

# Experimental and Computational Study on the Debenzylation of (2,4-dimethoxybenzyl)-protected 1,3-diazaoxindoles

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## Abstract

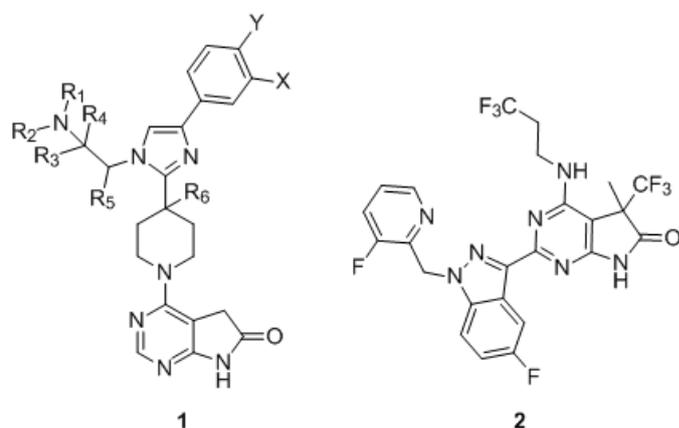
The introduction and removal of the 2,4-dimethoxybenzyl (DMB) moiety was studied in order to use it as a protecting group in the synthesis of diverse drug candidates containing the 1,3-diazaoxindole scaffold. The debenzylation of C(5)-unsubstituted and C(5)-isopropylidene-substituted 1,3-diazaoxindoles was investigated under various conditions. The DMB group could only be removed from the latter derivative using triflic acid. This observation can most likely be explained with electronic effects. In order to get a deeper insight into the reaction mechanism, quantum chemical calculations have been performed.

## Keywords

1,3-diazaoxindole, dimethoxybenzyl group, debenzylation, DFT, reaction mechanism

## 1 Introduction

The interest in 5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one derivatives (1,3-diazaoxindoles) increased in the last few years due to the biological relevance of compound families **1** and **2** (Scheme 1) [1-5].



X, Y = H, F, Cl, CF<sub>3</sub>, CN, CHF<sub>2</sub>  
 R<sub>1</sub>, R<sub>2</sub> = H, alkyl, cikloalkyl  
 R<sub>3</sub> = H, OH  
 R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> = various substituents  
 R<sub>6</sub> = H, OH

Scheme 1 Drug candidates with 1,3-diazaoxindole skeleton

In our earlier study, the easily available 2-(4-chloropyrimidin-5-yl)acetate derivatives **3a-d** were reacted with ammonia to afford the corresponding 2-(4-aminopyrimidin-5-yl)acetamides **4a-d**, which were finally cyclized to *N*-unsubstituted 1,3-diazaoxindoles **5a-d** (Scheme 2) [6].

Vaid et al. treated compound **6** with ammonia (3.7 equiv., 1.0 M propan-2-ol solution) at 90°C followed by the cyclization of non-isolated intermediate **7a** to give 4-chloro-1,3-diazaoxindole **8a** with 60% yield (Scheme 3) [7]. The complex workup procedure involved 3 steps: a) removal of the inorganic salts by filtration, b) concentration of the reaction mixture, c) dissolution of the residue in ethyl acetate followed by activated charcoal treatment, which was used to remove the majority of by-product **9**, d) aqueous extraction of the ethyl acetate layer and concentration of the solution to obtain the

