Monatshefte für Chemie 136, 619–624 (2005)
DOI 10.1007/s00706-004-0252-0

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

An Efficient One-Pot Synthesis of Pyrazolopyrimidines, Intermediates for Potential Phosphodiesterase Inhibitors

Raid J. Abdel-Jalil[1,*], **Monther Khanfar**[1], **Kayed Abu-Safieh**[1], **Samer Al-Gharabli**[2], **Mustafa El-Abadelah**[2], and **Wolfgang Voelter**[3,*]

[1] Chemistry Department, Faculty of Science, Hashemite University, Zarka-Jordan
[2] Chemistry Department, Faculty of Sciences and Arts, University of Jordan, Amman-Jordan
[3] Abteilung für Physikalische Biochemie des Physiologisch-chemischen Instituts der Universität Tübingen, D-72076 Tübingen, Germany

Received August 3, 2004; accepted August 16, 2004
Published online January 14, 2005

Summary. A simple high-yielding procedure is presented for the synthesis of pyrazolopyrimidinones overcoming limitations found in earlier work and of considerable utility for the production of intermediates for potential phosphodiesterase inhibitors.

Keywords. Pyrazolopyrimidones; Viagra®; Phosphodiesterase inhibitors.

Introduction

Sildenafil (**1**, Viagra®, Fig. 1) is a well-known selective phosphodiesterease type 5 (PDE5) inhibitor, used worldwide as an efficacious, orally active agent for the treatment of male erectile dysfunction (MED) [1–4]. 5-(2-Methoxyphenyl)-1-methyl-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]-pyrimidin-7-one (**4a**, Scheme 1), the key intermediate for the synthesis of Viagra®, is traditionally prepared by the reaction of 4-amino-1-methyl-3-propylpyrazole-5-carboxamide (**2**) with 2-ethoxybenzoyl chloride followed by cyclization using different reagents, *e.g.* *t-Bu*OK/*t-Bu*OH [5], H_2O_2 [6], or polyphosphoric acid (*PPA*) [7].

However, the reported methods for the preparation of this key intermediate suffer from moderate yields and tedious procedures. Herewith we would like to report an alternative approach for pyrazolopyrimidinone moieties (*e.g.* **4a**–**4f**) *via* condensing carboxamide **2** with the appropriate benzaldehydes to the corresponding

* Corresponding authors. E-mails: jalil@hu.edu.jo; wolfgang.voelter@uni-tuebingen.de

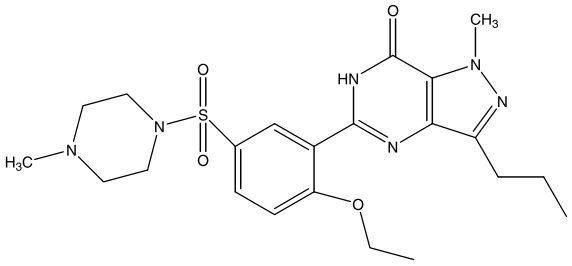
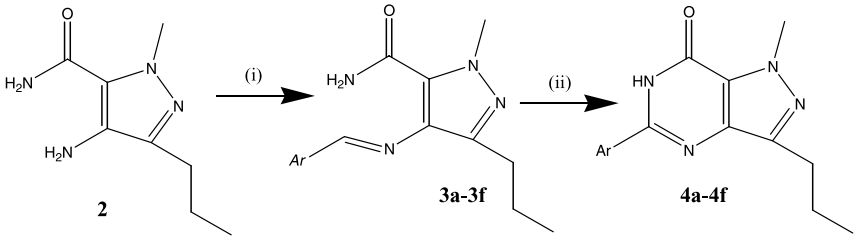
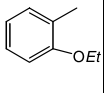
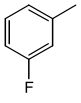
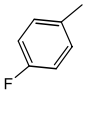


Fig. 1. Structure of Sildenafile (Viagra®)



	a	b	c	d	e	f
Ar						

Reaction conditions: i) *Ar*CHO, *Et*OH, 50°C; ii) *t-Bu*OK/*t-Bu*OH, 80°C, 4 h

Scheme 1

Schiff's bases (*e.g.* **3a**–**3f**) and subsequent ring closure in a mixture of *tert*-butanol/potassium *tert*-butoxide (Scheme 1).

