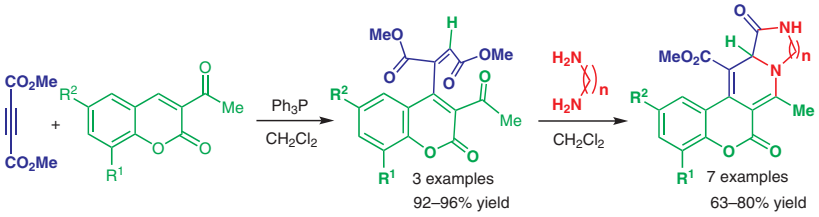
Synlett A. Alizadeh, P. Jamal Letter

Synthesis of Chromeno[4′,3′:4,5]pyrido[1,2-*a*]pyrazines and -diazepines by the Reaction of Substituted 2-(3-Acetyl-2-oxo-2*H*-chromen-4-yl)fumarates with 1,*n*-Diamines

Abdolali Alizadeh*
Parinaz Jamal

Department of Chemistry, Tarbiat Modares University, P.O. Box 14115-175, Tehran, Iran
aalizadeh@modares.ac.ir
abdol_alizad@yahoo.com



Received: 15.12.2017
Accepted after revision: 11.02.2018
Published online: 04.04.2018
DOI: 10.1055/s-0036-1591550; Art ID: st-2017-d0904-l

Abstract A two-step sequence was developed for the synthesis of chromeno[4′,3′:4,5]pyrido[1,2-*a*]pyrazine-13-carboxylates and -diazepine-14-carboxylates by the reaction of substituted dimethyl 2-(3-acetyl-2-oxo-2*H*-chromen-4-yl)fumarates with 1,*n*-diamines at room temperature. Advantages of this protocol include ease of handling and the absence of a metal catalyst.

Key words dimethyl acetyloxochromenfumarates, chromenopyridopyrazinecarboxylates, chromenopyridodiazepinecarboxylates, cyclization, polycyclic heterocycles

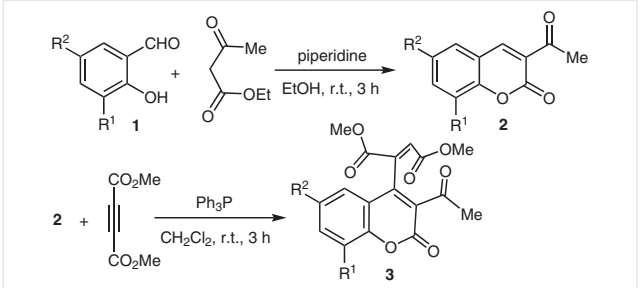
The synthesis of fused heterocyclic compounds has attracted much attention, because such heterocycles have important roles in the biological profiles of drugs.[1] Fused heterocyclic derivatives have been obtained by combining smaller heterocyclic compounds with one another, and such combinations containing two biologically active moieties can display synergistic effects, resulting in new biological activities compared with the parent compounds.[2–13]

Coumarin is present as a structural framework in many bioactive natural products.[14] Derivatives have also been found that demonstrate antitumor,[15] antioxidant,[16] or anti-inflammatory properties[17] or which act as nonpeptidic HIV protease inhibitors,[18] topoisomerase II inhibitors,[19] tyrosine kinase inhibitors,[20] diuretics, or analgesics.[21,22] Heterocycles fused at the 3,4-position of coumarin have also attracted attention.[23]

Among the various synthetic methods that have been developed for synthesis of heterocycles, zwitterion chemistry is one of the more interesting.[24] Nucleophilic addition of phosphorus at an unsaturated carbon of dialkyl acetylenedicarboxylates yields zwitterions that react with dipolarophiles to give phosphorus- or nonphosphorus-containing products. For example, 2,5-dihydro-1,2-oxaphospholes have been synthesized by the reaction of triphenylphosphine, alkynes, and ethyl 3-bromopyruvate.[25] Additionally, the three-component reactions of amines with diketene and dibenzoylacetylene in the presence of triphenylphosphine yields functionalized furamide derivatives.[26]

The widespread use of polycyclic nitrogen heterocycles in the discovery of novel bioactive compounds[27] promoted us to choose 1,*n*-diamines as ambidentate nucleophiles for reaction with various dimethyl 2-(3-acetyl-2-oxo-2*H*-chromen-4-yl)fumarate derivatives.