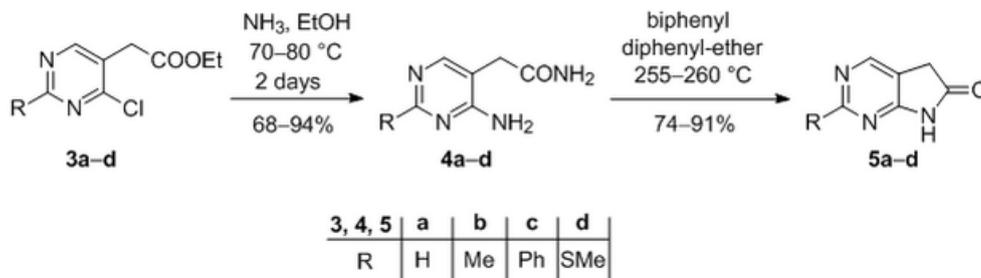
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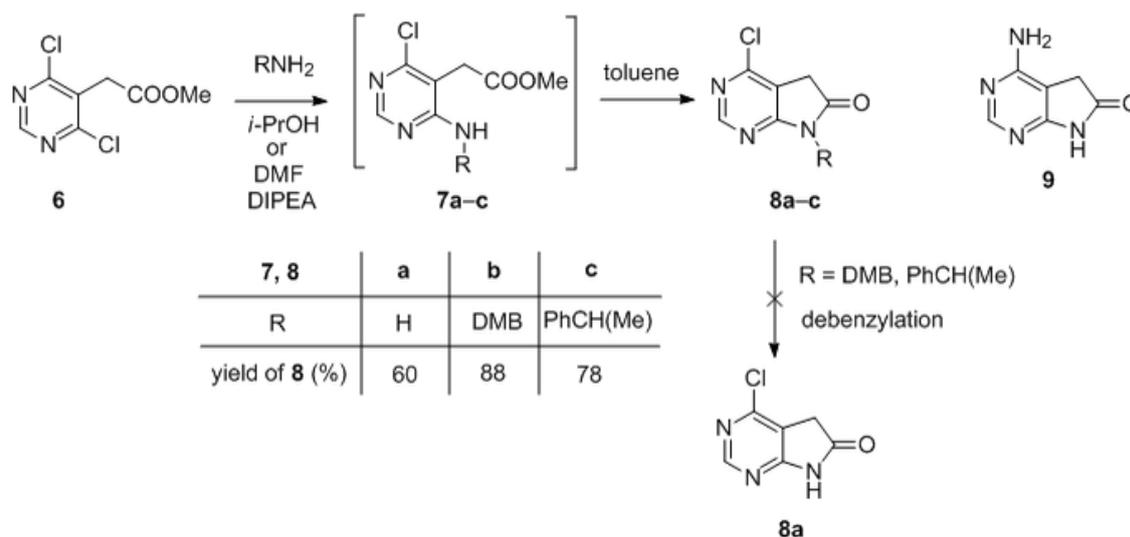
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Scheme 2 Synthesis of 5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-ones (1,3-diazaoxindoles)



Scheme 3 Synthesis of *N*(7)-substituted 4-chloro-1,3-diazaoxindoles (**8b,c**) and attempts for the removal of the protecting groups to give **8a**

crude product, and finally e) crystallization of the crude product from dichloromethane and heptane to obtain **8a**.

According to the literature, 2,4-dimethoxybenzylamine reacts under mild conditions with methyl (4,6-dichloropyrimidin-5-yl)acetate (**6**) and or its analogues (such as **10**, Scheme 4) and the products can be cyclized to the corresponding 1,3-diazaoxindoles [7, 8]. Vaid et al. treated compound **6** with 2,4-dimethoxybenzylamine and  $\alpha$ -methylbenzylamine in *N,N*-dimethylformamide (DMF) in the presence of *N,N*-diisopropylethylamine (DIPEA) followed by the cyclization of non-isolated intermediates **7b,c** to give 4-chloro-1,3-diazaoxindoles **8b,c** with 78–88% yields (Scheme 3) [7]. It is known that the 2,4-dimethoxybenzyl (DMB) group can be easily eliminated from amides by oxidation or under acidic conditions [9, 10]. Several attempts were made using this approach for the synthesis of *N*(7)-unsubstituted 4-chloro-1,3-diazaoxindole **8a** by treating **8b,c** with sulfonic acids such as methanesulfonic acid, *p*-TsOH and triflic acid. Nevertheless, the formation of the desired product **8a** was not observed [7, 9, 10].

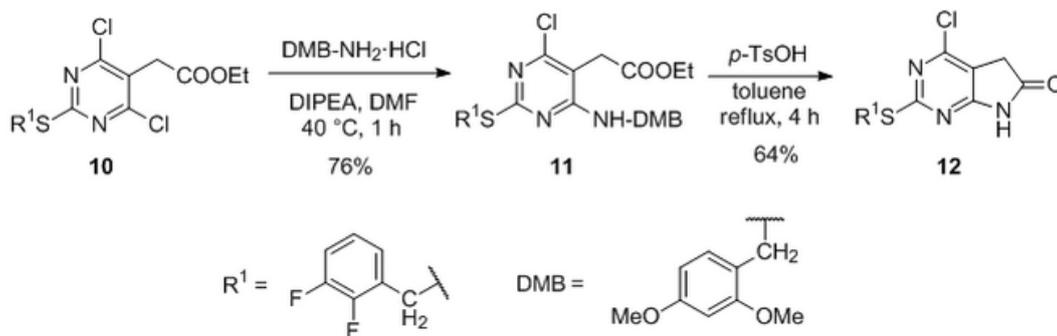
2,4-Dimethoxybenzylamine hydrochloride in presence of DIPEA was successfully used for the substitution of the halogen atom from chloro-ester compound **10**, yielding DMB amino ester derivative **11** in 76% yield [8]. Further the complete DMB group removal with *p*-TsOH under acidic conditions and

the subsequent cyclization step provided only the unprotected 2-substituted 4-chloro-1,3-diazaoxindole **12** with 64% yield in one-pot manner.

