Graphical Abstract

A short and convenient strategy for the synthesis of pyridazines *via* diaza-Wittig reaction

Hassen Bel Abed, Oscar Mammoliti, Guy Van Lommen and Piet Herdewijn

R = alkyl, cycloalkyl, aryl, heteroaryl

A short and convenient strategy for the synthesis of pyridazines *via* diaza-Wittig reaction

Hassen Bel Abed^a, Oscar Mammoliti^b, Guy Van Lommen^b and Piet Herdewijn^{a*}

^a Rega Institute for Medical Research, Laboratory of Medicinal Chemistry, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium

^b Galapagos, Laboratory of Medicinal Chemistry, General de Wittelaan L11 A3, B-2800 Mechelen, Belgium

ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

ABSTRACT

A convenient and selective synthesis of 6-substituted-4-hydroxy-3-methoxycarbonyl pyridazines has been developed *via* a diaza-Wittig reaction. The desired products substituted at the C6 position can be obtained from readily available starting materials under mild conditions. This represents an attractive new method for the synthesis of pyridazine derivatives.

Keywords:

Pyridazine

Diaza-Wittig

Diazo transfer reaction

Weiler dianion

Several compounds with pyridazine¹ rings demonstrate biological activity² and several examples of these structures are naturally occurring.³ In fact, pyridazines are key intermediates in the synthesis of several fused heterocycles⁴ such as JNJ-38877605 (Figure 1) and have been explored as RAF/VEGFR2 inhibitors by Takeda Pharmaceutical.⁵ They have also proven to be attractive scaffolds from a pharmacological point of view, acting for example as PDE10A inhibitors⁶ for the treatment of psychotic disorders. Pyridazine based drugs were recognized as selective GABA-A receptor antagonists,⁷ such as Minaprine (Figure 1).

Figure 1. Structures of some pharmaceutically important pyridazine derivatives.

Herein, we describe the synthesis of a new pyridazine derivative in four steps with moderate to good yields. To the best of our knowledge, the only existing procedure leading to 3-alkoxycarbonyl-4-hydroxy-6-substituted pyridazines is the one developed by Zelesov *et al.*,⁸ starting from furan-4,5-dione.

However, this method is limited to the synthesis of aryl substituted compounds at the C6 position such as compound **1** (Figure 2).

Figure 2. Pyridazines and dialkyl acetone dicarboxylate.

Importantly, and of particular value for the development of a versatile method for the synthesis of pyridazine derivatives, is that the obtained compounds can be further modified in a site-selective way. For example, selective reaction of 4,6-dichloro pyridazine⁹ **2** at position 4 and 6 is problematic. The starting material for the synthesis of 4,6-dichloro pyridazine **2** is a dialkyl acetone dicarboxylate (methyl or ethyl) **3** which after treatment with a diazo transfer reagent followed by cyclization under harsh conditions (reflux in acetic acid) and chlorination leads to the desired pyridazine **2** (Figure 2).

Prompted by the need for a more reliable and versatile preparation of pyridazines allowing the introduction of various substituents such as alkyls, cycloalkyls, aryls and heteroaryls, we envisioned a more convenient synthesis of 6-substituted-4-hydroxy-3-methoxycarbonyl pyridazines starting from methyl acetoacetate **4**.

* Tel.: +32 16 337387; fax: +32 16 337340; E-mail address: piet.herdewijn@rega.kuleuven.be

In our search for operationally simple processes, we have investigated a new method to prepare pyridazines under mild conditions. It has been decided to replace one of the ester groups of the dialkyl acetone dicarboxylate (methyl or ethyl) **3** by a ketone to facilitate the cyclization reaction. However, the diazo transfer reaction may then occur at two positions. One position can be privileged by the introduction of an alcohol group instead of an ester group or a ketone.

Scheme 1. Synthesis of 6-substituted-4-hydroxy-3-methoxycarbonyl pyridazines.

The synthesis starts with the reaction of Weiler dianion¹⁰ of methyl acetoacetate **4** with an aldehyde, which led to the β -hydroxy ketoester **5** in moderate yields. These aldol products are easily degraded (water elimination) to give the corresponding enone.¹¹ After treatment of **5** with *p*-ABSA (*p*-acetamido benzene sulfonyl azide) in acetonitrile, the diazo derivative **6** was obtained in good yields.¹² A mild oxidation of **6** using IBX¹³ (1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide) in acetonitrile for 2h under reflux led to the corresponding α -diazo- β -ketoester **7** in good yields. The final stages¹⁴ of the synthesis (the formation of phosphazine **8** and the subsequent diaza-Wittig reaction) occur as a tandem process to obtain the pyridazine **9** in moderate to good yields. Different attempts have been done using triphenyl phosphine to convert the α -diazo- β -ketoester **7** into the pyridazine **9** without success, while the use of HMPT (hexamethylphosphorous triamide) at room temperature led to phosphazine and pyridazine ring formation (Scheme 1).