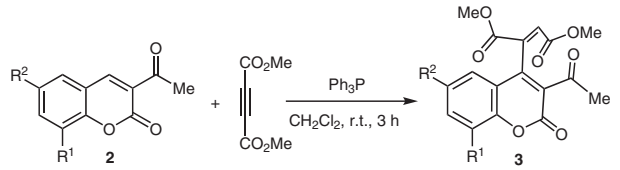
Initially, we explored the preparation of the dimethyl 2-(3-acetyl-2-oxo-2*H*-chromen-4-yl)fumarates **3**. A range of 3-acetylcoumarins were prepared by the reaction of the appropriate salicylaldehydes with ethyl 3-oxobutanoate in EtOH at room temperature in the presence of piperidine. The resulting 3-acetylcoumarins **3** reacted with dimethyl acetylenedicarboxylate in the presence of triphenylphosphine (100 mol%) in dichloromethane at room temperature to afford the desired dimethyl 2-(3-acetyl-2-oxo-2*H*-chromen-4-yl)fumarates **3** in 92–96% yields (Scheme 1).[28]



Scheme 1 Synthesis of dimethyl 2-(3-acetyl-2-oxo-2*H*-chromen-4-yl) fumarates **3**

The use of substoichiometric amounts of triphenylphosphine or the use of solvents other than dichloromethane led to decreased yields. The scope of the reaction was further explored with various 3-acetylcoumarins. All the products were isolated in good to high yields (Table 1).

Table 1 Synthetic Route to Dimethyl 2-(3-Acetyl-2-oxo-2*H*-chromen-4-yl)fumarates **3**



Entry	R^1	R^2	Product	Yield (%)
1	H	H	**3a**	95
2	H	Br	**3b**	92
3	MeO	H	**3c**	96

The structure of **3a** was determined by IR, NMR spectroscopy, and single-crystal X-ray analysis. The mass spectrum of **3a** showed a molecular-ion peak at *m/z* = 330, in agreement with the proposed structure. In the IR spectrum of **3a**, the absorption band at 1720 cm^{-1} was ascribed to the carbonyl stretching frequency. In the ^1H NMR spectrum, four singlets at δ = 7.09, 3.75, 3.55, and 2.55 ppm corresponded to the vinylic hydrogen, two methoxy groups, and the methyl group, respectively. In addition, the four aromatic hydrogen atoms gave rise to characteristic resonances in the aromatic region of the spectrum. Observation of 17 distinct signals in the ^1H-decoupled ^{13}C NMR spectrum of **3a** was also in agreement with the proposed structure. In the ^{13}C NMR spectrum of **3a**, two methoxy groups and one methyl group appeared at δ = 53.4, 52.3, and 30.9 ppm, respectively. Signals at 198.1, 164.2, and 163.8 ppm were attributed to the ketone carbonyl and two ester carbons. Final confirmation of the structure of this product was derived by an X-ray analysis (Figure 1).[29]