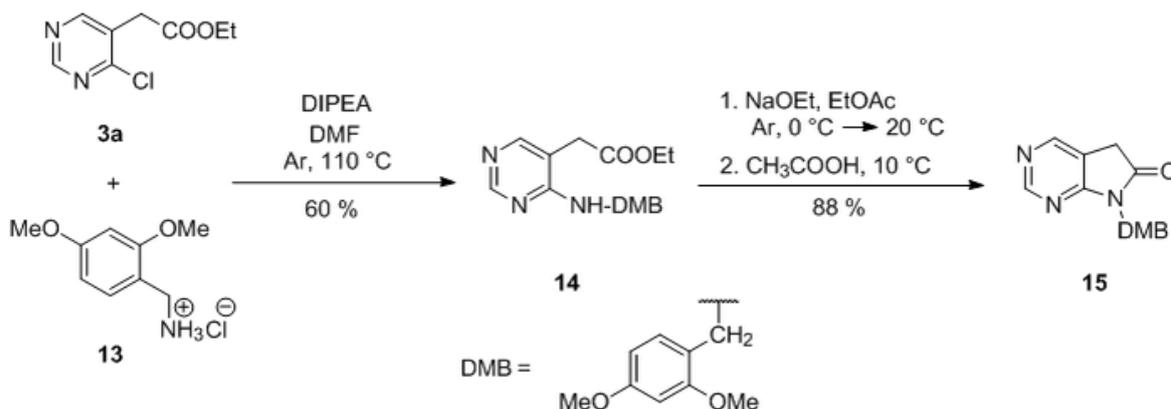
The selectivity of the alkylation reactions of *N*(7)-unprotected 1,3-diazaoxindoles has been recently described by us [11]. Herein the introduction and removal of DMB moiety on *N*(7) atom as an alternative approach to ensure C(5) selectivity is presented. As shown above, deprotection of DMB-amides usually occurs easily under acidic conditions [9]. However, the usefulness of DMB-protection/deprotection only in case of 2- and 4-substituted diazaoxindoles was already investigated. Our aim was to extend this approach to the unsubstituted analogue **5a** and to provide a suitable mechanism for the deprotection step.

## 2 Results and Discussion

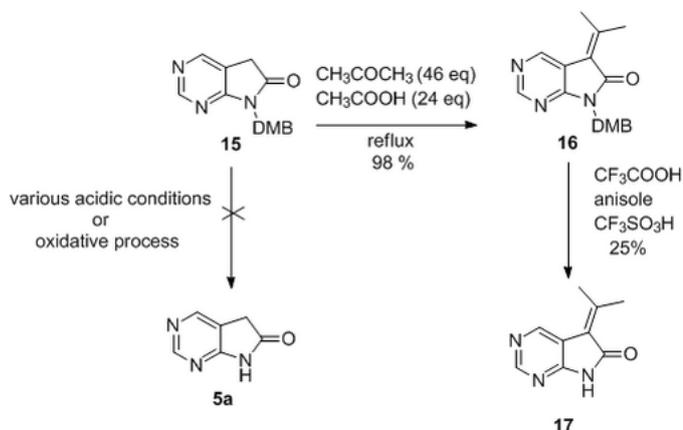
The synthesis of the *N*(7)-substituted target compound was carried out starting from 2-(4-chloropyrimidin-5-yl)acetate (**3a**), which was treated with 2,4-dimethoxybenzylamine hydrochloride (**13**) and DIPEA in DMF under argon atmosphere at 110°C (Scheme 5). In the cyclization step of the DMB-amino substituted pyrimidine **14** thus obtained, sodium ethoxide (NaOEt) was used in dry ethyl acetate (EtOAc) to give DMB-protected diazaoxindole **15**.



Scheme 4 Synthesis of 2-substituted 4-chloro-1,3-diazaoxindole 12



Scheme 5 Synthesis of *N*(7)-protected 1,3-diazaoxindole (15)



Scheme 6 Attempts for the debenzilation of compounds 15 and 16

Further debenzilation of **15** performed with *p*-TsOH, 5 M sulfuric acid, acetic acid, trifluoroacetic acid (TFA), methanesulfonic acid and triflic acid in the presence of anisole failed, the desired unprotected **5a** was not formed (Scheme 6). These results were in accordance with earlier finds concerning the stability of *N*-benzylated **8b,c** under acidic conditions [7]. The oxidative removing of DMB with cerium ammonium nitrate (CAN, 3 equiv.) in acetonitrile-water or with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, 1.5 equiv.) in DCM [9] was also useless for the deprotection of **15**.

