Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 45 (2004) 4105–4108

Facile synthesis of 1-substituted 4,5-diaminopyrazoles and its application toward the synthesis of pyrazolo[3,4-*b*]pyrazines

Tun-Cheng Chien,[a] Ronald A. Smaldone[a,†] and Leroy B. Townsend[a,b,*]

[a]*Department of Chemistry, College of Literature, Science and Arts, The University of Michigan, Ann Arbor, MI 48109-1065, USA*
[b]*Department of Medicinal Chemistry, College of Pharmacy, The University of Michigan, Ann Arbor, MI 48109-1065, USA*

Received 24 February 2004; revised 22 March 2004; accepted 24 March 2004

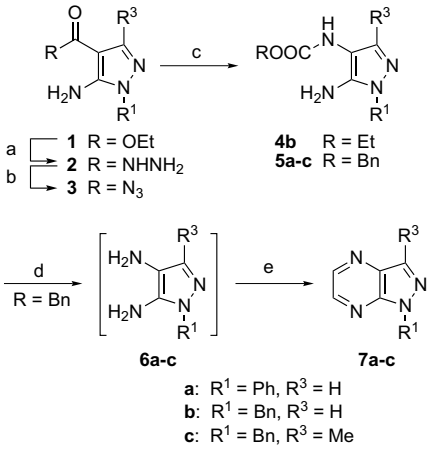
Abstract—1-Substituted 5-aminopyrazole-4-carbonylazides were prepared from the appropriate 5-aminopyrazole-4-carboxylates. The acyl azides undergo a Curtius rearrangement followed by quenching with alcohols to form the corresponding carbamates. The 1-substituted 5-amino-4-benzyloxycarbonylaminopyrazoles were unblocked by catalytic hydrogenolysis to give the desired 4,5-diaminopyrazoles. These 4,5-diaminopyrazoles were immediately condensed with glyoxal to afford 1-substituted pyrazolo[3,4-*b*]pyrazines.

Aromatic or heteroaromatic compounds possessing *ortho*-diamino groups are versatile building blocks for the synthesis of fused 1,4-diaza heterocycles such as fused [*d*]imidazoles, [*b*]pyrazines, and [*b*]diazepines. Our group had a particular interest in a facile synthesis of 4,5-diaminopyrazoles since they could then be used as precursors for the synthesis of pyrazolo[3,4-*b*]pyrazines. A perusal of the literature revealed that there are only a limited number of synthetic routes available for the preparation of 4,5-diaminopyrazoles.[1–7] The most common approach has used an electrophilic nitrosation of 4-unsubstituted 5-aminopyrazoles followed by a reduction of the 4-nitroso group to afford the 4,5-diaminopyrazoles.[1,4,6,7] Although this approach is effective, there are a few limitations: (1) both the nitroso intermediates and the resulting 4,5-diaminopyrazoles are unstable and can not be stored for an extended period of time; (2) some of the 4-unsubstituted 5-aminopyrazoles are not readily available by the usual synthetic procedures. In our preliminary studies, we encountered some difficulties in our attempts to prepare 4,5-diaminopyrazole nucleosides through the nitrosation-reduction approach. The condensation of ribosylhydrazone[8] with 1,3-dielectrophiles such as benzoylacetonitrile[9] or 3-aminocrotononitrile[10] did not afford the expected 4-unsubstituted 5-aminopyrazole nucleosides. The 4-unsubstituted 5-aminopyrazole nucleosides could be prepared from the corresponding ethyl 5-aminopyrazole-4-carboxylate nucleosides[11,12] by saponification followed by thermal decarboxylation.[13] However, nitrosation of the 5-aminopyrazole nucleosides gave the desired nitroso product only in low yields and was accompanied by undesired side products. These circumstances prompted us to look for an alternative route for the preparation of 4,5-diaminopyrazoles. We now report the preparation of 4,5-diaminopyrazoles from the 5-aminopyrazole-4-carbonylazides via a Curtius rearrangement strategy.

