextet, 2H,CH_2), 4.5 (t, 2H, CH_2), 2.52 (s, 3H, $COCH_3$), 7.2-8.0 (m, 4H, aromatic H), 11.10 (br, s, NH). IR (KBr): $\tilde{\nu}$ 2210 cm^{-1}, 1720 (CO), 3250 cm^{-1} (NH), Mass: m/e 255.

4d: Yield 96%, m.p. 108°C - ^{1}H NMR ($CDCl_3$): δ = 0.93 (t, 3H, CH_3), 1.25-2.06 (m, 4H, CH_2-CH_2), 4.47 (t, 2H, CH_2), 2.5 (s, 3H, $COCH_3$), 7.18-7.90(m, 4H, aromatic H), 11.07 (br, s, 1H, NH). IR (KBr) :$\tilde{\nu}$ 2210 (CN), 1715 (CO), 3200 cm^{-1} (NH). Mass: m/e 269.

4e: Yield 92%, m.p. 201°C - ^{1}H NMR ($CDCl_3$): δ = 4.21 (s, 3H, OCH_3), 7.5-8.3(m, 9H, aromatic H). $M^{+\cdot}$ 331.

4f: Yield 91%, m.p. 231°C - ^{1}H NMR ($CDCl_3$): δ = 1.5 (t, 3H, CH_3), 4.61 (q, 2H, CH_2), 7.7-8.8 (m, 9H, aromatic H). $M^{+\cdot}$ 345.

Acknowledgement: The authors are thankful to Dr A V Rama Rao, Director, IICT, for his constant encouragement.

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(Received in UK 17 April, 1991)