

Tetrahedron Letters 40 (1999) 2605-2606

TETRAHEDRON LETTERS

## First Synthesis of a Bromonitrilimine. Direct Formation of 3-Bromopyrazole Derivatives.

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Received 13 November 1998; accepted 25 January 1999

Abstract: The first example of the preparation of bromonitrilimine 3 is described. This precursor provides a convenient entry to a highly regioselective synthesis of 3-bromopyrazole derivatives 4 and 5. © 1999 Elsevier Science Ltd. All rights reserved.

Pyrazole ring systems continue to attract considerable attention because of their wide range of applications and activities.<sup>1,2</sup> In the course of a research program directed towards the synthesis and reactivity of nitrogen containing heterocyclic compounds, we found a new and convenient entry to a variety of 3-bromopyrazole derivatives of potential pharmacological interest.

3-Bromopyrazoles 4 and 5 are compounds whose formation is not straightforward: the direct halogenation of the pyrazole nucleus leads to formation of the 4-halo-derivative and only further addition of halogen permits substitution in other free positions of the ring.<sup>3a,b</sup> The few examples found in the literature describe the formation of 3-bromoderivatives only by laborious conversions of appropriate substrates.<sup>4a,d</sup> We report herein a facile and direct synthesis of compounds 4 and 5 by 1,3-dipolar cycloaddition of the novel nitrilimine 3 to selected dipolarophiles.

Treatment of glyoxylic acid (20 mmol) in  $H_2O$  (4 ml) with phenylhydrazine (20 mmol) in aqueous hydrochloric acid (20%, 20 ml) gave the expected hydrazone 1<sup>5</sup> in 70% yield, which served as the starting material for the synthesis of all the desired 3-bromopyrazole derivatives. Nitrilimine **3** was generated *in situ* at -5°C by treatment of 1 with N-bromosuccinimide (NBS) in dimethylformamide (DMF) and cycloadducts **4** and **5** were obtained by subsequent reaction with an appropriate dipolarophile (Scheme) in the presence of triethylamine (TEA).<sup>6</sup> The yields varied between 70-40%.<sup>7</sup>

As expected, <sup>8a,b</sup> in these reactions, only one regioisomer was detected. The intermediacy of 2 was unequivocally proven by its isolation:<sup>9</sup> a sample of 2 treated with a dipolarophile and TEA as reported in ref. 6 yielded identical cycloadducts.

Pyrazolines 4 were satisfactorily converted (yield 60%) into their corresponding pyrazoles  $5^{10}$  by reaction with nickel hydrate peroxide in refluxing benzene.<sup>11</sup>