Results and Discussions

Recently we have reported the synthesis of new and selective phospho-diesterase type 5 (PDE5) inhibitors [8, 9] which showed a significant activity in MED. In an attempt to improve and facilitate the synthesis of these inhibitors, a modification was investigated by replacing the appropriate benzoylchloride by benzaldehyde to yield the corresponding *Schiff*'s bases which were then transformed by potassium *tert*-butoxoide/*tert*-butanol to pyrazolopyrimidinones. The formation of the *Schiff*'s bases **3a**–**3f** were achieved within 30 min in almost quantitative yield by the reaction of **2** with substituted benzaldehydes in ethanol. The *Schiff*'s bases **3a**–**3f** were then cyclized in refluxing *tert*-butanol in the presence of *tert*-butoxide to give the corresponding pyrazolopyrimidinones in high yields (84–91%, Scheme 1).

As we demonstrate herein, this two step approach can be achieved in a one-pot reaction. Thus, **2**, prepared by following the published procedure [10], was refluxed with the appropriate aldehyde in *tert*-butanol for 30 min, followed by the addition of

one equivalent of potassium *tert*-butoxide, and then the reflux was continued for 4 hours to afford the corresponding pyrazolopyrimidinones (**4a**–**4f**) in similar yields.

The structures of the *Schiff*'s bases and the pyrazolopyrimidinone derivatives were determined on the basis of their spectral data and elemental analyses. Thus, the ^{1}H NMR of compounds **3a**–**3f** showed a singlet around 8.2 ppm assigned to the methine hydrogen, and the disappearance of this signal in the ^{1}H NMR of **4a**–**4f** indicates the successful formation of the pyrazolopyrimidinones. The mass spectra of **3a**–**3f** and **4a**–**4f** show the correct molecular ion peaks as base peaks. The elemental analyses and physical properties of the *Schiff*'s bases as well as the pyrazolopyrimidinone derivatives are in coincidence with the corresponding structures.

In conclusion, this alternative approach for the preparation of pyrazolopyrimidones is a simpler procedure of lower cost and higher yield compared to those published in literature.

Experimental

^{1}H NMR were measured on a Bruker AM 250 FT spectrophotometer operating at 300 K and using *TMS* as internal standard. Mass spectra (electron impact) were obtained on a Varian CH-7 spectrophotometer at 70 eV at an ion source formation of 200°C. Melting points were recorded on an electrothermal melting temperature apparatus. Elemental analyses were determined on a Perkin-Elmer elemental analyzer, model 240. Their results agreed favourably with the calculated values. Arylaldehydes were purchased from Aldrich and used without further purification. Compound **2** was obtained according to Ref. [10].

*General Procedure for the Synthesis of Pyrazolopyrimidinones **4a–4f***

A) Via the Two Step Method

(i) A mixture of 2.01 g of **2** (1 mmol) and 2 mmol of the corresponding aryl aldehyde in 10 cm^3 of absolute ethanol was heated under reflux for 1 h and then cooled to room temperature. The solid product was collected by filtration and recrystallized from ethanol to give pure **3a**–**3f**.

(ii) Potassium *tert*-butoxide (12 mmol) was added to a stirred suspension of 12 mmol of *Schiff*'s base in 30 cm^3 of *tert*-butanol, the resulting mixture was heated under reflux for 4–6 h, and then allowed to cool to room temperature. Water (30 cm^3) was then added and the resulting solution neutralized (*pH* 7) with dilute HCl (5%) and cooled to 5–10°C. The precipitated solid product was collected and dried.

B) Via the One Step Method

A mixture of 2.01 g of **2** (1 mmol) and 2 mmol of aryl aldehyde in 10 cm^3 of *tert-Bu*OH was heated under reflux for 30 min. Potassium *tert*-butoxide (12 mmol) was then added and the heating continued for additional 4 h. The reaction mixture was worked up as described in A(ii) above.

4-[(2-Ethoxybenzylidene)amino]-2-methyl-5-propyl-2H-pyrazole-3-carboxylic acid amide (**3a**, $C_{17}H_{22}N_4O_2$)

Yield 93%; mp 153–154°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.03$ (t, $J = 7.3$ Hz, $-CH_2CH_2\mathit{CH_3}$), 1.47 (t, $J = 7.0$ Hz, $-OCH_2\mathit{CH_3}$), 1.75 (m, $-CH_2\underline{CH_2}CH_3$), 2.73 (t, $J = 7.9$ Hz, $-\underline{CH_2}CH_2CH_3$), 4.13 (q,

$J = 7.0$ Hz, –O<u>CH$_2$</u>CH$_3$), 4.20 (s, N1–*CH$_3$*), 5.91 (bs, –NH<u>H</u>), 7.00–7.94 (m, C_6H_4), 8.77 (bs, –N<u>H</u>H), 9.04 (s, –N=C<u>H</u>–Ar); MS–EI: $m/z = 314$ (M^+).