This procedure allowed the introduction of different groups at the C6 position of the pyridazine ring, such as alkyls, cycloalkyls, aryls and heteroaryl by selecting the appropriate aldehyde as starting material (Table 1). In this respect this procedure proved to be more selective than a strategy based on palladium cross-coupling.

We observed that better yields were obtained with alkyl aldehydes or cycloalkyl aldehydes than with aryl aldehydes and heteroaryl aldehydes. In order to cover a wide variety of substitutions, different attempts using aryl aldehydes containing electron withdrawing groups like *p*-nitrobenzaldehyde have been explored but did not give the required β -hydroxy ketoester **5** in our hands.

Table 1. Synthesis of 6-substituted-4-hydroxy-3-methoxycarbonyl pyridazines from intermediate **6**.

Entry	Aldehyde derivative	Product	Yield (%) [*]
1	propionaldehyde		68
2	isobutyraldehyde		75
3	cyclohexane carboxaldehyde		62
4	benzaldehyde		60
5	<i>p</i> -anisaldehyde		45
6	2-furfural		27
7	thiophene-2-carboxaldehyde		33

^{*} yields are the average of 3 trials.

In conclusion, we have developed a concise and convenient procedure for the synthesis of 6-substituted-4-hydroxy-3-methoxycarbonyl pyridazines involving a diaza-Wittig reaction as key-step, allowing the introduction of a variety of substitutions from alkyls, cycloalkyls to aryls and heteroaryl at the C6 position. This method, likewise, allows the synthesis of pyridazines with different substitutions at C4 and C6 positions, which is more difficult starting from the 4,6-dichloro pyridazine **2**. In order to further extend the scope of this process, we are currently exploring the synthesis of fused pyridazines from 6-substituted-4-hydroxy-3-methoxycarbonyl pyridazine derivatives.

Acknowledgements

Hassen Bel Abed is indebted to the IWT (Agentschap voor Innovatie door Wetenschap en Technologie) and the Galapagos company for providing a PhD-scholarship (Baekeland-project 90704). He is also grateful to Dr. Mongi and Dr. Fouzia for their kind suggestions.