Condensation of *N*(7)-protected 1,3-diazaoxindole **15** with acetone in acetic acid afforded *N*(7)-substituted 5-isopropylidene-1,3-diazaoxindole **16** in 98% yield (Scheme 6) [11]. DMB

deprotection of **16** occurred using a mixture of trifluoroacetic acid and triflic acid in the presence of the leaving group entrapping anisole [12-13] yielding (25%) 5-isopropylidene-1,3-diazaoxindole (**17**). The difference in reactivity found for deprotection of **15** and **16** enforced us to investigate the reaction mechanism using quantum chemical calculations.

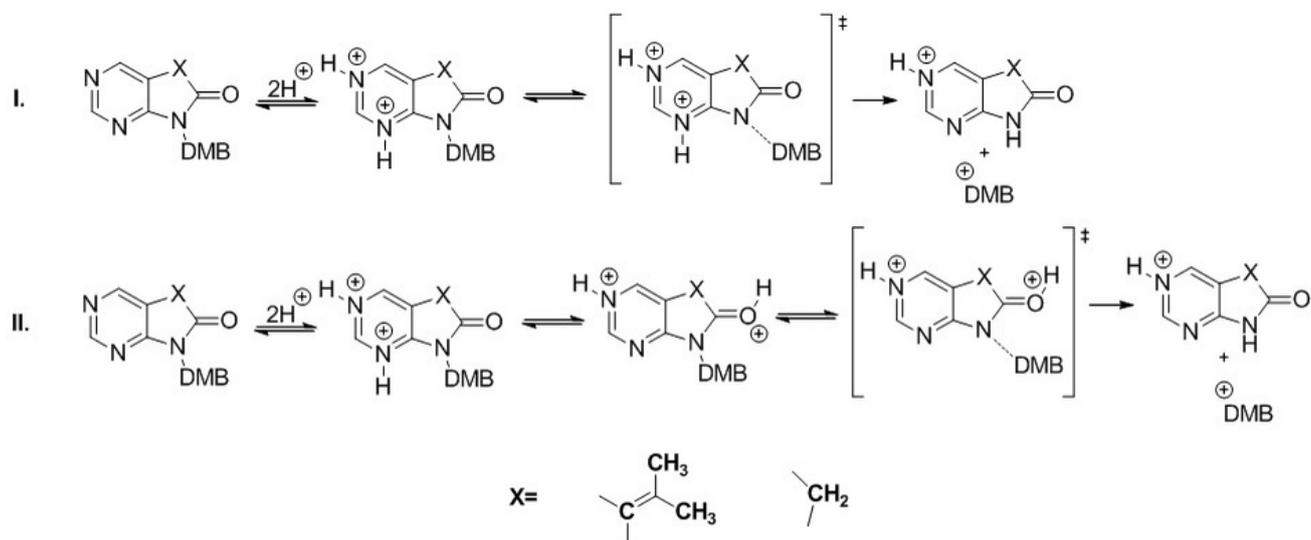
All calculations were carried out with the Gaussian09 software [14]. The calculations were performed on  $\omega$ B97XD/6-311++G(2df,2pd)// $\omega$ B97XD/6-31+G(d,p) level of theory in the presence of the IEF-PCM solvation model with UFF radii [15, 16]. TFA was selected as the solvent.

The reaction mechanism was also investigated with the variation of the dielectric constant, and it was found that there was no significant difference in the outcome of the calculations. For comparison, the ratio of the reaction rates was calculated based on the *Arrhenius*-equation, where the pre-exponential factor was considered the same for **15** and **16** since they are very similar compounds. (Fig. 1)

$$\frac{k_1}{k_2} = \exp \left[ \frac{E_{a,15} - E_{a,16}}{RT} \right]$$

Fig. 1 Calculation of the ratio of reaction rates

It was assumed that only protonated **15** and **16** could be transformed into free amides, since strong acidic reaction conditions were the prerequisite of DMB deprotection. Because  $pK_a$  of triflic acid is much lower than that of TFA, the formation