4-[(3-Fluorobenzylidene)amino]-2-methyl-5-propyl-2H-pyrazole-3-carboxylic acid amide
(**3b**, $C_{15}H_{17}FN_4O$)

Yield 97%; mp 135–136°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.02$ (t, $J = 7.3$ Hz, –CH_2CH_2*CH_3*), 1.75 (m, –CH_2<u>CH_2</u>CH_3), 2.73 (t, $J = 7.6$ Hz, –<u>CH_2</u>CH_2CH_3), 4.21 (s, N1–*CH_3*), 5.96 (bs, –NH<u>H</u>), 7.16–7.57 (m, <u>C_6H_4</u>), 8.44 (bs, 1H, –N<u>H</u>H), 8.53 (s, –N=C<u>H</u>–Ar); MS–EI: $m/z = 288$ (M^+).

4-[(4-Fluorobenzylidene)amino]-2-methyl-5-propyl-2H-pyrazole-3-carboxylic acid amide
(**3c**, $C_{15}H_{17}FN_4O$)

Yield 89%; mp 125–127°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.04$ (t, $J = 7.3$ Hz, –CH_2CH_2*CH_3*), 1.72 (m, –CH_2<u>CH_2</u>CH_3), 2.72 (t, $J = 7.6$ Hz, –<u>CH_2</u>CH_2CH_3), 4.19 (s, N1–*CH_3*), 6.04 (bs, –NH<u>H</u>), 7.30–7.84 (m, <u>C_6H_4</u>), 8.44 (bs, 1H, –N<u>H</u>H), 8.51 (s, –N=C<u>H</u>–Ar); MS–EI: $m/z = 288$ (M^+).

2-Methyl-5-propyl-4-[(pyridin-2-ylmethylene)amino]-2H-pyrazole-3-carboxylic acid amide
(**3d**, $C_{14}H_{17}N_5O$)

Yield 90%; mp 155–156°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.02$ (t, $J = 7.3$ Hz, –CH_2CH_2*CH_3*), 1.78 (m, –CH_2<u>CH_2</u>CH_3), 2.79 (t, $J = 7.6$ Hz, –<u>CH_2</u>CH_2CH_3), 4.22 (s, N1–*CH_3*), 6.30 (bs, –NH<u>H</u>), 7.39 (ddd, $J = 1.2$, 4.9, 7.6 Hz, 1H-py), 7.82 (ddd, $J = 1.8$, 7.6, 8.1 Hz, 1H-py), 8.02 (ddd, $J = 0.9$, 1.2, 8.1 Hz, 1H-py), 8.73 (ddd, $J = 0.9$, 1.5, 4.9 Hz, 1H-py), 8.57 (bs, –N<u>H</u>H), 8.69 (s, –N=C<u>H</u>–Ar); MS–EI: $m/z = 271$ (M^+).

2-Methyl-5-propyl-4-[(thien-2-ylmethylene)amino]-2H-pyrazole-3-carboxylic acid amide
(**3e**, $C_{13}H_{16}N_4OS$)

Yield 94%; mp 150–151°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.02$ (t, $J = 7.3$ Hz, –CH_2CH_2*CH_3*), 1.75 (m, –CH_2<u>CH_2</u>CH_3), 2.77 (t, $J = 7.6$ Hz, –<u>CH_2</u>CH_2CH_3), 4.19 (s, N1–*CH_3*), 5.76 (bs, –NH<u>H</u>), 7.16 (dd, $J = 3.7$, 4.9 Hz, 1H-th), 7.47 (dd, $J = 0.9$, 3.7 Hz, 1H-th), 7.52 (dd, $J = 0.9$, 4.9 Hz, 1H-th), 8.53 (bs, –N<u>H</u>H), 8.64 (s, –N=C<u>H</u>–Ar); MS–EI: $m/z = 276$ (M^+).