Non-nucleoside models were investigated first in order to explore and establish the reaction conditions. Ethyl esters of 5-aminopyrazole-4-carboxylates **1a–c** can be easily prepared by a condensation of alkylhydrazines with 2-cyano-3-ethoxyacrylate derivatives.[14,15] Reactions of the esters **1a–c** with hydrazine monohydrate gave the carbonyl hydrazides **2a–c** in quantitative yields. Treatment of **2a–c** with sodium nitrite in a 10% aqueous acetic acid solution at 0 °C afforded the acyl azides **3a–c**. These compounds were characterized by their significant IR absorptions around 2150 cm^{-1}. The acyl azides **3a–c** underwent Curtius rearrangements in the presence of excess amounts of primary alcohols to give the corresponding carbamates **4b** and **5a–c**, respectively. Since

Keywords: 4,5-Diaminopyrazole; Curtius rearrangement; Pyrazolo[3,4-*b*]pyrazine.
* Corresponding author. Address: Department of Medicinal Chemistry, College of Pharmacy, The University of Michigan, 428 Church St. Rm. 4567 CCL, Ann Arbor, MI 48109-1065, USA. Tel.: +734-764-7547; fax: +734-763-5633; e-mail: ltownsen@umich.edu
† Present address: Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA.

0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.03.142



Scheme 1. Reagents and conditions: (a) hydrazine monohydrate, EtOH, reflux; (b) $NaNO_2$, 10% acetic acid in H_2O, 0 °C, 30 min; (c) ROH, xylenes, reflux, (d) 10% Pd/C, H_2, MeOH, rt, 90 min; (e) 40% wt glyoxal, EtOH, rt.

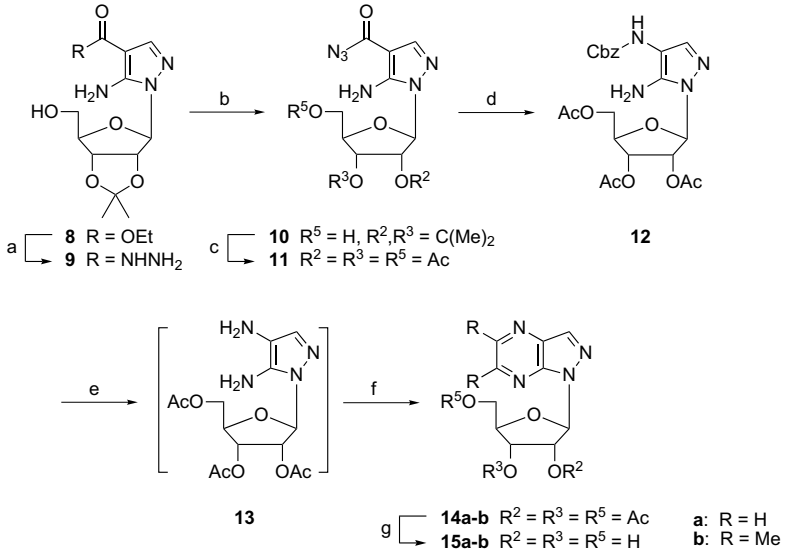
Table 1

Reactant	Product	R^1	R^3	Yield (%)
1a	**2a**	Ph	H	65[a]
1b	**2b**	Bn	H	73[a]
1c	**2c**	Bn	Me	44[a]
2a	**3a**	Ph	H	88[a]
2b	**3b**	Bn	H	82[a]
2c	**3c**	Bn	Me	78[b]
3b	**4b**[c]	Bn	H	71[a]
3a	**5a**[d]	Ph	H	33[b]
3b	**5b**[e]	Bn	H	71[b]
3c	**5c**[d]	Bn	Me	35[b]
5a	**7a**	Ph	H	83[b,f]
5b	**7b**	Bn	H	55[b,f]
5c	**7c**	Bn	Me	71[b,f]