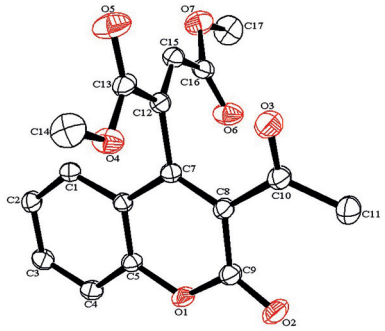
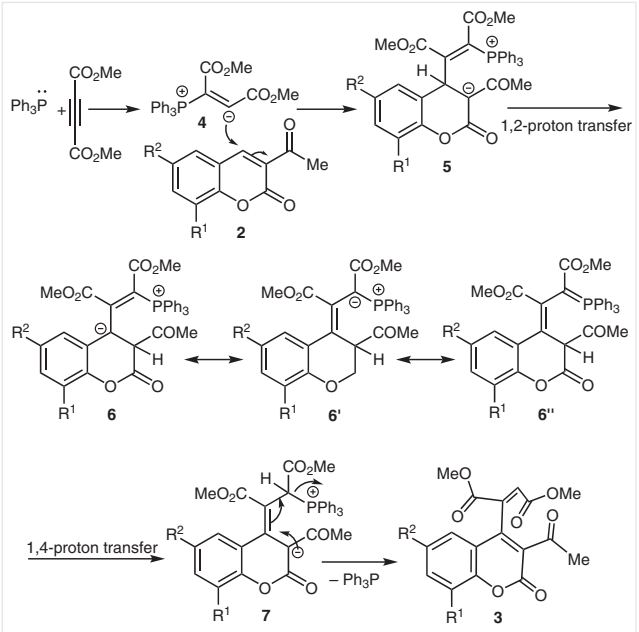


Figure 1 ORTEP diagram for compound **3a**

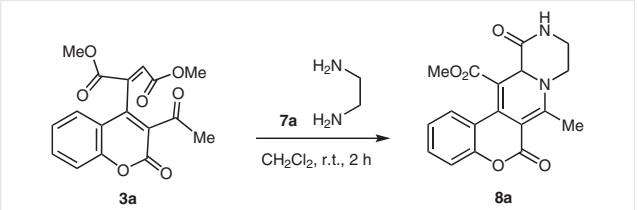
Although no detailed mechanistic studies have been carried out at this stage, a plausible mechanism for this transformation is outlined in Scheme 2. On the basis of the well-known chemistry of trivalent phosphorus nucleophiles,[25–28] it is reasonable to assume that initial addition of triphenylphosphine to the dimethyl acetylenedicarboxylate and subsequent attack of the resulting zwitterion **4** on the double bond of 3-acetylcoumarin **2** yields the intermediate **5**, which is converted into intermediates **6** by a 1,2-proton transfers. Subsequently, a 1,4-proton transfer converts **6′** into intermediate **7**, which gives rise to product **3** by the elimination of triphenylphosphine. Computational experiments showed that, unlike a 1,2-hydride shift, a direct intramolecular 1,2-proton transfer is impossible because it requires a high activation energy.[30] Computational studies and isotopic labelling have shown that 1,4- and 1,2-proton transfers require an external proton source and that these proton shifts should be corrected to a water-catalyzed 1,4- or 1,2-proton transfers.[31]



Scheme 2 Proposed mechanism for the first step of the reaction

In continuation, we were interested in synthesizing the polycyclic nitrogen heterocycle **8a** from **3a** and ethane-1,2-diamine (**7a**), as shown in Scheme 3.

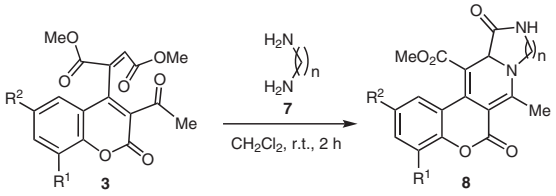
A solution of 3-acetylcoumarin (**2a**) and triphenylphosphine in anhydrous dichloromethane reacted with dimethyl acetylenedicarboxylate to give dimethyl 2-(3-acetyl-2-oxo-2*H*-chromen-4-yl)fumarate (**3a**). A solution of ethane-1,2-diamine (**7a**; 1 mmol) was added to give the desired methyl 7-methyl-6,12-dioxo-10,11,12,12*a*-tetrahydro-6*H*,9*H*-chromeno[4′,3′:4,5]pyrido[1,2-*a*]pyrazine-13-carboxylate (**8a**).[32]



Scheme 3 Approach to the synthesis of methyl 7-methyl-6,12-dioxo-10,11,12,12*a*-tetrahydro-6*H*,9*H*-chromeno[4′,3′:4,5]pyrido[1,2-*a*]pyrazine-13-carboxylate (**8a**)

We then probed the scope of this annulation with various substituted dimethyl 2-(3-acetyl-2-oxo-2*H*-chromen-4-yl)fumarates **3** and 1,*n*-diamines **7** which gave a range of chromeno[4′,3′:4,5]pyrido[1,2-*a*]pyrazine-13-carboxylates or -diazepine-14-carboxylates **8** in good to excellent yields (Table 2).