Scheme 7 The two most preferred mechanisms

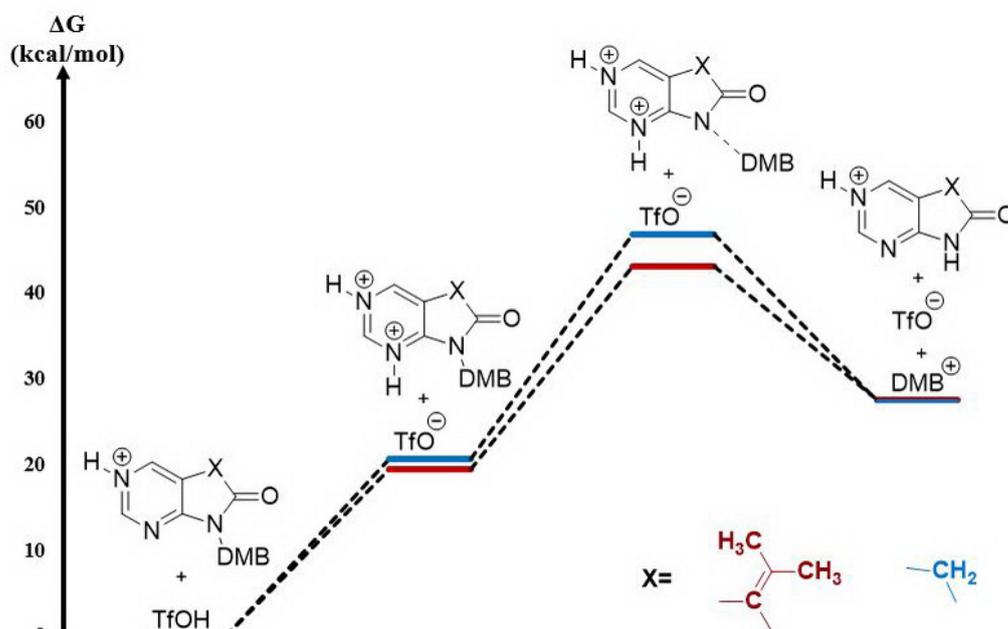


Fig. 2 Gibbs Free Energy diagram of deprotection of compounds **15** and **16**

energies for protonated **15** and **16** triflates were calculated. Detailed investigation of protonation, tautomerization and transition-state energies involving all proton-acceptor sites and tautomers revealed that DMB deprotection could proceed only from double protonated molecules. Two energetically close reaction mechanisms were formulated: (I.) the transition state occurs from the double protonated pyrimidine ring; or (II.) one of the two protons is migrating to the oxo group enhancing the debenzoylation by favouring the oxo-enol tautomerization in the transition state (Scheme 7).

It is important to note that triple-protonation of the molecules is energetically less favourable. Furthermore, transition states involving nitrogen protonated amide tautomer or protonated DMB group were energetically ruled out. Since calculations demonstrated that the second protonation of the

already protonated pyrimidine ring is energetically favoured, it was assumed that the most feasible mechanism is depicted in Scheme 7, path I.

It was also found a slight energetic difference (1.20 kcal/mol) for protonation but a more significant difference in transition state energies (3.64 kcal/mol) between **15** and **16** (Fig. 2), explaining why **16** is deprotected about 200 times faster than **15**.

Comparing in transition states the Mulliken charge distribution of the amide nitrogen atom and the methylene unit of DMB group (Fig. 3) it was found that in the double protonated **15** the electrostatic force between the amide nitrogen atom and the DMB methylene group is much stronger than in the similar transition state generated from compound **16**. A larger partial charge difference causes a greater cohesive force between the amide nitrogen and the leaving group, reducing the reactivity

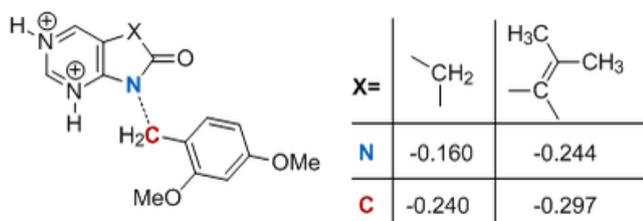


Fig. 3 Mulliken charges of the amide nitrogen and the DMB methylene

of **15** compared to **16**.

### 3 Conclusion

In order to explain the significant difference between the reactivity of compounds **15** and **16** in terms of removal of the DMB protecting group, the investigation of the reaction mechanism of these two 5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one derivatives has been performed. Due to the multiple proton-acceptor sites of both **15** and **16**, the exact mechanism of the deprotection reaction remains uncertain. It was found a slight energetic difference in protonation but a significant difference between the transition states of the most favoured mechanism. This result was explained taking into account the charge delocalizing effect of the isopropylidene group, enhancing the protonation of **16** compared to **15** and improving the formation of the unprotected product from **16**.