[a] Yields are isolated yields after recrystallization.
[b] Yields are isolated yields after flash column chromatography.
[c] Ethanol was used as co-solvent, EtOH–xylenes = 1:9 (v/v).
[d] Benzyl alcohol (4 equiv) was used.
[e] Benzyl alcohol (10 equiv) was used.
[f] Yields are after two-step reactions from **5a**–**c**.

carbamates are widely used protecting groups for amines,[16] a removal of the carbamates should occur to give the desired 1-substituted 4,5-diaminopyrazoles. Catalytic hydrogenolysis of the Cbz-masked diaminopyrazoles **5a**–**c** gave the desired 1-substituted 4,5-diaminopyrazoles (**6a**–**c**) in situ. The diamine intermediates were immediately condensed with glyoxal to afford the pyrazolo[3,4-*b*]pyrazines (**7a**–**c**) in good yields (Scheme 1 and Table 1).

A conversion of the nucleoside precursor, ethyl 5-amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)pyrazole-4-carboxylate[8,11,12] (**8**), into the corresponding acyl azide **10** was accomplished by the same procedures as described earlier for the model compounds. The isopropylidene group was removed and the three hydroxy groups were then fully protected with acetyl esters to provide compound **11**. Compound **11** then underwent a Curtius rearrangement in the presence of excess benzyl alcohol to give 5-amino-4-benzyloxycarbonylamino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole (**12**) in 51% yield. Catalytic hydrogenolysis of **12** afforded the diamine **13** in situ and compound **13** was immediately condensed with glyoxal or 2,3-butanedione to furnish the peracetylated pyrazolo[3,4-*b*]pyrazine nucleosides **14a**–**b**. The acetyl groups were removed with methanolic ammonia to afford the desired nucleosides **15a**–**b** (Scheme 2 and Table 2).



Scheme 2. Reagents and conditions: (a) hydrazine monohydrate/EtOH (2:1, v/v), reflux; (b) $NaNO_2$, 10% acetic acid in H_2O, 0 °C, 20 min, 71% from **8**; (c) (i) TFA/H_2O = 9:1, rt, 1 h; (ii) Ac_2O, pyr, rt, 1 h, 73% from **10** ; (d) 10 equiv BnOH, xylenes, reflux, 5 h, 51%; (e) 10% Pd/C, H_2, MeOH, rt, 90 min; (f) glyoxal or 2,3-butandione, EtOH, rt; (g) NH_3/MeOH, rt, 1 h.

Table 2

Reactant	Product	R^2	R^3	R^5	R	Yield (%)[a]
12	**14a**	Ac	Ac	Ac	H	68[b]
12	**14b**	Ac	Ac	Ac	Me	44[b]
14a	**15a**	H	H	H	H	76
14b	**15b**	H	H	H	Me	71

[a] The reported yields are isolated yields.
[b] Yields are after two-step reactions from **12**.

Our success in these Curtius rearrangement reactions has provided a viable alternative route for the preparation of 4,5-diaminopyrazoles. The synthesis of pyrazolo[3,4-*b*]pyrazine nucleosides from the pre-formed pyrazole nucleosides has established that the ribose is located at the N^1-position and avoids the formation of possible regioisomers by the Vobruggen or the fusion method.[17,18] Synthesis of the 4,5-diaminopyrazole nucleoside **13** and the nucleosides **15a**–**b**[19–23] also illustrates the potential for the synthesis of other nucleosides with pyrazole-fused bicyclic heterocycles.

Acknowledgements

This work was supported by Research Grant 5-PO1-AI46390 from the National Institutes of Health.

