SHORT PAPER

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A facile synthesis of novel 1,7-dihydropyrazolo [3,4-*b*]pyridine-4,6-diones†

Dekai Yuan, Zhengming Li*, and Weiguang Zhao

State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P.R. China

1,7-Dihydropyrazolo[3,4-*b*]pyridine-4,6-diones **4** were obtained from ethyl 3-methylthio-5-aminopyrazole-4-carboxylate and diketene in three steps. A series of 5-anilinomethylene-1,7-dihydropyrazolo[3,4-*b*]pyridine-4,6-diones **5** was easily derived from **4**.

Keywords: fused pyrazoles, fused pyridines, diketene

Pyrazolo[3,4-*b*]pyridines have diverse biological activities in pharmacology and agrochemistry.[1,2] It has been reported that a pyrazolopyridine, BAY 41-2272, can stimulate guanylate cyclase by a mechanism independent of NO and offer an approach for treating cardivascular diseases.[3-5] A tobacco company has found some compounds that could treat fibrosis effectively.[6] Other work has shown that they can also be used to treat diabetes[7] and malaria.[8] Furthermore, some derivatives have been found to have microbicidal[9] and herbicidal[10] activities in agrochemistry. Pyrazolo[3,4-*b*]pyridines are reported to be synthesised from 2-halo-3-carbonylpyridines or their derivatives with hydrazine hydrate,[11] or from 5-amino-4-cyanopyrazole with β-dicarbonyl compounds,[12] or from 5-aminopyrazoles with chalcones with long reaction times and in low yields.[13]

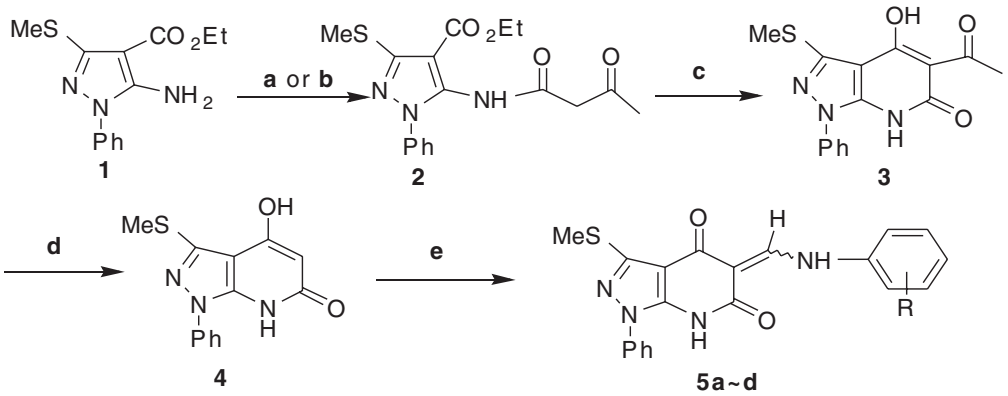
Heterocyclic rings containing the 1,3-dione structure have been discovered in many natural-products possessing biological activity,[14,15] and some 3-anilinemethylene-5,6-dihydro-6-(substituted phenyl)-2*H*-pyran-2,4-diones were found which possessed good fungicidal and plant growth regulation activity in our earlier work.[16] So several 5-anilinomethylenepyrazolo[3,4-*b*]pyridine-4,6-diones (**5**) were designed and obtained from 4-hydroxypyrazolo[3,4-*b*]pyridin-6-one (**4**) with triethyl orthoformate and substituted aniline. A novel three-step route to 4-hydroxy-1-phenyl-1,7-dihydropyrazolo[3,4-*b*]pyridin-6-one (**4**) was devised using ethyl 5-amino-3-methylthiopyrazole-4-carboxylate (**1**) and diketene as starting materials (Scheme 1).