### 4 Experimental section

Melting points were determined on an OptiMelt Automated Melting Point System by Stanford Research Systems. IR spectra were obtained on a Bruker IFS-113v FT spectrometer. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance III (400 and 100 MHz for <sup>1</sup>H and <sup>13</sup>C NMR spectra, respectively). Chemical shifts ( $\delta$ ) and coupling constants ( $J$ ) are given in parts per million and in Hertz. The ESI+ mass spectra were recorded on a Thermo LTQ XL mass spectrometer coupled with an Acquity<sup>TM</sup> UPLC. The reactions were followed by analytical thin layer chromatography on silica gel 60 F<sub>254</sub>. All unspecified reagents were purchased from commercial sources.

**Ethyl (4-[(2,4-dimethoxyphenyl)methyl]amino}pyrimidin-5-yl)acetate (14).** To a stirred solution of ethyl 2-(4-chloropyrimidin-5-yl)acetate (**3a**, 2.10 g, 10.5 mmol) in DMF (25 mL) 2,4-dimethoxybenzylamine hydrochloride (**13**, 2.24 g, 11 mmol) and DIPEA (3.67 mL, 2.71 g, 21 mmol) were added at room temperature (rt) under argon. The reaction mixture was stirred at 110°C for 3 hours. After the reaction was complete and cooled to rt, water (150 mL) was added to the mixture and stirred for 30 min. The crystalline precipitate was filtered off, washed with water (2×30 mL) and dried to give **14** pale brown crystals (2.08 g, 6.0 mmol, 60%). An analytical sample was obtained by recrystallization from toluene to give colourless crystals. Mp. 123-125°C (toluene). IR (KBr):  $\nu$

1717, 1598, 1588 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.56 (s, 1H), 8.00 (s, 1H), 7.26-7.22 (t,  $J=8.2$  Hz, 1H), 6.48 (d,  $J=2.3$  Hz, 1H), 6.44-6.42 (dd,  $J=8.2, 2.3$  Hz, 1H), 6.00 (s, 1H), 4.64 (d,  $J=5.5$  Hz, 2H), 4.13-4.08 (q,  $J=7.1$  Hz, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 3.36 (s, 2H), 1.21-1.18 (t,  $J=7.2$  Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  170.3, 160.6, 160.5, 158.7, 157.8, 154.7, 130.2, 119.0, 110.9, 103.8, 98.6, 61.5, 55.4, 55.3, 40.3, 35.7, 14.0. MS: 332.23 (M+H)<sup>+</sup>.

**7-(2,4-Dimethoxybenzyl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one (15).** To a vigorously stirred suspension of sodium ethoxide (3.35 g, 47.3 mmol) and ethyl acetate (60 mL), a solution of ethyl (4-[(2,4-dimethoxyphenyl)methyl]amino}pyrimidin-5-yl)acetate (**14**, 7.12 g, 21.5 mmol) in ethyl acetate (210 mL) was added at 0°C. The cooling bath was removed and stirring was continued at 20°C for 10 min. After the reaction was complete, it was cooled to 10°C and acetic acid (5.32 mL, 5.58 g, 92.9 mmol) was added to the mixture. Stirring was continued for 30 min, and then the volatile components were evaporated at 40°C. The residue was dissolved in distilled water (180 mL) and stirred for 2 hours. The crystalline precipitate was filtered off, washed with water (2×30 mL) and dried to give **15** as pale brown crystals (5.42 g, 19.0 mmol, 88%). An analytical sample was obtained by recrystallization from EtOAc to give colourless crystals. Mp. 122.5-123.5°C (EtOAc). IR (KBr):  $\nu$  1730, 1470 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.79 (s, 1H), 8.32 (s, 1H), 7.12-7.10 (d,  $J=8.3$  Hz, 1H), 6.44 (d,  $J=2.4$  Hz, 1H), 6.41-6.39 (dd,  $J=8.3, 2.4$  Hz, 1H), 4.95 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.36 (s, 2H), 3.60 (s, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  173.5, 164.9, 160.6, 158.3, 157.8, 148.7, 129.6, 116.7, 115.7, 103.9, 98.6, 55.4, 55.3, 38.0, 32.8. MS: 286.09 (M+H)<sup>+</sup>.