References and notes

1. Musante, C. *Gazz. Chim. Ital.* **1943**, *73*, 355–365.
2. Osdene, T. S.; Taylor, E. C. *J. Am. Chem. Soc.* **1956**, *78*, 5451–5452.
3. Taylor, E. C.; Barton, J. W.; Osdene, T. S. *J. Am. Chem. Soc.* **1958**, *80*, 421–427.
4. Vicentini, C. B.; Ferretti, V.; Veronese, A. C.; Guarneri, M.; Manfrini, M.; Giori, P. *Heterocycles* **1995**, *41*, 497–506.
5. Vicentini, C. B.; Veronese, A. C.; Manfrini, M. *J. Heterocycl. Chem.* **1997**, *34*, 629–632.
6. Blass, B. E.; Srivastava, A.; Coburn, K. R.; Faulkner, A. L.; Seibel, W. L. *Tetrahedron Lett.* **2003**, *44*, 3009–3011.
7. Holschbach, M. H.; Wutz, W.; Olsson, R. A. *Tetrahedron Lett.* **2003**, *44*, 41–43.
8. Acevedo, O. L.; Krawczyk, S. H.; Townsend, L. B. *J. Org. Chem.* **1986**, *51*, 1050–1058.
9. Snyder, H. R., Jr. *J. Heterocycl. Chem.* **1975**, *12*, 1303–1304.
10. Ganesan, A.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 6155–6157.
11. Bhattacharya, B. K.; Robins, R. K.; Revankar, G. R. *J. Heterocycl. Chem.* **1990**, *27*, 787–793.
12. Schmidt, R. R.; Guilliard, W.; Karg, J. *Chem. Ber.* **1977**, *110*, 2445–2455.
13. Sanghvi, Y. S.; Larson, S. B.; Robins, R. K.; Revankar, G. R. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2943–2950.
14. Xia, Y.; Chackalamannil, S.; Hsingan, C.; Tsai, H.; Vaccaro, H.; Cleven, R.; Cook, J.; Fawzi, A.; Watkins, R.; Zhang, H. *J. Med. Chem.* **1997**, *40*, 4372–4377.
15. Dorn, H.; Zubek, A. *Chem. Ber.* **1968**, *101*, 3265–3277.
16. Greene, T. W.; Wuts, P. G. M. 7. Protection for the Amino Group—Carbamates. In *Protective Groups in Organic Synthesis*; Wiley: New York, 1999; pp 503–550.
17. Korbukh, I. A.; Preobrazhenskaya, M. N.; Dorn, H.; Kondakova, N. G.; Kostyuchenko, N. P. *J. Gen. Chem. USSR (Engl. Transl.)* **1974**, *10*, 1108–1113.
18. Korbukh, I. A.; Yakunina, N. G.; Preobrazhenskaya, M. N. 1-β-D-Ribofuranosylpyrazolo[3,4-*b*]pyrazine. Isomerization of 2-Glycosyl Derivatives of Fused Pyrazoles to 1-Glycosyl Derivatives. In *Nucleic Acid Chemistry: Improved and New Synthetic Procedures, Methods and Techniques*; Townsend, L. B., Tipson, R. S., Eds.; Wiley: New York, 1978; Vol. 2, pp 745–747.
19. *General procedure for the preparation of 1-substituted 5-aminopyrazole-4-carbonylazides* **3a**–**c** *and* **10**: A solution of sodium nitrite (11 mmol, 1.1 equiv) in H_2O (5 mL) was added dropwise to a suspension of the 1-substituted 5-aminopyrazole-4-carboxhydrazide (**2a**–**c** or **9**, 10 mmol) in 10% aqueous acetic acid (50 mL) at 0 °C for 15 min. The mixture was stirred for an additional 15 min then extracted with EtOAc. The organic layer was collected and washed with saturated Na_2CO_3 solution, saturated NaCl solution, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the product was purified by recrystallization or column chromatography.