Compound **1**, as a weak amine, does not react with diketene directly or when catalysed by Et_3N, but in HOAc or catalysed by DMAP in CH_2Cl_2, it could be acetoacetylated by diketene and ethyl 5-acetoacetylamino-3-methylthio-1-phenyl-1*H*-pyrazole-4-carboxylate (**2**) was obtained in good yield. Then 5-acetyl-4-hydroxypyrazolo[3,4-*b*]pyridin-6-one (**3**) was prepared from **2** by Dieckmann cyclisation in refluxing EtONa/EtOH[17] in excellent yield. Treated with H_2SO_4 and then ice-water, **3** was converted into 4-hydroxypyrazolo[3,4-*b*]pyridin-6-one **4**, again in good yield. The 5-anilinomethylene-1,7-dihydropyrazolo [3,4-*b*]pyridine-4,6-diones **5** were prepared in refluxing EtOH in a "one-pot" reaction of **4**, triethyl orthoformate and a substituted aniline.[18] The products **5** were found by ^{1}H NMR spectra to be composed of pairs of *Z* and *E* isomers containing intramolecular hydrogen bonds as earlier reported.[18]

Since 5-amino-1*H*-pyrazole-4-carboxylates **1** can be easily prepared from dithioacetals or N,S-acetals and hydrazines, pyrazolo[3,4-*b*]pyridine-4,6-diones with different substituents are readily obtainable under mild conditions by our method.

Experimental

^{1}H NMR spectra were obtained at 300MHz using a 300 Bruker AC 300F spectrometer. Because of poor solubility, some of the spectra were run at 70 °C. IR spectra were taken on an Equinox 55 IR spectrometer (KBr). Mass spectra were obtained using a VG ZAB-HS mass spectrometer (E.I. source). Elemental analyses were carried out



Reagents: a: diketene, HOAc; **b**: diketene, DMAP, CH_2Cl_2; **c**: NaOEt, EtOH, reflux; **d**: H_2SO_4 (90%); **e**: $CH(OEt)_3$, aniline

5a: R = 4-Me, **5b**: R = 2-Cl; **5c**: R = 2-Br, **5d**: R = 2-Me

Scheme 1 Synthesis of pyrazolo[3,4-*b*]pyridine-4,6-diones

* To receive any correspondence. E-mail: yuandekai@eyou.com

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on a Yanaco CHN Corder MT-3 elemental analyzer. Melting points were taken using a Yanaco 500 melting-point apparatus.

Ethyl 5-acetoacetyl-3-methylthio-1-phenyl-1H-pyrazole-4-carboxylate (**2**) was prepared from pyrazole **1** with diketene in the following ways:

Method a: Pyrazole **1** (1.36 g , 0.005 mol) and diketene (0.55 g, 0.0072 mol) were dissolved in 5 ml HOAc and reacted at 80 °C for 10 h. The solvent was removed under reduced pressure and 20 ml water was added. After extraction with CH_2Cl_2, the organic layer was washed to neutral with saturated aqueous $NaHCO_3$ and dried with anhydrous $MgSO_4$ for 24 h. After the solvent was removed, **2** (1.4 g) was purified with reduced pressure chromatography (petroleum ether/ethyl acetate v/v 4:1) as white solid, m.p. 117–120 °C, yield 78 %; ^{1}H NMR δ ($CDCl_3$, ppm): 1.36 (t, 3H, *J* = 7.1 Hz), 2.22 (s, 3H), 2.54 (s, 3H), 3.44 (s, 2H), 4.31 (q, 2H, *J* = 7.1 Hz), 7.41–7.46 (m, 5H); Anal. Calcd. for $C_{17}H_{19}N_3O_4S$: C 56.50, H 5.26, N 11.63. Found: C 56.13, H 5.07, N 11.41 %.

Method b: **1** (1.36 g , 0.005 mol), diketene (0.55 g, 0.0072 mol) and DMAP (0.01 g) were dissolved in CH_2Cl_2 (30 ml) at 0 °C, and then refluxed for 4 h. After the solvent was removed, **2** was obtained in a yield of 77 % after purification by reduced pressure chromatography.