**7-(2,4-Dimethoxybenzyl)-5-(propan-2-ylidene)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one (16).** 7-(2,4-Dimethoxybenzyl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one (**15**, 0.45 g, 1.6 mmol) was stirred in acetone (6.80 mL, 5.37 g, 90.9 mmol) and acetic acid (2.40 mL, 2.52 g, 41.9 mmol) at 60°C for 7 hours under argon atmosphere. The solvent was removed in vacuo, water (40 mL) and ethanol (2 mL) were added to the residue, and it was stirred for 1 hour. The crystalline precipitate was filtered off, washed with water (5×10 mL) and dried in a desiccator over phosphorous pentoxide in vacuo to give **16** as pale brown crystals (0.51 g, 1.57 mmol, 98%). An analytical sample was obtained by recrystallization from EtOAc to give colourless crystals. Mp. 164-165.5°C (EtOAc). IR (KBr):  $\nu$  1712, 1480 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.73 (s, 1H), 8.59 (s, 1H), 6.99-6.97 (d,  $J=8.4$  Hz, 1H), 6.44 (d,  $J=2.4$  Hz, 1H), 6.39-6.36 (dd,  $J=8.4, 2.4$  Hz, 1H), 5.01 (s, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 2.64 (s, 3H), 2.41 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.6, 160.4, 160.3, 160.158.1, 156.4, 146.5, 128.7, 118.9, 116.4, 116.4, 104.0, 98.6, 55.4, 55.3, 37.3, 25.7, 23.3. MS: 326.22 (M+H)<sup>+</sup>.

**5-(Propan-2-ylidene)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one (17).** 7-(2,4-Dimethoxybenzyl)-5-(propan-2-ylidene)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one (**16**, 75 mg, 0.23 mmol) was stirred in a mixture of triflic acid (1.00 mL, 1.70 mg, 11.3 mmol) and trifluoroacetic acid (1 mL, 1.49 g, 13.00 mmol) in the presence of anisole (1.00 mL, 96.00 mg, 9.12 mmol) at 25°C for overnight, then 1 h at reflux temperature. The volatile compounds were removed in vacuo and water (5 mL) was added. It was extracted with DCM (3×5 mL). The combined organic layer was washed with cc. aqueous NaHCO<sub>3</sub> solution (3×10 mL) and brine (20 mL), then dried and evaporated to give the crude **17** product. It was purified by column chromatography using EtOAc as the eluent. The product **17** (31 mg, 25%) was obtained as white crystals. Mp. 200°C decomp. (DMF). IR (KBr):  $\nu$  1718 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  11.52 (s, 1H), 8.66 (s, 1H), 8.63 (s, 1H), 2.53 (s, 3H), 2.36 (s, 3H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  167.6, 160.4 (2 signals: 160.40, 160.36), 156.1, 147.3, 119.1, 116.5, 25.7, 22.7. MS: 175.98 (M+H)<sup>+</sup>.

