Pergamon

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**.

Pyrazole ring systems continue to attract considerable attention because of their wide range of applications and activities.[1,2] 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.

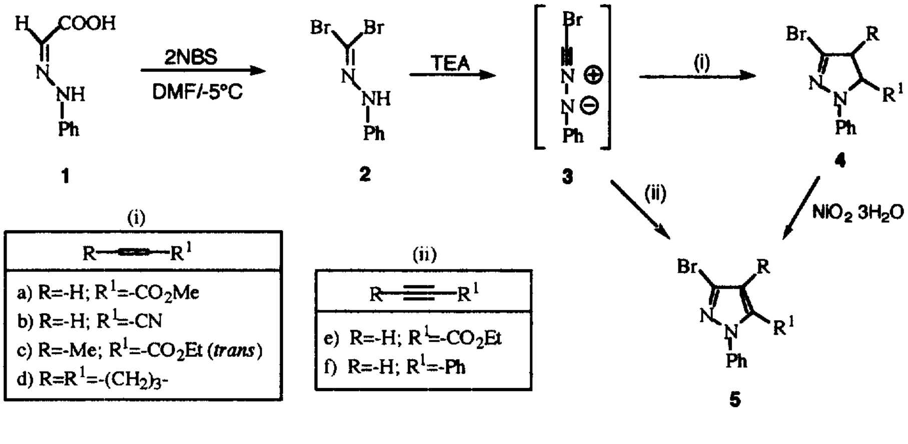
3-Bromopyrazoles **4** and **5** are compounds whose formation is not straightforward: the direct halogenation of the pyrazole nucleus leads to formation of the 4-halo-derivative and only further addition of halogen permits substitution in other free positions of the ring.[3a,b] The few examples found in the literature describe the formation of 3-bromoderivatives only by laborious conversions of appropriate substrates.[4a,d] 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**[5] 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).[6] The yields varied between 70-40%.[7]

As expected, [8a,b] in these reactions, only one regioisomer was detected. The intermediacy of **2** was unequivocally proven by its isolation:[9] 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.[11]

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00227-0



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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 (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).
7. All new cycloadducts were fully characterized by spectroscopic methods: **4a** (liquid) IR (nujol): 1743, 1597, 1498 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.32 (dd, J_{23}=7.3 Hz, J_{21}=17.3 Hz, 1H), 3.54 (dd, J_{13}=12 Hz, J_{12}=17.3 Hz, 1H), 3.76 (s, 3H), 4.68 (dd, J_{32}=7.3 Hz, J_{31}=12 Hz, 1H), 6.94 (m, 3H), 7.30 (m, 2H); EIMS *m/z* 282/284 (M^+). **4b** (mp 77°C) IR (nujol): 1599 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.57 (m, 2H), 4.87 (m, 1H), 7.10 (m, 3H), 7.36 (m, 2H); EIMS *m/z* 249/251 (M^+). **4c** (liquid) IR (nujol): 1749, 1597, cm^{-1}; ^1H NMR ($CDCl_3$) 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^+). **4d** (liquid) IR (nujol): 1600cm^{-1}; ^1H NMR ($CDCl_3$) 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^+). **5e** (mp 139°C) IR (nujol): 1733cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, 3H), 4.25 (m, 2H), 7.02 (s, 1H), 7.44 (m, 5H); EIMS *m/z* 294/296 (M^+). **5f** (liquid) IR (nujol): 1601, 1497 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.07 (s, 1H), 7.24 (m, 10H); EIMS *m/z* 298/300 (M^+).

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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^{-1} ; ^1H NMR ($CDCl_3$) δ 7.60 (s, 1H, exchangeable by D_2O), 7.33-7.28 (m, 2H), 7.08-6.96 (m, 3H); EIMS *m/z* 276/278/280 (M^+)
10. **5a** (mp 75°C, 50% yield) IR (nujol): 1734, 1459 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H), 7.01 (s, 1H), 7.44 (m, 5H); EIMS *m/z* 280/282 (M^+). **5b** (mp 79°C, 60% yield) IR (nujol): 1675, 1509 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.02 (s, 1H), 7.60 (m, 5H); EIMS *m/z* 247/249 (M^+). **5c** (mp 104°C, 15% yield) IR (nujol): 1731, 1654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 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^+). **5d** (mp 65°C, 51% yield) IR (nujol): 1600, 1505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.63 (m, 4H), 3.04 (m, 2H), 7.42 (m, 5H); EIMS *m/z* 262/264 (M^+).

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