20. *General procedure for the preparation of 1-substituted 5-amino-4-benxyloxycarbonylaminopyrazoles* **5a**–**c** *and* **12**: A mixture of 1-substituted 5-aminopyrazole-4-carbonylazide (**3a**–**c** or **11**, 10 mmol) and benzyl alcohol (100 mmol, 10 equiv) in xylenes (125 mL) was heated at reflux temperature under an argon atmosphere. After cooling to room temperature, the solvent was evaporated under reduced pressure and the product was purified by column chromatography.
21. *5-Amino-1-(2,3-O-isopropylidene-*β*-D-ribofuranosyl)pyrazole-4-carbonylazide* (**10**): mp 119–121 °C (dec.) (Hex/EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (s, 1H, 3-H), 5.76 (d, 1H, $J = 2.3$ Hz, 1′-H), 5.73 (br s, 2H, NH_2), 5.24 (dd, 1H, 2′-H), 5.02 (dd, 1H, 3′-H), 4.49 (br s, 1H, 5′-OH), 4.46 (dd, 1H, 4′-H), 3.84 (dt, 1H, 5′-H), 3.68 (ddd, 1H, 5′-H), 1.60 (s, 3H, CH_3), 1.39 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.1, 151.1, 140.9 (3-CH), 113.9, 98.6, 92.7 (CH), 88.7 (CH), 84.9 (CH), 82.2 (CH), 64.0 (5′-CH_2), 27.4 (CH_3), 25.4 (CH_3); IR (KBr, cm^{-1}) 3434, 3333, 2139, 1664, 1630, 1546; MS (CI, NH_3) m/z 83 (27), 125 (93), 297 (100) (M^+-N_2+1), 325 (24) (M^++1); HRMS calcd for $C_{12}H_{17}N_6O_5$ (M+1): 325.1260. Found: 325.1246. Anal. Calcd for $C_{12}H_{16}N_6O_5$: C, 44.44; H, 4.97; N, 25.91. Found: C, 44.52; H, 5.09; N, 25.74.
22. *5-Amino-4-benzyloxycarbonylamino-1-(2,3,5-tri-O-acetyl-*β*-D-ribofuranosyl)pyrazole* (**12**): ^{1}H (DMSO-d_6, 500 MHz) δ 8.56 (br s, 1H, NH), 7.41–7.35 (m, 6H, Ph and 3-H), 6.01 (d, 1H, $J = 2.7$ Hz, 1′-H), 5.74 (dd, 1H), 5.58 (t, 1H), 5.29 (br s, 2H, NH_2), 5.10 (s, 2H, CH_2), 4.32–4.25 (m, 2 H), 3.99 (dd, 1H, 5′-H), 2.10 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.00 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 170.9, 170.3, 170.2, 155.4, 141.1, 137.7, 136.9 (3-CH), 129.3 (CH), 128.9 (CH), 128.8 (CH), 103.8, 86.9 (CH), 79.4 (CH), 73.9 (CH), 71.7 (CH), 66.7 (CH_2), 64.3 (CH_2), 21.4 (CH_3), 21.2 ($2 \times CH_3$); MS (ESI) m/z 513 (100) (M+Na); HRMS calcd for $C_{22}H_{26}N_4O_9$·Na: 513.1597. Found: 513.1597.
23. *1-(*β*-D-Ribofuranosyl)pyrazolo[3,4-b]pyrazine* (**15a**): mp 187–189 °C (dec.) (EtOH) [lit.[18] 180–181 °C (MeOH)]; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.74 (d, 1H, $J = 2.0$ Hz), 8.68 (d, 1H, $J = 2.0$ Hz), 8.62 (s, 1H, 3-H), 6.30 (d, 1H, $J = 4.7$ Hz, 1′-H), 5.46 (d, 1H, OH), 5.23 (d, 1H, OH), 4.77–4.73 (m, 2H, $1 \times$OH and $1 \times$CH), 4.28 (dd, 1H), 3.96 (dd, 1H), 3.62–3.57 (m, 1H, 5′-H), 3.47–3.43 (m, 1H, 5′-H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 144.3, 144.1

(CH), 142.8 (CH), 135.3 (CH), 135.0, 89.5 (CH), 86.2 (CH), 73.9 (CH), 71.7 (CH), 63.0 (CH_2); MS (EI, 70 eV) m/z 121 (100), 133 (27), 149 (43), 163 (21), 175 (13), 252 (3) (M^+); HRMS calcd for $C_{10}H_{12}N_4O_4$: 252.0859. Found: 252.0857. Anal. Calcd for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.57; H, 4.92; N, 22.28.