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SHORT COMMUNICATION

Synthesis of novel 1-benzoylhexahydro-2*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(3*H*)-dione

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Abstract: We report an efficient [3+2] cycloaddition involving non-stabilized electron-rich azomethine ylides and 1,3-dibenzoyl-pyrimidine-2,4(1*H*,3*H*)-dione. The 1,3-dipole was prepared *in situ* under TFA catalysis, and we obtained the product in good yield and with full control of the regioselectivity.

Keywords: 1-benzoylhexahydro-2*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(3*H*)-dione; [3+2] cycloaddition; azomethine ylide; bicyclic pyrrolidine.

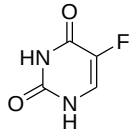
Introduction

The pursuit of novel synthetic methodologies for the preparation of nitrogen-containing heterocycles remains a central focus in modern organic and medicinal chemistry. Among such compounds, uracil derivatives stand out as important representatives of naturally occurring pyrimidine systems. They continue to attract strong scientific interest due to their wide range of biological activities and promising pharmacological potential.

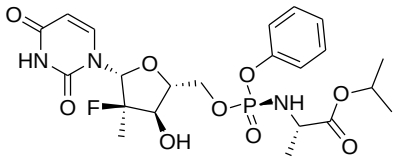
1,3-Dipolar cycloaddition reactions are well-known and widely used for the construction of five-membered heterocycles. Reactions with azomethine ylides have become especially popular due to their ability to form pyrrolidine rings in a single step with good regio- and stereoselectivity [1-5]. Pyrrolidine scaffolds represent biologically relevant motifs that are commonly found in numerous bioactive compounds and emerging heterocyclic frameworks of pharmaceutical interest [6-8]. The structures of more than 50 drugs contain the pyrrolidine fragment.

Uracil-based compounds exhibit a wide range of biological activities including antiviral (Sofosbuvir, a uracil-based nucleotide analog) and antitumour (Efudex, fluorouracil-based) examples of which are shown in Figure 1. To date, 264 bioactive compounds containing an uracil fragment have been reported, highlighting the relevance and continued interest in the investigation of this class of compounds [9]. Modifications of uracil at positions 5 and 6 have already been partially studied, but to our knowledge, the [3+2] cycloaddition reaction involving a double bond at position 5 and 6 is poorly understood.

In a study [10], the [3+2] cycloaddition was performed on 3´,5´-bis-*o*-silylthymidines using highly reactive non-stabilized azomethine ylide which was generated from trimethylamine *N*-oxide to obtain *N*-methyl nucleoside



Efudex
antimethabolite, thymidylate synthase inhibitor
(actinic keratosis, superficial basal cell carcinoma)



Sofosbuvir
nucleotide analog, HCV NS5B polymerase inhibitor
(hepatitis C therapy)

Figure 1. Examples of bioactive uracil-based compounds.

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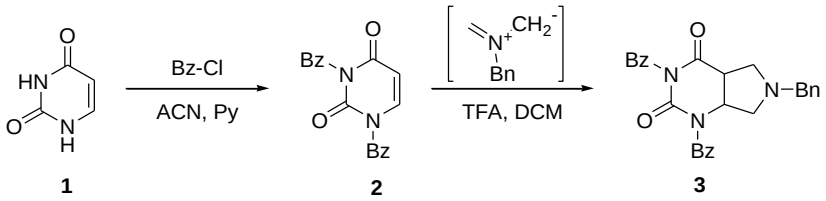
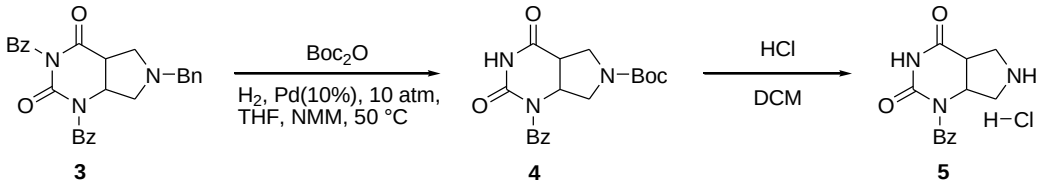


Scheme 1. Synthesis of 1,3-dibenzoyl-6-benzylhexahydro-2*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(3*H*)-dione (**3**).