5-Acetyl-4-hydroxy-3-methylthio-1-phenyl-1,7-dihydro-6H-pyrazolo[3,4-b]pyridin -6-one (**3**): Compound **2** (3.57g, 0.01mol) was dissolved in EtOH (30 ml) containing NaOEt (1.04 g, 0.02 mol) and refluxed for 4 h. During the reaction the sodium salt of **3** precipitated as a white solid. After the solvent was removed under reduced pressure, water (10 ml) was added to the residue and a colorless solution was formed. The solution was acidified to pH <3 with dilute HCl and **3** separated. After drying *in vacuo*, **3** was obtained as white needles, m.p. 270 °C(dec.), yield 96 %; ^{1}H NMR δ ($CDCl_3$, ppm): 2.47 (s, 3H), 2.62 (s, 3H) , 7.52 (m, 5H), 17.64 (s, 1H); Anal. Calcd. for $C_{15}H_{13}N_3O_3S$: (%) C 57.13, H 4.13, N 13.33. Found: C 56.98, H 4.15, N 13.43.

4-Hydroxy-3-methylthio-1-phenyl-1,7-dihydro-6H-pyrazolo[3,4-b]pyridin-6-one (**4**): Pyrazole **3**[19] (1.5 g, 0.0048 mol) was added to H_2SO_4 (90%, 6 ml) and heated at 130 °C for 20 min. The mixture was then added dropwise to an ice-water mixture (100 g), when **4** precipitated out as a white solid. The solid was filtered off and washed with ice-cold water to neutral and dried, m.p. 263–266 °C (dec.), yield 92 %; ^{1}H NMR δ (DMSO-d_6, ppm): 2.60 (s, 3H), 4.05 (s, 2H), 5.87 (s, 1H), 7.18–8.16 (m, 5H); Anal. Calcd. for $C_{13}H_{11}N_3O_2S$: C 57.14, H 4.03, N 15.38. Found: C 56.97, H 3.97, N 15.35 %.

3-Methylthio-1-phenyl-5-phenylaminomethylene-1,7-dihydropyrazolo[3,4-b]pyridine-4,6-diones (**5**)*, general procedure*: Compound **4** (0.40 g, 0.0015 mol), triethyl orthoformate (0.67g, 0.0045 mol), and a substituted aniline were refluxed in 10ml ethanol and **5** precipitated out as a yellow solid in 5–10 min. The mixture was refluxed for 5h and then cooled, and **5** was filtered off and recrystallised from DMF as yellow needles.

5a: m.p. >330 °C (dec.), yield 90 %; IR (KBr, cm^{-1}): 3423, 3089, 2923, 2863, 1659, 1563, 1468, 1272, 845, 806, 768, 701; ^{1}H NMR δ (DMSO-d_6, 70 °C, ppm): 2.32 (s, 3H), 2.50 (s, 3H), 7.24–7.57 (m, 9H), 8.64–8.72 (2d, 1H, *J* = 15 Hz), 11.20 (s, 1H), 12.22, 12.24 (dd, *J* = 15 Hz), 13.30, 13.5 (2d, *J* = 15 Hz); ^{1}H NMR δ (F_3CCO_2D, 70 °C, ppm): 2.31 (s, 3H), 2.70 (s, 3H), 7.27–7.67 (m, 9H), 8.90–9.10 (wide peak, 1H); MS *m*/*z*: 390 (M^+), 313 (M-77)$^+$, 299 (M-91)$^+$, 284 (M-106)$^+$, 73 (MeSCN)$^+$, 44 (base peak); Anal. Calcd. for $C_{21}H_{18}N_4O_2S$: C 64.61, H 4.65, N 14.35; Found: C 64.52, H 4.39, N 14.20 %.