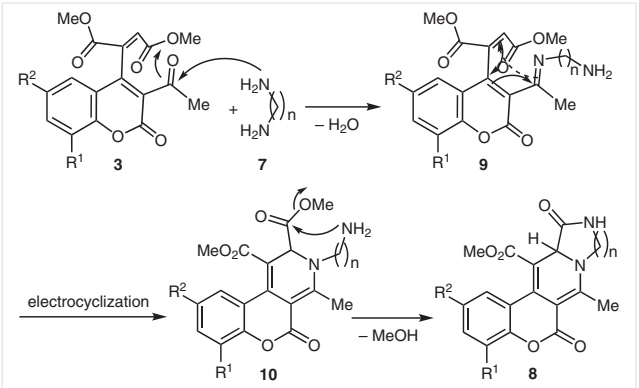
Table 2 Synthesis of Chromeno[4′,3′:4,5]pyrido[1,2-*a*]pyrazine-13-carboxylates or -diazepine-14-carboxylates **8**



Entry	R^1	R^2	Diamine **7**	Product	Yield (%)
1	H	H	$H_2N(CH_2)_2NH_2$	**8a**	63
2	H	H	$H_2N(CH_2)_3NH_2$	**8b**	65
3	H	H	$Me_2C(CH_2NH_2)_2$	**8c**	65
4	H	Br	$H_2N(CH_2)_2NH_2$	**8d**	60
5	H	Br	$Me_2C(CH_2NH_2)_2$	**8e**	70
6	OMe	H	$H_2N(CH_2)_2NH_2$	**8f**	80
7	OMe	H	$Me_2C(CH_2NH_2)_2$	**3g**	80

The structures of products **8a–g** were deduced from their IR, ^{1}H NMR, ^{13}C NMR, and mass spectra. The mass spectrum of **8a** displayed a molecular-ion peak at *m*/*z* = 340. In the IR spectrum of **8a**, absorption bands at 3425, 1685, and 1620 cm^{-1} were attributed to the NH, CO_2Me, and NHC=O stretching frequencies, respectively. In the ^{1}H NMR spectrum of **8a**, four singlets at δ = 2.56, 3.61, 5.06, and 8.16 ppm were assigned to the Me, OMe, CH, and NH groups, respectively. The CH_2NH and CH_2N groups appeared as multiplets at δ = 3.36–3.40, 3.70–3.74, and 4.23–4.27 ppm. Finally, the observation of 18 distinct signals in the ^{1}H-decoupled ^{13}C NMR spectrum of **8a** was in agreement with the proposed structure.

Based on these results, a plausible mechanism for the formation of **8** is proposed in Scheme 4. Formation of imine **9** occurs through condensation of amine **7** with the acyl group of intermediate **3**. Imine **9** then undergoes a 6π electrocyclization to produce chromenopyridine **10**. Finally, product **8** is produced through N-cyclization of chromenopyridine **10** through attack on the C=O double bond and loss of methanol.



Scheme 4 Proposed mechanism for the second step of the reaction

In conclusion, we have synthesized novel chromeno[4′,3′:4,5]pyrido[1,2-*a*]pyrazine-13-carboxylates and -diazepine-14-carboxylates by the reaction of substituted dimethyl 2-(3-acetyl-2-oxo-2*H*-chromen-4-yl)fumarates with 1,*n*-diamines. Substrates for these transformations are readily accessible by a sequential three-component reaction of 3-acetylcoumarin, dimethyl acetylenedicarboxylate, and triphenylphosphine.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591550.