Scheme 2. Synthesis of 1-benzoylhexahydro-2*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(3*H*)-dione hydrochloride (**5**).

pyrrolidines. The problem with this method is that the resulting pyrrolidines can no longer be selectively modified at the nitrogen atom, and the generation of azomethine ylide requires the prior preparation of lithium diisopropylamide and work at -78 °C.

In another study [11], the [3+2] cycloaddition was performed using nitrone dipole to the formation of fused isoxazolidines and the cycloaddition took place with complete regioselectivity and with stereospecific generation of two consecutive stereocenters what was deduced by the coupling constant values in ^{1}H NMR spectra between newly formed ring juncture atoms.

Only a few examples of uracil derivatives bearing a fused pyrrolidine ring have been reported in the literature, therefore we aimed to develop a novel synthetic approach to access these previously unexplored structures.

We report an efficient [3+2] cycloaddition involving unstabilized electron-rich azomethine ylide and 1,3-dibenzoylpyrimidine-2,4(1*H*,3*H*)-dione. The 1,3-dipole was generated *in situ* using trifluoroacetic acid (TFA) as a catalyst, and the product was obtained in a good yield and regioselectivity control. The obtained reaction products can be selectively modified at each of the nitrogen atoms.

Results and Discussion

In this paper we present our investigations and development of the effective approach to synthesize 1-benzoylhexahydro-2*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(3*H*)-dione (**5**) *via* [3+2] cycloaddition between nonstabilized *N*-benzyl azomethyne ylide and 1,3-dibenzoyluracil.

Initially, our aim was to attempt a 3+2 cycloaddition reaction on unprotected uracil, drawing an analogy with pyridone, where the double bond is activated. However, after applying all available protocols for this reaction, we consistently obtained either unreacted uracil or a complex mixture of products, from which the isolation of individual compounds proved difficult. As a result, we decided to carry out the transformation on dibenzoyl-protected uracil, as this approach allows for the subsequent selective removal of the protecting groups.

So the synthesis of condensed *N*-benzyl pyrrolidine derivative based on dibenzoyluracil was initiated by the introduction of a benzoyl protecting group (Scheme 1).

This was accomplished in acetonitrile using pyridine and benzoyl chloride according to known procedure [12]. The subsequent [3+2] cycloaddition was carried out in DCM at 0 °C in the presence of a catalytic amount of TFA, which was used to generate unstable *N*-benzyl azomethine ylide from *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine to obtain 1,3-dibenzoyl-6-benzylhexahydro-2*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(3*H*)-dione (**3**). Structure was confirmed by analyzing with 2D NMR (COSY, HSQC, NOE) (Figure 2).

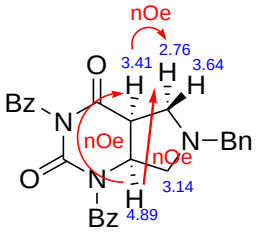


Figure 2. NMR correlations for 1,3-dibenzoyl-6-benzylhexahydro-2*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(3*H*)-dione (**3**).

All attempts to remove the benzyl and benzoyl protecting groups to obtain the corresponding amine as a base proved to be challenging. In all cases either the starting material **3** was recovered, or complex mixture were formed, from which the target 1-benzoylhexahydro-2*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(3*H*)-dione (**5**) could not be isolated (Scheme 2).

However, when catalytic hydrogenation over palladium was performed in the presence of di-*tert*-butyl dicarbonate (Boc_2O) as an amine-trapping reagent in an autoclave under heating, the removal of the benzyl protecting group occurred along with the selective cleavage of one benzoyl group. This transformation afforded *tert*-butyl 1-benzoyl-2,4-dioxooctahydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carbo-

xylate (**4**), whose structure was confirmed by analyzing with 2D NMR (COSY, HSQC, ROE) (Figure 3).