References and notes

- For reviews on pyridazines, see: (a) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781–794. (b) Boger, D. L.; Patel, M. *Prog. Heterocycl. Chem.* **1989**, *1*, 30–84. (c) Sauer, J. In *Comprehensive Heterocyclic Chemistry II*; Pergamon: London, **1996**; Vol. 6; pp 901–955. (d) Bourguignon, J. J.; Oumouch, S.; Schmitt, M. *Curr. Org. Chem.* **2006**, *10*, 277–295. For representative examples of pyridazine synthesis, see: (e) Draper, T. L.; Bailey, T. R. *J. Org. Chem.* **1995**, *60*, 748–750. (f) Helm, M. D.; Moore, J. E.; Plant, A.; Harrity, J. P. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3889–3892. (g) Yang, X.; Knochel, P. *Org. Lett.* **2006**, *9*, 1941–1943. (h) Hamasaki, A.; Ducray, R.; Boger, D. L. *J. Org. Chem.* **2006**, *71*, 185–193. (i) Wermuth, C. G. *Med. Chem. Commun.* **2011**, *2*, 935. (j) Galiullina, S. V.; Zakharova, V. M.; Kantin, G. P.; Nikolaev, V. A. *Zhurnal Organicheskoi Khimii* **2007**, *43*, 607–614. (k) Supurgibekov, M. B.; Hennig, L.; Schulze, B.; Nikolaev, V. A. *Zhurnal Organicheskoi Khimii* **2008**, *44*, 1840–1843. (l) Supurgibekov, M. B.; Yanyuk, N. S.; Nikolaev, V. A. *Zhurnal Organicheskoi Khimii* **2011**, *47*, 1252–1255.
- (a) Benson, S. C.; Palabrica, C. A.; Snyder, J. K. *J. Org. Chem.* **1987**, *52*, 4610–4614. (b) Rohet, F.; Rubat, C.; Coudert, P.; Couquelet, J. *Bioorg. Med. Chem.* **1997**, *5*, 655–659. (c) Tucker, J. A.; Allwine, D. A.; Grega, K. C.; Barbachyn, M. R.; Klock, J. L.; Adamski, J. L.; Brickner, S. J.; Hutchinson, D. K.; Ford, C. W.; Zurenko, G. E.; Conradi, R. A.; Burton, P. S.; Jensen, R. M. *J. Med. Chem.* **1998**, *41*, 3723–3735. (d) Gyoten, M.; Nagaya, H.; Fukuda, S.; Ashida, Y.; Kawano, Y. *Chem. Pharm. Bull.* **2003**, *51*, 122–133. (e) Tamayo, N.; Liao, L.; Goldberg, M.; Powers, D.; Tudor, Y. Y.; Yu, V.; Wong, L. M.; Henkle, B.; Middleton, S.; Syed, R.; Harvey, T.; Jang, G.; Hungate, R.; Dominguez, C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2409–2413.
- (a) Tisler, M.; Stanovnik, B. *Adv. Heterocycl. Chem.* **1990**, *49*, 385–474 and references cited therein. (b) Joule, J. A.; Mills, K. *Heterocyclic chemistry*; Mir Press: Moscow, Russia, **2004**.
- (a) Ellis, G. P. In *Synthesis of Fused Heterocycles*; John Wiley and Sons Inc.: New York, **1987**; pp 226–239. (b) Naud, S.; Pipelier, M.; Viault, G.; Adjou, A.; Huet, F.; Legoupy, S.; Aubertin, A. M.; Evain, M.; Dubreuil, D. *Eur. J. Org. Chem.* **2007**, 3296–3310.
- Okaniwa, M.; Hirose, M. M.; Imada, T.; Ohashi, T.; Hayashi, Y.; Miyazaki, T.; Arita, T.; Yabuki, M.; Kakoi, K.; Kato, J.; Takagi, T.; Kawamoto, T.; Yao, S.; Sumita, A.; Tsutsumi, S.; Tottori, T.; Oki, H.; Sang, B.; Yano, J.; Aertgeerts, K.; Yoshida, S.; Ishikawa, T. *J. Med. Chem.* **2012**, *55*, 3452–3478.
- Alberati, D.; Gobbi, L.; Koerner, M.; Kuhn, B.; Peters, J.; Rodriguez Sarmiento, R. M.; Roger-Evans, M.; Rudolph, M. Patent WO2010/063610.
- Blackaby, W.; Blurton, P.; Burkamp, F.; Fletcher, S.; Jennings, A.; Lewis, R.; Macleod, A.; Street, L.; Thomas, S.; Vanniel, M.; Wilson, K. Patent WO2004/014865.
- (a) Zelesov, V. V. *et al. Zhurnal Organicheskoi Khimii* **1995**, *32*, 735–740. (b) Aliev, Z. G.; Vyaznikova N. G.; Zalesov, V. V.; Kataev, S. S.; Andreichikov, Y. S.; Atovmyan, L.O. *Russ. Chem. Bull.* **1997**, *46*, 2142–2145.
- Xie, L.; Han, B.; Xu, Y.; Maynard, G. Patent WO2004/031174.
- (a) Huckin, S.; Weiler, L. *Tetrahedron Lett.* **1971**, *50*, 4835–4838. (b) Huckin, S.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 2157–2164.
- Clarke, P. A.; Martin W. H. C.; Hargreaves J. M.; Wilson C.; Blake A. *J. Org. Biomol. Chem.* **2005**, *3*, 3551–3563.
- (a) Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press: London, **1986**, 65–198. (b) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223–269. (c) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, **1998**. (d) Davies, H. M. L.; Beckwith, R. E. *J. Chem. Rev.* **2003**, *103*, 2861–2903. (e) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577–6605. For a recent review on the synthesis of diazo compounds, see: (a) Maas, G. *Angew. Chem. Int. Ed.* **2009**, *48*, 8186–8195. For selected reports on remote functionalized diazo compounds, see: (b) Xu, X.; Hu, W.-H.; Doyle, M. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 6392–6395. (c) Zhou, L.; Doyle, M. P. *Org. Lett.* **2010**, *12*, 796–799. (d) Yu, L.; Zhang, Y.; Jee, N.; Doyle, M. P. *Org. Lett.* **2008**, *10*, 1605–1608. (e) Doyle, M. P.; Kundu, K.; Russell, A. E. *Org. Lett.* **2005**, *7*, 5171–5174. (f) Deng, G.; Tian, X.; Qu, Z.; Wang, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 2773–2776. (g) Liao, M.; Dong, S.; Deng, G.; Wang, J. *Tetrahedron Lett.* **2006**, *47*, 4537–4540. (h) Zhao, Y.; Wang, J. *Synlett* **2005**, 2886–2892. (i) Dong, C.; Mo, F.; Wang, J. *J. Org. Chem.* **2008**, *73*, 1971–1974. (j) Dong, C.; Deng, G.; Wang, J. *J. Org. Chem.* **2006**, *71*, 5560–5564. (k) Padwa, A.; Zhang, Z. J.; Zhi, L. *J. Org. Chem.* **2000**, *65*, 5223–5232.
- Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538.
- Typical procedure for **9e**: To a solution of **7e** (7.24 mmol, 1.0 equiv) in 20 mL of dichloromethane was added 1.32 mL of HMPT (hexamethylphosphorous triamide) (7.24 mmol, 1.0 equiv). The mixture was then stirred at room temperature overnight. After completion of the reaction (TLC), the reaction mixture was quenched with the addition of water. The organic phase was then washed several times with water, dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography on silica gel (ethyl acetate/methanol 90/10) afforded the desired product **9e** as an orange powder (850 mg, 45%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.77 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.81 (s, 1H), 3.84 (s, 6H). ¹³C NMR (125 MHz, DMSO-*d*₆) δ 164.2, 161.7, 148.2, 129.0, 122.8, 115.0, 114.7, 55.6, 52.5. HRMS calcd for C₁₃H₁₂N₂O₄ 261.0831, found 261.0871.