5-o-Chloroanilinomethyl derivative **5b:** m.p. >330 °C (dec.), yield 91 %; ^{1}H NMR δ (DMSO-d_6, 70 °C, ppm): 2.49 (s, 3H), 7.20–7.80 (m, 9H), 8.80 (m, 1H), 11.20 (s, 1H), 12.80 (d, *J* = 12 Hz), 13.70 (dd, *J* = 12 Hz); ^{1}H NMR δ (F_3CCO_2D, 70 °C, ppm): 2.70 (s, 3H), 7.20–7.69 (m, 9H), 9.03, 9.23 (ds, 1H); Anal. Calcd. for $C_{20}H_{15}ClN_4O_2S$: C 58.46, H 3.65, N13.64; Found: C 58.46, H 3.87, N 13.88 %.

5-o-Bromoanilinomethyl derivative **5c:** m.p. >330 °C (dec.), yield 88 %; ^{1}H NMR δ (DMSO-d_6, 70 °C, ppm): 2.51 (s, 3H), 7.19–7.94 (m, 9H), 8.76 (dd, 1H, *J* = 15 Hz), 12.80 (d, *J* = 12 Hz), 13.6 (d, *J* = 15 Hz); Anal. Calcd. for $C_{20}H_{15}BrN_4O_2S$: C 52.75, H 3.30, N 12.31; Found: C 52.62, H 3.19, N 12.41 %.

5-o-Toluidinomethyl derivative **5d:** m.p. >330 °C(dec.), yield 92 %; ^{1}H NMR δ (DMSO-d_6, 70 °C, ppm): 2.41(s, 3H), 2.49 (s, 3H), 7.32–7.52 (m, 9H), 8.75 (dd, 1H, *J* = 12 Hz), 11.20 (s, 1H), 12.60 (d, *J* = 12 Hz), 13.60 (d, *J*=15 Hz); Anal. Calcd. for $C_{21}H_{18}N_4O_2S$: (%) C 64.62, H 4.62, N 14.35; Found: C 64.62, H4.47, N 14.35.

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References

1 (a) M. Hisadome, T. Fukuda and M. Terasawa, *Int. J. Immunopharmacol.,* 1992, **14**, 1195; (b) H. Kobayashi and M. Kudame, JP 05 331 168 (1994) (*Chem. Abstr.,* **121**, 108 778r); (c) S.A. Lipton, WO 9 203 137 (1992) (*Chem. Abstr.,* **117**, 83 454j); (d) S. Christian, T. Aknad, M. Markus and M. Friedrich, DE 4 230 755 (1994) (*Chem. Abstr.,* **120**, 236 189r).

2 (a) H. Takashi, T. Katasuhira, H. Yamaguchi, Y. Kawabata, H. Harayama, Y. Oda and M. Murai, WO 0006594 (1998) (*Chem. Abstr.* **132,** 151 835w); (b) A.A. Abdel Hafez, I.M.A. Awad and M.F. El-Zahry, *J. Chem. Technol. Biotechnol.,* 1992, **54**, 369.

3 J.P. Stasch, E.M. Becker, C. Alonso-Alija, H. Apeler, K. Dembowsky, A. Feurer, H. Schroder, W. Schroeder, E. Stahl, W. Steinke, A. Straub and M. Schramm,, *Nature*, 2001, **410** (6825), 212.

4 A. Straub, J. Benet-Buckholz, R. Frode, A. Kern, C. Kohlsdorfer, P. Schmitt, T. Schwarz, H.M. Siefert and J.P. Stasch, *Bioorg. Med. Chem. ,* 2002, **10**, 1771.

5 J.P. Stasch, A. Feurer, S. Weigand, E. Stahl, D. Flubacher, C. Alonso-Alija, F. Wunder, D. Lang, K. Debowsky, A. Straub and E. Perzborn, *DE 10131987*(23/5/2002) (*Chem. Abstr.,* **136**, 401 774); *DE 10057754* (23/5/2002) (*Chem. Abstr.,* **136**, 401 773); *DE 10057751* (23/5/2002) (*Chem. Abstr.,* **136**, 401 772); *DE 10122895* (23/5/2002) (*Chem. Abstr.,* **136**, 386 130).