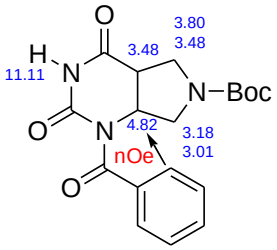


Figure 3. NMR correlations for *tert*-butyl 1-benzoyl-2,4-dioxo-octahydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate (**4**).

In the absence of Boc_2O, the removal of the benzyl protecting group did not occur, and in some cases, partial cleavage of the benzoyl group was observed. Subsequent treatment of compound **4** with 4M hydrochloric acid in dioxane provided the target compound 1-benzoylhexa-hydro-2*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(3*H*)-dione (**5**) as HCl salt.

Conclusions

In summary, we have developed an efficient [3+2] cycloaddition-based approach toward the synthesis of previously undescribed 1-benzoyl-substituted pyrrolo[3,4-d]pyrimidine derivatives. The obtained target compound can be selectively and sequentially modified at multiple functional groups, providing convenient access to a wide range of potentially bioactive molecules derived from this heterocyclic scaffold. Our results are expected to stimulate further exploration of uracil derivatives fused with a pyrrolidine ring as promising scaffolds for the design and development of novel bioactive compounds in medicinal chemistry.

Notes

Acknowledgments and finances. We would like to thank Enamine Ltd. for the material and technical support for the synthetic part of this work.

The authors declare no conflict of interest.

Experimental section

All reagents and solvents were purchased from Enamine Ltd. (www.enamine.net). TLC characterization was performed with pre-coated silica gel GF254 (0.2mm). For column flash chromatography Silica gel 230-400mesh was used. ^{1}H NMR spectra were recorded at 400, 500, or 600 MHz (Varian).^{13}C NMR spectra were recorded at 100, 126, or 151 MHz (Varian). ^{1}H NMR chemical shifts are calibrated using residual undeuterated solvents $CHCl_3$ (δ = 7.26 ppm) or DMSO (δ = 2.50 ppm). ^{13}C NMR chemical shifts for ^{13}C NMR are reported relative to the central $CHCl^3$ (δ = 77.16 ppm) or DMSO (δ = 39.52 ppm). Coupling constants are given in hertz. LC-MS spectra were recorded on an Agilent 1100 Series HPLC equipped with a diode array and Agilent LC/MSD SL mass selective detector, ionization method – chemical ionization at atmospheric pressure, m/z scan range from 80 to 1000.

Synthesis

*1,3-Dibenzoylpyrimidine-2,4(1H,3H)-dione (**2**).*

To 900 ml of dry acetonitrile 60 g (0.54 mol) of compound **1** was added. To this suspension was added pyridine 338.7 g (4.28 mol) first and then 225.7 g (1.6 mol) of benzoyl chloride was slowly added dropwise. The reaction mixture was stirred at room temperature for 2 days. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (eluent was hexane with a gradient of ethyl acetate from 0 to 70%) to obtain 150 g (0.47 mol, 87%) of **2**.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (t, J = 8.1 Hz, 3H), 7.77 (d, J = 7.7 Hz, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.48 (dt, J = 19.7, 7.7 Hz, 4H), 6.07 (d, J = 8.3 Hz, 1H). LCMS $(M+H)^+$: 321.