## **REFERENCES AND NOTES**

- Elguero, J. Pyrazole and Their Benzoderivatives. In: Katritzky, A.R.; Rees, C.W. Comprehensive
- Heterocyclic Chemistry. Pergamon 1984, 5, 291.
   Irving, C.C.; Daniel, D. S. Biochemical Pharmacology, 1988, 37, 1642.
   a) Brain, E.G.; Finar, I.L. J. Chem. Soc., 1958, 2426; b) Behr, L.C.; Fusco, R.; Jarboe, C.H. Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings. Edited by R.H.Wiley 1967, 5, 87 and references therein.
- a)Liegler, K.; Spath, A.; Schaaf, F.; Scumann, W.; Winkelmann, E. Liebigs Ann. Chem., 1942, 551, 80
  b)Gorelik, M. V.; Titova, S. P.; Rybinov; V. I. Zh. Org. Khim, 1985, 21, 851; Chem. Abst., 1986, 104, 479 c) Juffermans, J. P. H.; Habraken, C. L. J. Org. Chem., 1986, 51, 4656 d) Jain, R.; Sponsler, M. B.; Coms, F. D.; Dougherty, D. A. J. Am. Chem. Soc., 1988, 110, 1356.
  M.Busch, F. Achterfeldt, R. Seufert, J. Prakt. Chem., 1915, 92, 1.
- 6. A typical procedure for the cycloaddition: To a stirred solution of phenylhydrazone 1 (10 mmol) in DMF (20 ml) at -5°C was added dropwise a solution of NBS (20 mmol) in DMF (20 ml) under an atmosphere of nitrogen. After additional stirring (15 min) at room temperature, dipolarophile a (50 mmol) was added and then dropwise TEA (10 mmol). The reaction mixture was left to stand for 2 hours, poured into cold water the dipolarophile to the dipolarophile to cold water the dipolarophile to the dipolarophile to cold water the dipolarophile to cold water to cold water the dipolarophile to cold water (100 ml) and extracted three times with ether; the organic layer was washed with water and brine, dried over anhydrous sodium sulphate and concentrated. The cycloadduct 4a was isolated by flash chromatography on silica gel (eluent: ethyl ether/petroleum ether=1/4).
- silica gel (eluent: ethyl ether/petroleum ether=1/4).
  All new cycloadducts were fully characterized by spectroscopic methods: 4a (liquid) IR (nujol): 1743, 1597, 1498 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.32 (dd, J<sub>23</sub>=7.3 Hz, J<sub>21</sub>=17.3 Hz, 1H), 3.54 (dd, J<sub>13</sub>=12 Hz, J<sub>12</sub>=17.3 Hz, 1H), 3.76 (s, 3H), 4.68 (dd, J<sub>32</sub>=7.3 Hz, J<sub>31</sub>=12 Hz, 1H), 6.94 (m, 3H), 7.30 (m, 2H); EIMS m/z 282/284 (M<sup>+</sup>). 4b (mp 77°C) IR (nujol): 1599 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.57 (m, 2H), 4.87 (m, 1H), 7.10 (m, 3H), 7.36 (m, 2H); EIMS m/z 249/251 (M<sup>+</sup>). 4c (liquid) IR (nujol): 1749, 1597, cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.25 (t, J=7.1 Hz, 3H), 1.42 (d, J=7.5 Hz, 3H), 3.47 (m, 1H), 4.25 (m, 3H), 6.94 (m, 3H), 7.29 (m, 2H); EIMS m/z 310/312 (M<sup>+</sup>). 4d (liquid) IR (nujol): 1600cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.89 (m, 6H), 3.82 (m, 1H), 4.59 (m, 1H), 6.92 (m, 3H), 7.29 (m, 2H); EIMS m/z 264/266 (M<sup>+</sup>). 5e (mp 139°C) IR (nujol): 1733cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.26 (t, 3H), 4.25 (m, 2H), 7.02 (s, 1H), 7.44 (m, 5H); EIMS m/z 294/296 (M<sup>+</sup>). 5f (liquid) IR (nujol): 1601, 1497 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.07 (s, 1H), 7.24 (m, 10H); EIMS m/z 294/296 (M<sup>+</sup>). 5g (m) 10H; EIMS m/z 298/300 (M<sup>+</sup>).
  8. a) Huiseen, R.; Seidel, M.; Wallbien, G.; Knupfer, H. Tetrahedron 1962, 17 3 b)Fleming, L in Frontier

- EIMS m/z 298/300 (M<sup>+</sup>).
  8. a) Huisgen, R.; Seidel, M.; Wallbien, G.; Knupfer, H. Tetrahedron, 1962, 17, 3. b)Fleming, I. in Frontier Orbitals and Organic Chemical Reactions; Wiley, 1976, 148-160;
  9. Intermediate 2 is isolated by stopping the reaction after the addition of NBS to the solution of hydrazone 1. It crystallises from petroleum ether and decomposes easily giving blue pitch-like products; m.p. 58 °C (yield 70 %); IR (nujol): 3307, 1604 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) & 7.60 (s, 1H, exchangeable by D<sub>2</sub>O), 7.33-7.28 (m, 2H), 7.08-6.96 (m, 3H); EIMS m/z 276/278/280 (M<sup>+</sup>)
  10. 5a (mp 75°C, 50% yield) IR (nujol): 1734, 1459 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) & 3.82 (s, 3H), 7.01 (s, 1H), 7.44 (m, 5H); EIMS m/z 280/282 (M<sup>+</sup>). 5b (mp 79°C, 60% yield) IR (nujol): 1675, 1509 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) & 7.02 (s, 1H), 7.60 (m, 5H); EIMS m/z 247/249 (M<sup>+</sup>). 5c (mp 104°C, 15% yield) IR (nujol): 1731, 1654 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) & 1.23 (t, J=7.1 Hz, 3H), 2.30 (s, 3H), 4.25 (q, J=7.1 Hz, 2H), 7.4 (m, 5H); EIMS m/z 308/310 (M<sup>+</sup>). 5d (mp 65°C, 51% yield) IR (nujol): 1600, 1505 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) & 2.63 (m, 4H), 3.04 (m, 2H), 7.42 (m, 5H); EIMS m/z 262/264 (M<sup>+</sup>).
  11. Balachandran, K.S.; Bhatnagar, I.; George, M. V. J. Org. Chem., 1968, 33, 3891.
- 11. Balachandran, K.S.; Bhatnagar, I.; George, M. V. J. Org. Chem., 1968, 33, 3891.