References and Notes

(1) Brack, W.; Schirmer, K. *Environ. Sci. Technol.* **2003**, *37*, 3062.
(2) Parikh, P. K.; Marvaniya, H. M.; Sen, D. J. *Int. J. Drug Dev. Res.* **2011**, *3*, 44.
(3) Saini, M. S.; Kumar, A.; Dwivedi, J.; Singh, R. *Int. J. Pharm. Sci. Res.* **2013**, *4 (3)*, 66.
(4) Goyal, A.; Jain, S. *Chem. Sin.* **2012**, *3*, 249.
(5) Koduru, B.; Shinde, A.; Jaya, P.; Kumar, P.; Rajavel, R.; Sivakumar, T. *Asian J. Pharm. Technol.* **2012**, *2*, 47.
(6) Kumar, A.; Rout, S.; Sahoo, D.; Kumar, R. *Int. J. Res. Dev. Pharm. Life Sci.* **2013**, *2*, 349.
(7) Abbas, A.; Naseer, M. *Acta Chim. Slov.* **2014**, *61*, 792.
(8) Kirkham, J. D.; Edeson, S. J.; Stokes, S.; Harrity, J. P. A. *Org. Lett.* **2012**, *14*, 5354.
(9) Kumbar, M. N.; Kamble, R. R.; Kamble, A. K.; Salian, S. R.; Kumari, S.; Nair, R.; Kalthur, G.; Kumar, S. A.; Prasad, D. J. *Int. J. Med. Chem.* **2016**, 9890630; DOI: 0.1155/2016/9890630.

(10) Chaudhary, J.; Patel, K.; Patel, C. N. *Int. J. Univers. Pharm. Bio Sci.* **2014**, *3*, 128.
(11) Sheehan, J. C. *Chem. Eng. News* **1959**, *37*, 43.
(12) Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc.* **1962**, *84*, 2983.
(13) Mortazavi, Z. F. A.; Islami, M. R. *Khaleghi M.* **2015**, *17*, 3034.
(14) (a) Arango, V.; Robledo, S.; Séon-Méniel, B.; Figadère, B.; Cardona, W.; Sáez, J.; Otálvaro, F. *J. Nat. Prod.* **2010**, *73*, 1012. (b) Li, G.; Wang, D.; Sun, M.; Li, G.; Hu, J.; Zhang, Y.; Yuan, Y.; Ji, H.; Chen, N.; Liu, G. *J. Med. Chem.* **2010**, *53*, 1741. (c) Leonetti, F.; Favia, A.; Rao, A.; Aliano, R.; Paluszcak, A.; Hartmann, R. W.; Carotti, A. *J. Med. Chem.* **2004**, *47*, 6792. (d) Catto, M.; Nicolotti, O.; Leonetti, F.; Carotti, A.; Favia, A. D.; Soto-Otero, R.; Méndez-Álvarez, E.; Carotti, A. *J. Med. Chem.* **2006**, *49*, 4912. (e) Neyts, J.; De Clercq, E.; Singha, R.; Chang, Y. H.; Das, A. R.; Chakraborty, S. K.; Hong, S. C.; Tsay, S. C.; Hsu, M. H.; Hwu, J. R. *J. Med. Chem.* **2009**, *52*, 1486.
(15) Santana, L.; Uriarte, E.; Dalla Via, L.; Gia, O. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 135.
(16) Guiotto, A.; Chilin, A.; Manzini, P.; Dall'Acqua, F.; Bordin, F.; Rodighiero, P. *Farmaco* **1995**, *50*, 479.
(17) Ploypradith, P.; Mahidol, C.; Sahakitpichan, P.; Wongbundit, S.; Ruchirawat, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 866.