4-[(Furan-2-ylmethylene)amino]-2-methyl-5-propyl-2H-pyrazole-3-carboxylic acid amide
(**3f**, $C_{13}H_{16}N_4O_2$)

Yield 94%; mp 172–173°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.01$ (t, $J = 7.3$ Hz, –CH_2CH_2*CH_3*), 1.74 (m, –CH_2<u>CH_2</u>CH_3), 2.73 (t, $J = 7.6$ Hz, –<u>CH_2</u>CH_2CH_3), 4.19 (s, N1–*CH_3*), 5.84 (bs, –NH<u>H</u>), 6.58 (dd, $J = 1.8$, 3.4 Hz, 1H-fu), 6.92 (dd, $J = 0.6$, 3.4 Hz, 1H-fu), 7.62 (d, $J = 1.8$ Hz, 1H-fu), 8.78 (bs, –N<u>H</u>H), 8.34 (s, –N=C<u>H</u>–Ar); MS–EI: $m/z = 260$ (M^+).

5-(2-Ethoxyphenyl)-1-methyl-3-propyl-1,6-dihydropyrazolo[4,3-d]pyrimidin-7-one
(**4a**, $C_{17}H_{20}N_4O_2$)

Yield 85%; mp 144–145°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.04$ (t, $J = 7.3$ Hz, –CH_2CH_2*CH_3*), 1.60 (t, $J = 7.0$ Hz, –OCH_2*CH_3*), 1.88 (m, –CH_2<u>CH_2</u>CH_3), 2.93 (t, $J = 7.9$ Hz, –<u>CH_2</u>CH_2CH_3), 4.30 (q, $J = 7.0$ Hz, –O<u>CH_2</u>CH_3), 4.27 (s, N1–*CH_3*), 7.03–8.46 (m, C_6H_4), 11.13 (bs, –N<u>H</u>); MS–EI: $m/z = 260$ (M^+).

5-(3-Fluorophenyl)-1-methyl-3-propyl-1,6-dihydropyrazolo[4,3-d]pyrimidin-7-one
(**4b**, $C_{15}H_{15}FN_4O$)

Yield 89%; mp 188–190°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.02$ (t, $J = 7.3$ Hz, $-CH_2CH_2\underline{CH_3}$), 1.75 (m, $-CH_2\underline{CH_2}CH_3$), 2.73 (t, $J = 7.6$ Hz, $-\underline{CH_2}CH_2CH_3$), 4.21 (s, N1–$\underline{CH_3}$), 7.16–7.57 (m, $\underline{C_6H_4}$), 11.75 (bs, –N$\underline{H}$); MS–EI: $m/z = 286$ (M^+).

5-(4-Fluorophenyl)-1-methyl-3-propyl-1,6-dihydropyrazolo[4,3-d]pyrimidin-7-one
(**4c**, $C_{15}H_{15}FN_4O$)

Yield 91%; mp 241–242°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.02$ (t, $J = 7.3$ Hz, $-CH_2CH_2\underline{CH_3}$), 1.85 (m, $-CH_2\underline{CH_2}CH_3$), 2.89 (t, $J = 7.4$ Hz, $-\underline{CH_2}CH_2CH_3$), 4.25 (s, N1–$\underline{CH_3}$), 7.17–8.15 (m, $\underline{C_6H_4}$), 11.75 (bs, –N$\underline{H}$); MS–EI: $m/z = 286$ (M^+).

1-Methyl-3-propyl-5-pyridin-2-yl-1,6-dihydropyrazolo[4,3-d]pyrimidin-7-one
(**4d**, $C_{14}H_{15}N_5O$)

Yield 86%; mp 156–157°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.04$ (t, $J = 7.3$ Hz, $-CH_2CH_2\underline{CH_3}$), 1.85 (m, $-CH_2\underline{CH_2}CH_3$), 2.93 (t, $J = 7.6$ Hz, $-\underline{CH_2}CH_2CH_3$), 4.29 (s, N1–$\underline{CH_3}$), 7.42 (ddd, $J = 1.2$, 4.9, 7.6 Hz, 1H-py), 7.88 (ddd, $J = 1.5$, 7.6, 7.9 Hz, 1H-py), 8.49 (ddd, $J = 0.9$, 1.2, 7.9 Hz, 1H-py), 8.62 (ddd, $J = 0.9$, 1.5, 4.9 Hz, 1H-py), 10.91 (bs, –N$\underline{H}$), 8.69; MS–EI: $m/z = 269$ (M^+).