*1,3-Dibenzoyl-6-benzylhexahydro-2H-pyrrolo[3,4-d]pyrimidine-2,4(3H)-dione (**3**).*

To 100 ml of dry DCM 10 g (0.031 mol) of compound **2** and 11.11 g (0.047 mol) of *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine were added. The reaction mixture was cooled to 0 °C in an ice-water bath and 0.36 g (3.1 mmol) of trifluoroacetic acid was added dropwise at this temperature. The mixture was stirred for 16 h at room temperature. The mixture was neutralized with a 0.1 M solution of $NaHCO_3$. The organic layer was washed with brine (1 × 100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent was $CHCl_3$ with a gradient of ACN from 0 to 70%) to obtain 8.2 g (0.018 mol, 58%) of compound **3**.^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01-7.97 (d, J = 7.3 Hz, 2H), 7.66-7.60 (m, 3H), 7.49 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 7.42-7.28 (m, 7H), 4.89 (td, J = 8.6, 4.6 Hz, 1H), 3.86 (d, J = 12.8 Hz, 1H), 3.63 (t, J = 10.9 Hz, 2H), 3.41 (dd, J = 8.6, 5.0 Hz, 1H), 3.18-3.09 (m, 2H), 2.76 (dd, J = 9.3, 5.2 Hz, 1H).^{13}C NMR (151 MHz, $CDCl_3$) δ 172.44, 170.22, 168.36, 150.00, 137.60, 135.13, 134.48, 132.49, 131.51, 130.56, 129.12, 128.72, 128.59, 128.34, 128.30, 127.54, 60.02, 59.56, 57.61, 53.54, 43.56. LCMS $(M+H)^+$: 454.4

*Tert-butyl 1-benzoyl-2,4-dioxooctahydro-6H-pyrrolo-[3,4-d]pyrimidine-6-carboxylate (**4**).*

The compound **3** was dissolved in THF (80 mL) at autoclave and 7.89 g (0.036 mol) of di-*tert*-butyl decarbonate and 1.82 g (0.018 mol) of 4-methylmorpholine were added. Then 0.8 g of Pd/C (10%) was added to the solution. The mixture was degassed and filled with H_2 and heated 50 °C for 1 d. Pd/C was filtered, and the reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (eluent was $CHCl_3$ with a gradient of ACN from 0 to 15%) to obtain 4.3 g (0.012 mol, 66%) of compound **4**.^{1}H NMR (600 MHz, DMSO-d_6) δ 11.11 (s, 1H), 7.70 (d, J = 7.6 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 4.84 (m, 1H), 3.84

(m, 2H), 3.48 (m, 2H), 3.02 (m, 1H), 1.39 (d, *J* = 8.1 Hz, 9H).^{13}C NMR (151 MHz, DMSO-d_6) δ 173.11, 171.25, 153.60, 150.50, 135.79, 79.57, 60.20, 48.77, 48.42, 46.52, 46.18, 40.41, 40.27, 40.13, 7.92. LCMS (M+H)+ : 360.4

*1-Benzoylhexahydro-2H-pyrrolo[3,4-d]pyrimidine-2,4(3H)-dione hydrochloride (**5**).*

1 M HCl in dioxane (20 mL) was added to the solution of 4 g (0.011 mol) **4** in 40 ml DCM and the mixture was stirred overnight at room temperature. The product as hydrochloride salt was filtered off, and triturated MTBE to obtain 2.55 g (9.8 mmol, 88%) of compound **5**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.27 (s, 1H), 10.01-9.47 (m, 2H), 7.71 (d, *J* = 7.7 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 4.86 (q, *J* = 8.5 Hz, 1H), 3.76-3.5 (m, 4H), 3.08 (d, *J* = 12.9 Hz, 1H). LCMS $(M+H)^+$: 260.4.

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Синтез нового 1-бензоїлгексагідро-2*H*-піроло[3,4-*d*]піримідин-2,4(3*H*)-діону

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Резюме: Досліджено ефективне [3+2] циклоприєднання за участю нестабілізованого, багатого на електрони азометинового іліду та 1,3-дибензоїлпіримідин-2,4(1*H*,3*H*)-діону. 1,3-Диполь було одержано *in situ* під дією каталітичної кількості трифтороцтової кислоти, що дозволило отримати продукт з високим виходом та повною регіоселективністю.

Ключові слова: 1-гексагідро-2*H*-піроло[3,4-*d*]піримідин-2,4(3*H*)-діон; [3+2] циклоприєднання; азометиновий ілід; конденсований піролідин.