(18) Thaisrivongs, S.; Janakiraman, M. N.; Chong, K.-T.; Tomich, P. K.; Dolack, L. A.; Turner, S. R.; Strohbach, J. W.; Lynn, J. C.; Horng, M.-M.; Hinshaw, R. R.; Watenpaugh, K. D. *J. Med. Chem.* **1996**, *39*, 2400.
(19) Rappa, G.; Shyam, K.; Lorico, A.; Fodstad, O.; Sartorelli, A. C. *Oncol. Res.* **2000**, *12*, 113.
(20) Yang, E.-B.; Zhao, Y.-N.; Zhang, K.; Mack, P. *Biochem. Biophys. Res. Commun.* **1999**, *260*, 682.
(21) Bonsignore, L.; Cottiglia, F.; Lavagna, S. M.; Loy, G.; Secci, D. *Farmaco* **1998**, *53*, 693.
(22) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (b) Riveiro, M. E.; Maes, D.; Vázquez, R.; Vermeulen, M.; Mangelinckx, S.; Jacobs, J.; Debenedetti, S.; Shayo, C.; De Kimpe, N.; Davio, C. *Bioorg. Med. Chem.* **2009**, *17*, 6547. (c) Riveiro, M. E.; De Kimpe, N.; Moglioni, A.; Vázquez, R.; Monczor, F.; Shayo, C.; Davio, C. *Curr. Med. Chem.* **2010**, *17*, 1325.
(23) (a) Darbarwar, M.; Sundaramurthy, V. *Synthesis* **1982**, 337. (b) Bandyopadhyay, C.; Sur, K. R.; Patra, R.; Sen, A. *Tetrahedron* **2000**, *56*, 3583. (c) Mulakayala, N.; Rambabu, D.; Raja, M. R.; Chaitanya, M.; Kumar, C. S.; Kalle, A. M.; Krishna, G. R.; Reddy, C. M.; Rao, M. V. B.; Pal, M. *Bioorg. Med. Chem.* **2012**, *20*, 759. (d) Iaroshenko, V. O.; Erben, F.; Mkrtchyan, S.; Hakobyan, A.; Vilches-Herrera, M.; Dudkin, S.; Bunescu, A.; Villinger, A.; Sosnovskikh, V. Y.; Langer, P. *Tetrahedron* **2011**, *67*, 7946. (e) Iaroshenko, V. O.; Ali, S.; Babar, T. M.; Dudkin, S.; Mkrtchyan, S.; Rama, N. H.; Villinger, A.; Langer, P. *Tetrahedron Lett.* **2011**, *52*, 373.
(24) Jose, A.; Jayakrishnan, A. J.; Vedhanarayanan, B.; Menon, R. S.; Varughese, S.; Suresh, E.; Nair, V. *Chem. Commun.* **2014**, *50*, 4616.
(25) Yavari, I.; Alizadeh, A.; Anary-Abbasinejad, M. *Tetrahedron Lett.* **2003**, *44*, 2877.
(26) Alizadeh, A.; Zohreh, N.; Rostamnia, S. *Tetrahedron* **2007**, *63*, 8083.
(27) (a) James, M. J.; Grant, N. D.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. *Org. Lett.* **2016**, *18*, 6256. (b) Zhang, Z.; Xiao, F.; Huang, B.; Hu, J.; Fu, B.; Zhang, Z. *Org. Lett.* **2016**, *18*, 908.
(28) **Dimethyl 2-(3-Acetyl-2-oxo-2*H*-chromen-4-yl)fumarates 3a–c; General Procedure**