1-Methyl-3-propyl-5-thien-2-yl-1,6-dihydropyrazolo[4,3-d]pyrimidin-7-one
(**4e**, $C_{13}H_{14}N_4OS$)

Yield 82%; mp 249–250°C; ^{1}H NMR ($CDCl_3$): $\delta = 0.99$ (t, $J = 7.3$ Hz, $-CH_2CH_2\underline{CH_3}$), 1.80 (m, $-CH_2\underline{CH_2}CH_3$), 2.81 (t, $J = 7.5$ Hz, $-\underline{CH_2}CH_2CH_3$), 4.19 (s, N1–$\underline{CH_3}$), 7.10 (dd, $J = 4.0$, 5.2 Hz, 1H-th), 7.54 (dd, $J = 0.9$, 5.2 Hz, 1H-th), 8.07 (dd, $J = 0.9$, 4.0 Hz, 1H-th), 12.31 (bs, –N$\underline{H}$); MS–EI: $m/z = 269$ (M^+).

5-Furan-2-yl-1-Methyl-3-propylyl-1,6-dihydropyrazolo[4,3-d]pyrimidin-7-one
(**4f**, $C_{13}H_{14}N_4O_2$)

Yield 86%; mp 228–229°C; ^{1}H NMR ($CDCl_3$): $\delta = 0.97$ (t, $J = 7.3$ Hz, $-CH_2CH_2\underline{CH_3}$), 1.78 (m, $-CH_2\underline{CH_2}CH_3$), 2.79 (t, $J = 7.5$ Hz, $-\underline{CH_2}CH_2CH_3$), 4.17 (s, N1–$\underline{CH_3}$), 6.62 (dd, $J = 1.8$, 3.6 Hz, 1H-fu), 7.48 (dd, $J = 0.8$, 3.5 Hz, 1H-fu), 7.82 (dd, $J = 0.8$, 1.8 Hz, 1H-fu), 12.30 (bs, –N$\underline{H}$); MS–EI: $m/z = 258$ (M^+).

Acknowledgements

We are grateful to the Hashemite University for financial support. We express our gratitude to Internationales Büro of BMBF, Jülich, for a fellowship granted to Dr. *R. J. A.-J.*

References

[1] Hideki N, Tsunehisa I, Hirotaka Y, Koji K (2004) Eur J Pharm **485**: 283
[2] Rotella DP, Sun Z, Zhu Y, Krupinski J, Pongrac R, Seliger L, Normandin D, Macor JE (2000) J Med Chem **43**: 5037
[3] Dale DJ, Dunn PJ, Golightly C, Hughes ML, Levett PC, Pearce AK, Searle PM, Ward G, Wood AS (2000) Org Process Res Devel **4**: 17

[4] Ballard SA, Gingell CJ, Tang K, Turner LA, Price ME, Naylor AM (1998) J Urology (Baltimore) **159**: 2164
[5] Yu G, Mason H, Wu X, Wang J, Chong S, Beyer B, Henwood A, Pongrac R, Seliger L, He B, Normandin D, Ferrer P, Zhang R, Adam L, Humphrey WG, Krupinski J, Macor JE (2003) J Med Chem **46**: 57
[6] Kim D-K, Lee JY, Lee N, Ryu DH, Kim J-S, Lee S, Choi J-Y, Ryu J-H, Kim N-H, Im G-J, Choi W-S, Kim T-K (2001) Inorg Med Chem **9**: 3013
[7] Anon S (2001) Schweiz Lab Z **58**: 132
[8] El-Abadelah MM, Sabri SS, Khanfar MA, Voelter W, Abdel-Jalil RJ, Maichle-Mossmer C, Al-Abed Y (2000) Heterocycles **53**: 2643
[9] Al-Bojuk NR, El-Abadelah MM, Sabri SS, Michel A, Voelter W, Maichle-Mossmer C, Al-Abed Y (2001) Heterocycles **55**: 1789
[10] Abdel-Jalil RJ, Al-Abed Y, El-Abadelah MM, Khanfar M, Sabri SS (2001) Voelter US Patent A2 20010118
[11] Nicholas KT, Andrew SB, David B, Peter E (1996) Bioorg Med Chem Lett **6**: 1819