6 H. Kawasaki, K. Ozawa and K. Yamamoto, WO 2001 098 301 (27/12/2001) (*Chem. Abstr.,* **136**, 69807).

7 S. Garland, D. Haigh, D.M.B. Hickey, J. Liddle, D.G. Smith, J. Witherington and R.W. Ward, WO 2002 024 694 (28/4/2002) (*Chem. Abstr.,* **136**, 263 167).

8 C.M.S. Menezes, C.M.R. Sant'Anna, C.R. Rodrigues and E.J. Barreiro *J. Mol. Struct. - Theochem.,* 2002, **579**, 31.

9 A.W. Erian, S. El-Gohary, F.M. Nmanhi and F.A. Ali, *Pharmazie*, 1998, **53**, 748.

10 C. Neubing, D.W. Von, H. Theobald, K.O. Westphalen, U. Kardorff, H. Walter, T. Kappe and M. Gerber, DE 4 227 747 (1994) (*Chem. Abstr.,* **120**, 323 554).

11 T. Ooe, H. Kabayashi, R. Ikezawa and M. Kudome, JP 06 206 872 (1994) (*Chem. Abstr.,* **122**, 187 576v).

12 W.G. Zhao, Z.M. Li, and D.K. Yuan, *J. Chem. Research (S)*, 2002, 454.

13 (a) A. Diaz-Ortiz, J.R. Carrillo, M.J. Gomez-Escalonilla, A. de la Hoz, A. Moreno and P. Prieto, *Synlett.* 1998, 10, 1069; (b) S. Rednekar and S. Gosavi, *Indian J. Heterocycl. Chem.* 1998, 8, 89; (c) R.N. Misra, S.D. Kimball, D.B. Rawlins, K.R. Webster and I. Bursuker, *WO 99 30 710* (1999) (*Chem. Abstr.,* 131, 116 184r); (d) J. Quiroga, B. Insuasty, A. Hormaza, P. Cabildo and R.S. Claramut, *Heterocycl. Commun.* 1999, 5, 115; (e) J. Quiroga, M. Alvarado, B. Insuasty, R. Moreno, E. Ravina, I. Estevez and R.H. de Almeida, *J. Heterocycl. Chem.* 1999, 36, 1311; (f) T.L. El-Emary, A.M. Hussan and H.S. El-Kasshef, *Pharmazie* 2000, 55, 356; (g) J. Quiroga, S. Craz, B. Insuasty and R. Abonia, *Heterocycl. Commun.* 2000, 6, 275. (h) J. Quiroga, S. Craz, B.Insuasty, R. Abonia, J. Cobo, A. Sanchez, M. Nogueras and J. N. Low, *J. Heterocycl. Chem.,* 2001, 38, 53.

14 J.C. Russell and D.O.H. Davids, *J. Chem. Soc., Perkin Trans. I,* 1991, 2537.

15 M.T. Cocco, C. Congiu and V. Onnis, *Eur. J. Med. Chem.*, 2000, **35**, 545.

16 Y.M. Wang, Z.M. Li and J.F. Li, *Chem. J. Chinese Universities*, 1999, **20**, 1559.

17 (a) C.V. Augusto, C. Rosella and F.M. Caelo, *Tetrahedron,* 1995, **51**, 12 277; (b) J.N. Collie, *J. Chem. Soc.,* 1891, **59**, 609, 617.

18 Y.M. Wang, K. He and G.F. Zhao, *Chinese Chem. Lett.*, 2003, **14**, 221.

19 Y. Tominaga, Y. Honkawa, M. Hara and A. Hosomi, *J. Heterocyclic Chem.*, 1990, **27**, 775.