A solution of dimethyl acetylenedicarboxylate (1 mmol) in CH_2Cl_2 (3 mL) was added dropwise over 15 min to a magnetically stirred solution of the appropriate 3-acetylcoumarin (1 mmol) and Ph_3P (1 mmol) in anhyd CH_2Cl_2 (3 mL) at r.t., and the mixture was stirred for 4 h. When the reaction was complete, the solvent was removed and the product was precipitated by adding hexane, collected by filtration, and washed with EtOH.

Dimethyl (2*E*)-2-(3-Acetyl-2-oxo-2*H*-chromen-4-yl)but-2-enedioate (3a)

Cream powder; yield: 0.31 g (95%); mp 111–113 °C. IR (KBr): 1720 (C=O), 1598 and 1533 (Ar) cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ = 2.56 (s, 3 H, CH_3), 3.55 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 7.09 (s, 1 H, CH^3 of butenedioate), 7.23 (t, $^3J_{HH}$ = 8.6 Hz, 1 H, CH^6), 7.33 (d, $^3J_{HH}$ = 7.8 Hz, 1 H, CH^8), 7.35 (d, $^3J_{HH}$ = 7.8 Hz, 1 H, CH^5), 7.57 (t, $^3J_{HH}$ = 7.7 Hz, 1 H, CH^7). ^{13}C NMR (75.46 MHz, $CDCl_3$) δ = 30.9 (CH_3), 52.3 (OCH_3), 53.42 (OCH_3), 117.2 (C^3), 118.4 (CH^8), 123.7 (C^{4a}), 125.1 (CH^6), 126.9 (CH^7), 128.3 (CH^5), 133.8 (C^2 of butenedioate), 141.3 (CH^3 of butenedioate), 152.3 (C^{8a}), 153.7 (C^4), 158.8 (C^2=O), 163.8 (CO_2Me), 164.2 (CO_2Me), 198.1 (C=O). MS (EI, 70 eV): *m/z* (%) = 331 $[M + 1]^+$ (2), 330 $[M]^+$ (1), 288 (14), 287 (71), 272 (46), 271 (100), 257 (16), 243 (15), 229 (11), 227 (12), 213 (12), 197 (23), 113 (18), 59 (17), 43 (30). Anal. Calcd for $C_{17}H_{14}O_7$ (330.07): C, 61.82; H, 4.27. Found: C, 61.79; H, 4.29.

Crystal data for **3a** ($C_{17}H_{14}NO_7$): M_W = 330.28, monoclinic, P21/n, *a* = 13.8388(18) Å, *b* = 8.6354(8) Å, *c* = 14.095(2) Å, β = 113.541(17), *V* = 1544.2(3) $Å^3$, *Z* = 4, D_c = 1.421 mg/m^3, *F* (000) = 688; crystal dimensions, 0.45 × 0.40 × 0.38 mm; radiation, Mo Kα (λ = 0.71073 Å). 2.84 ≤ 2 ≤ 25.09, intensity data were collected at 293(2) K with a Bruker APEX area-detector diffractometer by employing an ω/2θ scanning technique in the range −16 ≤ *h* ≤ 13, −10 ≤ *k* ≤ 8, −16 ≤ *l* ≤ 15. The structure was solved by direct methods; all nonhydrogen atoms were positioned, and anisotropic thermal parameters were refined from 1699 observed reflections with *R* (into) = 0.1124 by a full-matrix least-squares technique, converging to *R* = 0.0754 and R_{aw} = 0.2308 [$I > 2\sigma(I)$].

Dimethyl (2*E*)-2-(3-Acetyl-6-bromo-2-oxo-2*H*-chromen-4-yl)but-2-enedioate (3b)

Cream powder; yield: 0.37 g (92%); mp 135–137 °C. IR (KBr): 1722 (C=O), 1601 and 1530 (Ar) cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ = 2.58 (s, 3 H, CH_3), 3.64 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 7.13 (s, 1 H, CH^3 of butenedioate), 7.30 (d, $^3J_{HH}$ = 8.8 Hz, 1 H, CH^8), 7.50 (d, $^4J_{HH}$ = 2.0 Hz, 1 H, CH^5), 7.78 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 2.1 Hz, 1 H, CH^7). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 30.9 (CH_3), 52.6 (OCH_3), 53.6 (OCH_3), 117.9 (C^3), 119.0 (CH^8), 120.0 (C-Br), 124.5 (C^{4a}), 128.8 (CH^7), 129.0 (CH^5), 136.5 (C^2 of butenedioate), 140.8 (CH^3 of butenedioate), 151.0 (C^{8a}), 152.5 (C^4), 158.2 (C^2=O), 163.6 (CO_2Me), 164.2 (CO_2Me), 197.8 (C=O). Anal. Calcd for $C_{17}H_{13}BrO_7$ (409.19): C, 49.90; H, 3.20. Found: C, 49.87; H, 3.22.

(29) CCDC 1526737 contains the supplementary crystallographic data for compound **3a**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(30) Wang, Y.; Cai, P.-J.; Yu, Z.-X. *J. Org. Chem.* **2017**, *82*, 4604.
(31) (a) Liang, Y.; Liu, S.; Xia, Y.; Li, Y.; Yu, Z.-X. *Chem. Eur. J.* **2008**, *14*, 4361. (b) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470.