Supporting Information

A short and convenient strategy for the synthesis of pyridazines *via* diaza-Wittig reaction

Hassen Bel Abed^a, Oscar Mammoliti^b, Guy Van Lommen^b and Piet Herdewijn^a

*^aRega Institute for Medical Research, Laboratory of Medicinal Chemistry, Katholieke Universiteit Leuven,
Minderbroedersstraat 10, B-3000 Leuven, Belgium*

^bGalapagos, Laboratory of Medicinal Chemistry, General de Wittelaan L11 A3, B-2800 Mechelen, Belgium

List of contents

List of contents.....	S2
General Information.....	S3
Experimental Procedures and Data.....	S4-S10
^1H and ^{13}C NMR spectra for 9	S11-S17

General Information

For all reactions, analytical grade solvents were used. All moisture-sensitive reactions were carried out in oven-dried glass-ware (135°C). ^1H and ^{13}C NMR spectra: Bruker Advance 500 (^1H -NMR: 500 MHz, ^{13}C -NMR: 125 MHz), using tetramethylsilane as internal standard for ^1H -NMR spectra and DMSO- d_6 (39.5 ppm) or CDCl_3 (77.2 ppm) for ^{13}C -NMR spectra. Abbreviations used are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. s = broad singlet. Coupling constants (J) are expressed in Hz. Mass spectra were obtained with a Finnigan LCQ Advantage Max (ion trap) mass spectrophotometer from Thermo Finnigan, San Jose, CA, USA. High resolution mass spectrometry: spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Samples were infused at 3 $\mu\text{L}/\text{min}$ and spectra were obtained in positive (or negative) ionization mode with a resolution of 15000 (FWHM) using leucine enkephalin as lock mass. Electrospray MS spectra were obtained on a Micromass platform LC/MS spectrometer. Column used for all LC/MS analysis: Waters Acquity UPLC BEH C18 1.7 μm , 2.1 mm ID x 50 mm L. All the methods are using MeCN/ H_2O gradients. Water contains either 0.1 % TFA or 0.1 % NH_3 . Precoated aluminum sheets (Fluka Silica gel/TLC-cards, 254 nm) were used for TLC. Column chromatography (CC) was performed on ICN silica gel 63-200, 60 Å.

Experimental Procedures and Data

General procedure for preparation of 5-hydroxy-5-substituted-3-oxo-pentanoates **5**:

To a suspension of 60% sodium hydride (44.5 mmol, 1.2 equiv.) in 60 mL of dry THF under argon at 0°C was slowly added methyl acetoacetate **4** (37.1 mmol, 1 equiv.). After hydrogen evolution had ceased (30 minutes), the reaction mixture was cooled to -78°C and 2.5 M butyllithium (44.5 mmol, 1.2 equiv.). The mixture was stirred for 30 minutes, after which time aldehyde was added and the mixture stirred for 5 hours. The reaction was allowed to warm to room temperature and was diluted with water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The organic layer was dried (Na₂SO₄), concentrated, and the residue chromatographed (hexane/ethyl acetate = 4/1 to 1/1 as eluent) to afford the desired compound **5**.