## References

- [1] Shepherd, T. A., Dally, R. D., Joseph, S. "Preparation of pyrrolopyrimidinone derivatives as AKT and p70S6 kinase inhibitors." *US 2010120801 U.S. Pat. Appl.*; *WO 2010056563 PCT Intern. Pat. Appl.*; *Chemical Abstracts*, 152, 568154, 2010.
- [2] Mitchell, I. S., Spencer, K. L., Stengel, P., Han, Y., Kallan, N. C., Munson, M., Vigers, G. P. A., Blake, J., Piscopio, A., Josey, J., Miller, S., Xiao, D., Xu, R., Rao, C., Wang, B., Bernacki, A. L. "AKT protein kinase inhibitors for use in treatment of hyperproliferative diseases." *WO 2005051304 PCT Intern. Pat. Appl.*; *Chemical Abstracts*, 143, 40007, 2005
- [3] Follmann, M., Stasch, J.-P., Redlich, G., Lang, D., Vakalopoulos, A., Wunder, F., Tersteegen, A. "Trifluoromethyl-substituted fused pyrimidines and their use." *US 2014249168 U.S. Pat. Appl.*; *Chemical Abstracts*, 161, 404656, 2014.
- [4] Follmann, M., Stasch, J.-P., Redlich, G., Ackerstaff, J., Griebenow, N., Knorr, A., Wunder, F., Li, V. M.-J., Kroh, W., Baerfacker, L. "Preparation of ring-fused pyrimidines and triazines as guanylate cyclase inhibitors and use thereof for the treatment and/or prophylaxis of cardiovascular diseases." *WO 2012004258 PCT Intern. Pat. Appl.*; *Chemical Abstracts*, 156, 175315, 2012.
- [5] Raghavan, S., Stelmach, J. E., Smith, C. J., Li, H., Whitehead, A., Waddell, S. T., Chen, Y.-H., Miao, S., Ornoski, O. A., Garfinkle, J., Liao, X., Chang, J., Han, X., Guo, J., Groeper, J. A., Brockunier, L. L., Rosauer, K., Parmee, E. R. "Pyrrolopyrimidinone derivatives as soluble guanylate cyclase activators and their preparation." *WO 2011149921 PCT Intern. Pat. Appl.*; *Chemical Abstracts*, 155, 11159, 2011.
- [6] Kókai, E., Nagy, J., Tóth, T., Kupai, J., Huszthy, P., Simig, Gy., Volk, B. "Convenient synthesis of 2-substituted 5,7-dihydro-6H-pyrrolo-[2,3-d]pyrimidin-6-ones." *Monatshfte für Chemie – Chemical Monthly*. 147, pp. 767–773. 2016.  
<https://doi.org/10.1007/s00706-015-1634-1>
- [7] Vaid, R. K., Spittler, J. T., Boini, S., May, S. A., Hoying, R. C. "An Efficient Synthesis of 4-Chloro-2-pyrrolo[2,3-d]pyrimidin-6-one and Its 7-Substituted Analogues." *Synthesis*. pp. 2396–2400. 2012.  
<https://doi.org/10.1055/s-0031-1290408>
- [8] Bonnert, R., Cage, P., Hunt, F., Walters, L., Willis, P. "Preparation of pyrimidine compounds as modulators of chemokine receptor activity." *WO 0158902A1 PCT Intern. Pat. Appl.*; *Chemical Abstracts*. 135, 166840. 2001.
- [9] Kocienski, P. J. "Protecting Groups." (pp. 224–225.), G. Thieme, 1994.
- [10] Chern, C.-Y., Huang, Y.-P., Wai, M. K. "Selective *N*-debenzylation of amides with *p*-TsOH." *Tetrahedron Letters*. 44, pp. 1039–1041. 2003.  
[https://doi.org/10.1016/S0040-4039\(02\)02738-7](https://doi.org/10.1016/S0040-4039(02)02738-7)
- [11] Kókai E., Halász, J., Dancsó, A., Nagy, J., Simig, Gy., Volk, B. "Study on the Alkylation Reactions of *N*(7)-Unsubstituted 1,3-Diazaoxindoles." *Molecules*. 22, pp. 846–869. 2017.  
<https://doi.org/10.3390/molecules22050846>
- [12] Jolicoeur, B., Chapman, E. E., Thompson, A., Lubell, W. D. "Pyrrole protection." *Tetrahedron*. 62, pp. 11531–11563. 2006.  
<https://doi.org/10.1016/j.tet.2006.08.071>
- [13] Knölker, H.-J., Reddy, K. R. "Chapter 5 - Chemistry of Carbazole Alkaloids." *The Alkaloids: Chemistry and Biology*. 65, pp. 195–383. 2008.  
[https://doi.org/10.1016/S1099-4831\(07\)00005-3](https://doi.org/10.1016/S1099-4831(07)00005-3)
- [14] Gaussian 09, Revision A.02, Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Scalmani, G., Barone, V., Petersson, G. A., Nakatsuji, H., Li, X., Caricato, M., Marenich, A., Bloino, J., Janesko, B. G., Gomperts, R., Mennucci, B., Hratchian, H. P., Ortiz, J. V., Izmaylov, A. F., Sonnenberg, J. L., Williams-Young, D., Ding, F., Lipparini, F., Egidi, F., Goings, J., Peng, B., Petrone, A., Henderson, T., Ranasinghe, D., Zakrzewski, V. G., Gao, J., Rega, N., Zheng, G., Liang, W., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Vreven, T., Throssell, K., Montgomery, J. A., Peralta, Jr., J. E., Ogliaro, F., Bearpark, M., Heyd, J., Brothers, E., Kudin, K. N., Staroverov, V. N., Keith, T., Kobayashi, R., Normand, J., Raghavachari, K., Rendell, A., Burant, J. C., Iyengar, S. S., Tomasi, J., Cossi, M., Millam, J. M., Klene, M., Adamo, C., Cammi, R., Ochterski, J. W., Martin, R. L., Morokuma, K., Farkas, O., Foresman, J. B., Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.
- [15] Chai, J.-D., Head-Gordon, M. "Long-range corrected hybrid density functionals with damped atom-atom dispersion corrections." *Physical Chemistry Chemical Physics*. 10, pp. 6615–6620. 2008.  
<https://doi.org/10.1039/B810189B>
- [16] Scalmani, G., Frisch, M. J. "Continuous surface charge polarizable continuum models of solvation. I. General formalism." *The Journal of Chemical Physics*. 132, pp. 114110–114125. 2010.  
<https://doi.org/10.1063/1.3359469>