Methyl 5-hydroxy-3-oxoheptanoate (**5a**)

Yellow oil; ¹H NMR (500 MHz, CDCl₃): δ 3.98-4.07 (m, 1H), 3.75 (s, 3H), 3.50 (s, 2H), 2.62-2.76 (m, 2H), 1.48-1.55 (m, 2H), 0.94-0.97 (m, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 203.6, 167.3, 68.9, 52.4, 49.7, 49.2, 29.3, 11.7. HRMS calcd for C₈H₁₄O₄ (M+Na)⁺: 197.0785, found: 197.0791.

Methyl 5-hydroxy-6-methyl-3-oxoheptanoate (**5b**)

Yellow oil; ¹H NMR (500 MHz, CDCl₃): δ 3.85-3.87 (m, 1H), 3.75 (s, 3H), 3.53 (s, 2H), 2.73 (dd, *J* = 17.2, 2.6 Hz, 1H), 2.65 (dd, *J* = 17.3, 9.4 Hz, 1H), 1.69-1.72 (m, 1H), 0.92-0.95 (m, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 204.0, 167.4, 72.1, 52.4, 49.7, 46.7, 33.0, 18.3, 17.6. HRMS calcd for C₉H₁₆O₄ (M+Na)⁺: 211.0941, found: 211.0940.

Methyl 5-cyclohexyl-5-hydroxy-3-oxopentanoate (**5c**)

Yellow oil; ^1H NMR (500 MHz, CDCl_3): δ 3.85 (m, 1H), 3.75 (s, 3H), 3.52 (s, 2H), 2.73 (dd, J = 17.3, 2.6 Hz, 1H), 2.67 (dd, J = 17.4, 9.6 Hz, 1H), 1.82-1.85 (m, 1H), 1.75-1.77 (m, 3H), 1.64-1.68 (m, 2H), 1.33-1.39 (m, 1H), 1.11-1.27 (m, 4H), 1.07-0.97 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 204.1, 167.4, 71.6, 52.4, 49.7, 46.8, 42.9, 28.8, 28.1, 26.3, 26.1, 25.9. HRMS calcd for $\text{C}_{12}\text{H}_{20}\text{O}_4$ ($\text{M}+\text{Na}$) $^+$: 251.1254, found: 251.1249.

Methyl 5-hydroxy-3-oxo-5-phenylpentanoate (5d)

Yellow oil; ^1H NMR (500 MHz, CDCl_3): δ 7.35-7.36 (m, 4H), 7.28-7.30 (m, 1H), 5.19 (dd, J = 9.4, 2.6 Hz, 1H), 3.74 (s, 3H), 3.51 (s, 2H), 3.00 (dd, J = 17.5, 9.4 Hz, 1H), 2.91 (dd, J = 17.3, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 202.8, 167.3, 142.4, 128.6, 127.8, 125.6, 69.8, 52.5, 51.5, 49.6. HRMS calcd for $\text{C}_{12}\text{H}_{14}\text{O}_4$ ($\text{M}+\text{Na}$) $^+$: 245.0785, found: 245.0778.

Methyl 5-hydroxy-5-(4-methoxyphenyl)-3-oxopentanoate (5e)

Yellow oil; ^1H NMR (500 MHz, CDCl_3): δ 7.27-7.29 (m, 2H), 6.87-6.89 (m, 2H), 5.15 (dd, J = 9.4, 3.2 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.50 (s, 2H), 3.00 (dd, J = 17.2, 9.3 Hz, 1H), 2.88 (dd, J = 17.2, 3.2 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 202.7, 167.3, 159.2, 134.6, 126.9, 114.0, 69.5, 55.3, 52.4, 51.5, 49.7. HRMS calcd for $\text{C}_{13}\text{H}_{16}\text{O}_5$ ($\text{M}+\text{Na}$) $^+$: 275.0890, found: 275.0885.

Methyl 5-(furan-2-yl)-5-hydroxy-3-oxopentanoate (5f)

Yellow oil; ^1H NMR (500 MHz, CDCl_3): δ 7.37-7.38 (m, 1H), 6.33 (dd, J = 3.2, 1.8 Hz, 1H), 6.28 (d, J = 3.3 Hz, 1H), 5.20 (dd, J = 8.9, 3.3 Hz, 1H), 3.75 (s, 3H), 3.54 (s, 2H), 3.18 (dd, J = 17.6, 8.9 Hz, 1H), 3.04 (dd, J = 17.6, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 202.1, 167.2, 154.4, 142.2, 110.3, 106.5, 63.5, 52.5, 49.5, 47.7. HRMS calcd for $\text{C}_{10}\text{H}_{12}\text{O}_5$ ($\text{M}+\text{Na}$) $^+$: 235.0577, found: 235.0576.

Methyl 5-hydroxy-3-oxo-5-(thiophen-2-yl)-pentanoate (5g)

Yellow oil; ^1H NMR (500 MHz, CDCl_3): δ 7.25-7.27 (m, 1H), 6.96-6.98 (m, 2H), 5.44 (dd, $J = 8.9, 3.1$ Hz, 1H), 3.75 (s, 3H), 3.53 (s, 2H), 3.13 (dd, $J = 17.6, 8.9$ Hz, 1H), 3.05 (dd, $J = 17.5, 3.4$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 202.2, 167.1, 146.1, 126.7, 124.9, 123.7, 66.0, 52.5, 51.3, 49.6. HRMS calcd for $\text{C}_{10}\text{H}_{12}\text{O}_4\text{S}_1$ ($\text{M}+\text{Na}$) $^+$: 251.0349, found: 251.0344.

General procedure for preparation of 2-diazo-5-hydroxy-5-substituted-3-oxo-pentanoates **6**:

To a solution of compound **5** (1 equiv.) in 50 mL of acetonitrile under argon at 0°C was added successively triethylamine (1.3 equiv.) and *p*-acetamido benzene sulfonyl azide (ABSA) (1 equiv.). The mixture was stirred for 2 hours and was allowed to warm to room temperature and was diluted with a mixture of diethyl ether/hexane (1/1 100 mL) and then filtered. The filtrate was concentrated and the residue chromatographed (hexane/ethyl acetate = 5/1 to 2/1 as eluent) to afford the desired compound **6**.

Methyl 2-diazo-5-hydroxy-3-oxoheptanoate (6a)

Yellow oil; ^1H NMR (500 MHz, CDCl_3): δ 4.01-4.02 (m, 1H), 3.85 (s, 3H), 3.10 (dd, $J = 17.1, 2.4$ Hz, 1H), 3.04 (d, $J = 3.3$ Hz, 1H), 2.91 (dd, $J = 17.1, 9.4$ Hz, 1H), 1.50-1.61 (m, 2H), 0.98 (t, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 193.0, 161.7, 69.4, 52.3, 46.3, 29.5, 9.8. HRMS calcd for $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_4$ ($\text{M}+\text{Na}$) $^+$: 223.0690, found: 223.0690.

Methyl 2-diazo-5-hydroxy-6-methyl-3-oxoheptanoate (6b)

Yellow oil; ^1H NMR (500 MHz, CDCl_3): δ 3.80-3.85 (m, 4H), 3.08 (dd, $J = 17.0, 2.3$ Hz, 1H), 2.90-2.95 (m, 2H), 1.72-1.78 (m, 1H), 0.95-0.98 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3):

δ 193.4, 161.7, 72.8, 52.3, 43.9, 33.3, 18.4, 17.7. **HRMS** calcd for $C_9H_{14}N_2O_4$ ($M+Na$)⁺: 237.0846, found: 237.0847.

Methyl 2-diazo-5-cyclohexyl-5-hydroxy-3-oxopentanoate (6c)

Yellow oil; **¹H NMR (500 MHz, CDCl₃)**: δ 3.85 (m, 4H), 3.09 (dd, J = 16.8, 2.3 Hz, 1H), 2.94 (dd, J = 16.9, 9.9 Hz, 2H), 1.87-1.89 (m, 1H), 1.75-1.78 (m, 2H), 1.65-1.71 (m, 2H), 1.38-1.44 (m, 1H), 1.00-1.28 (m, 5H); **¹³C NMR (125 MHz, CDCl₃)**: δ 193.4, 161.7, 72.1, 52.3, 44.0, 43.2, 28.7, 28.2, 26.4, 26.1, 26.0. **HRMS** calcd for $C_{12}H_{18}N_2O_4$ ($M+Na$)⁺: 277.1159, found: 277.1159.

Methyl 2-diazo-5-hydroxy-3-oxo-5-phenylpentanoate (6d)

Yellow oil; **¹H NMR (500 MHz, CDCl₃)**: δ 7.39-7.41 (m, 2H), 7.34-7.37 (m, 2H), 7.26-7.29 (m, 1H), 5.20-5.22 (m, 1H), 3.83 (s, 3H), 3.39 (d, J = 3.1 Hz, 1H), 3.27-3.29 (m, 2H); **¹³C NMR (125 MHz, CDCl₃)**: δ 192.1, 161.5, 142.6, 128.5, 127.6, 125.7, 70.2, 52.4, 48.6. **HRMS** calcd for $C_{12}H_{12}N_2O_4$ ($M+Na$)⁺: 271.0690, found: 271.0687.

Methyl 2-diazo-5-hydroxy-5-(4-methoxyphenyl)-3-oxopentanoate (6e)

Yellow oil; **¹H NMR (500 MHz, CDCl₃)**: δ 7.31-7.33 (m, 2H), 6.87-6.89 (m, 2H), 5.13-5.17 (m, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.22-3.32 (m, 2H); **¹³C NMR (125 MHz, CDCl₃)**: δ 192.1, 161.6, 159.1, 134.9, 127.0, 113.9, 69.9, 55.3, 52.3, 48.5. **HRMS** calcd for $C_{13}H_{14}N_2O_5$ ($M+Na$)⁺: 301.0795, found: 301.0795.

Methyl 2-diazo-5-(furan-2-yl)-5-hydroxy-3-oxopentanoate (6f)

Yellow oil; ¹H NMR (500 MHz, CDCl₃): δ 7.37-7.38 (m, 1H), 6.33 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.30 (d, *J* = 3.5 Hz, 1H), 5.23 (dd, *J* = 9.2, 2.9 Hz, 1H), 3.85 (s, 3H), 3.50 (dd, *J* = 17.4, 9.0 Hz, 1H), 3.32 (dd, *J* = 17.4, 3.2 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 191.5, 161.5, 154.8, 142.1, 110.2, 106.2, 64.0, 52.4, 45.0. HRMS calcd for C₁₀H₁₁N₂O₅ (M+Na)⁺: 261.0482, found: 261.0485.

Methyl 2-diazo-5-hydroxy-3-oxo-5-(thiophen-2-yl)-pentanoate (6g)

Yellow oil; ¹H NMR (500 MHz, CDCl₃): δ 7.25-7.27 (m, 1H), 6.99-7.00 (m, 1H), 6.96-6.98 (m, 1H), 5.45-5.47 (m, 1H), 3.85 (s, 3H), 3.57 (d, *J* = 4.1 Hz, 1H), 3.45 (dd, *J* = 17.3, 8.9 Hz, 1H), 3.40 (dd, *J* = 17.3, 3.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 191.7, 161.5, 146.4, 126.7, 124.7, 123.5, 66.5, 52.4, 48.2. HRMS calcd for C₁₀H₁₀N₂O₄S₁ (M+Na)⁺: 277.0254, found: 277.0257.

General procedure for preparation of pyridazine derivatives 9:

To a solution of compound **6** (1 equiv.) in 50 mL of acetonitrile under argon at 0°C was added IBX (1-hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide) (1.3 equiv.). The mixture was refluxed for 2 hours and was allowed to warm to room temperature and was then filtered. The filtrate was concentrated to afford the α-diazo-β-ketoester **7** used directly without further purification for the next step.

To a solution of **7** (1.0 equiv) in 20 mL of dichloromethane was added HMPT (hexamethylphosphorous triamide) (1.0 equiv). The mixture was then stirred at room temperature overnight. After completion of the reaction (TLC), the reaction mixture was quenched with the addition of water. The organic phase was then washed several times with water, dried over Na₂SO₄ and concentrated in vacuo. Flash column chromatography on silica gel (ethyl acetate/methanol = 9/1) afforded the desired product **9**.

Methyl 6-ethyl-4-hydroxypyridazine-3-carboxylate (9a)

Pale yellow powder; mp 188-190°C; ^1H NMR (500 MHz, DMSO-d_6): δ 13.37 (br. s, 1H), 6.40 (s, 1H), 3.80 (s, 3H), 2.56 (m, 2H), 1.19 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.8, 164.2, 156.6, 148.6, 116.2, 52.4, 24.0, 12.5. LC/MS t_R = 0.58 min, purity: 99%, mass found: 182.7.

Methyl 4-hydroxy-6-isopropylpyridazine-3-carboxylate (9b)

Yellow powder; mp 189-192°C; ^1H NMR (500 MHz, DMSO-d_6): δ 13.38 (br. s, 1H), 6.42 (s, 1H), 3.81 (s, 3H), 2.85 (m, 1H), 1.22 (m, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.9, 164.2, 160.4, 148.6, 114.4, 52.4, 30.2, 21.0. LC/MS t_R = 0.75 min, purity: 99%, mass found: 197.1.

Methyl 6-cyclohexyl-4-hydroxypyridazine-3-carboxylate (9c)

Yellow powder; mp 215-217°C; ^1H NMR (500 MHz, DMSO-d_6): δ 6.37 (s, 1H), 3.80 (s, 3H), 1.77-1.84 (m, 4H), 1.67-1.69 (m, 1H), 1.18-1.46 (m, 5H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.9, 164.1, 159.3, 148.5, 114.9, 52.4, 30.9, 25.7, 25.1. LC/MS t_R = 0.64 min, purity: 99%, mass found: 237.0.

Methyl 4-hydroxy-6-phenylpyridazine-3-carboxylate (9d)

Brown powder; mp 212-214°C; ^1H NMR (500 MHz, DMSO-d_6): δ 13.72 (br. s, 1H), 7.79-7.81 (m, 2H), 7.60 (m, 3H), 6.86 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 164.1, 152.2, 148.4, 131.2, 131.0, 129.2, 127.4, 115.9, 52.4. LC/MS t_R = 0.84 min, purity: 99%, mass

found: 231.0.

Methyl 4-hydroxy-6-(4-methoxyphenyl)pyridazine-3-carboxylate (9e)

Orange powder; mp 217-219°C; ^1H NMR (500 MHz, DMSO-d_6): δ 7.77 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.8 Hz, 2H), 6.81 (s, 1H), 3.84 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 164.2, 161.7, 148.2, 129.0, 122.8, 115.0, 114.7, 55.6, 52.5. LC/MS t_R = 0.94 min, purity: 99%, mass found: 261.1.

Methyl 6-(furan-2-yl)-4-hydroxypyridazine-3-carboxylate (9f)

Brown powder; mp 197-199°C; ^1H NMR (500 MHz, DMSO-d_6): δ 8.04 (m, 1H), 7.44-7.45 (m, 1H), 6.87 (s, 1H), 6.78 (dd, J = 3.6, 1.8 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 163.9, 146.8, 113.3, 113.1, 111.5, 52.4. LC/MS t_R = 0.82 min, purity: 99%, mass found: 220.8.

Methyl 4-hydroxy-6-(thiophen-2-yl)pyridazine-3-carboxylate (9g)

Brown powder; mp 205-208°C; ^1H NMR (500 MHz, CDCl_3): δ 10.91 (s, 1H), 7.76-7.77 (m, 1H), 7.58-7.59 (m, 1H), 7.32 (s, 1H), 7.19 (dd, J = 5.0, 3.8 Hz, 1H), 4.13 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 169.1, 160.0, 157.7, 139.6, 136.6, 131.0, 128.4, 127.9, 108.2, 53.5. LC/MS t_R = 0.91 min, purity: 99%, mass found: 236.8.

¹H and ¹³C NMR Spectra for 9a-9h

Methyl 6-ethyl-4-hydroxypyridazine-3-carboxylate (9a)

¹H NMR (500 MHz, DMSO-d₆)

¹³C NMR (125 MHz, DMSO-d₆)

Methyl 4-hydroxy-6-isopropylpyridazine-3-carboxylate (9b)

¹H NMR (500 MHz, DMSO-d₆)

¹³C NMR (125 MHz, DMSO-d₆)

Methyl 6-cyclohexyl-4-hydroxypyridazine-3-carboxylate (9c)

^1H NMR (500 MHz, DMSO- d_6)

^{13}C NMR (125 MHz, DMSO- d_6)

Methyl 4-hydroxy-6-phenylpyridazine-3-carboxylate (9d)

¹H NMR (500 MHz, DMSO-d₆)

¹³C NMR (125 MHz, DMSO-d₆)

Methyl 4-hydroxy-6-(4-methoxyphenyl)pyridazine-3-carboxylate (9e)

^1H NMR (500 MHz, DMSO- d_6)

^{13}C NMR (125 MHz, DMSO- d_6)

Methyl 6-(furan-2-yl)-4-hydroxypyridazine-3-carboxylate (9f)

^1H NMR (500 MHz, DMSO- d_6)

^{13}C NMR (125 MHz, DMSO- d_6)

Methyl 4-hydroxy-6-(thiophen-2-yl)-pyridazine-3-carboxylate (9g)

^1H NMR (500 MHz, CDCl_3)

^{13}C NMR (125 MHz, CDCl_3)