(32) **Polycyclic Heterocycles 8a–g; General Procedure**

A solution of the appropriate diester **3** (1 mmol) and 1,*n*-diamine **7** (1 mmol) in CH_2Cl_2 was magnetically stirred at r.t. for 2 h until the reaction was complete (TLC). The mixture was then filtered, and the residue was purified by column chromatography [silica gel (Merck 230–240 mesh), EtOAc].

Methyl 7-Methyl-6,12-dioxo-10,11,12,12a-tetrahydro-6*H*,9*H*-chromeno[4′,3′:4,5]pyrido[1,2-*a*]pyrazine-13-carboxylate (8a)

Yellow powder; yield: 0.214 g (63%); mp 170 °C (dec.). IR (KBr): 3425 (NH), 1686 (C=O), 1620 (NCO), 1527 and 1458 (Ar), 1221 (C–O) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 2.56 (s, 3 H, Me), 3.36–3.40 (m, 2 H, CH_2NH), 3.61 (s, 3 H, OMe), 3.70–3.74 (m, 1 H, CH_2N), 4.23–4.027 (m, 1 H, CH_2N), 5.06 (s, 1 H, CH^{12a}), 7.07 (d, $^3J_{HH}$ = 7.7 Hz, 1 H, CH^4 of chromene), 7.08 (t, $^3J_{HH}$ = 7.1 Hz, 1 H, CH^2 of chromene), 7.23 (t, $^3J_{HH}$ = 7.3 Hz, 1 H, CH^3 of chromene), 7.37 (d, $^3J_{HH}$ = 7.3 Hz, 1 H, CH^1 of chromene), 8.16 (s, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.92 (Me), 43.75 (CH_2–NH), 50.26 (CH_2–N), 56.90 (OMe), 66.10 (CH^{12a}), 98.78 (C^{6a}), 110.51 (C^{13}), 122.04 (C^{13b} of chromene), 123.01 (CH^4 of chromene), 128.42 (CH^2 of chromene), 132.76 (CH^1 of chromene), 136.37 (CH^3 of chromene), 137.20 (C^{13a} of chromene), 157.15 (C^{4a} of chromene), 165.77 (C^7), 169.31 (COOMe), 172.23 (COO), 173.5 (CONH). MS (EI, 70 eV): *m*/*z* (%) = 340 [M^+] (58), 325 (11), 282 (20), 281 (100), 212 (15), 211 (12), 210 (20), 155 (12), 140 (21), 139 (24), 128 (12), 127 (20), 126 (12), 115 (18), 77 (10), 70 (11), 63 (15), 59 (48), 56 (11), 44 (11), 43 (24), 42 (37), 41 (16). Anal. Calcd for $C_{18}H_{16}N_2O_5$ (340.33): C, 63.53; H, 4.74; N, 8.23. Found: C, 63.49; H, 4.75; N, 8.28.

Methyl 7-Methyl-6,13-dioxo-9,10,11,12,13,13a-hexahydro-6*H*-chromeno[4′,3′:4,5]pyrido[1,2-*a*][1,4]diazepine-14-carboxylate (8b)

Yellow powder; yield: 0.230 g (65%); mp 245 °C (dec.). IR (KBr): 3424 and 3351 (NH), 1661 (C=O), 1611 (NCO), 1514 and 1455 (Ar), 1245 and 1099 (C–O) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 1.77–1.93 (m, 2 H, CH_2), 2.55 (s, 3 H, Me), 3.30–3.32 (m, 1 H, CH_2N), 3.59–3.61 (m, 2 H, CH_2NH), 3.60 (s, 3 H, OMe), 4.36–4.38 (m, 1 H, CH_2N), 5.44 (s, 1 H, CH^{13a}), 7.07 (d, $^3J_{HH}$ = 7.7 Hz, 1 H, CH^4 of chromene), 7.08 (t, $^3J_{HH}$ = 7.1 Hz, 1 H, CH^2 of chromene), 7.37 (t, $^3J_{HH}$ = 7.3 Hz, 1 H, CH^3 of chromene), 7.60 (d, $^3J_{HH}$ = 7.3 Hz, 1 H, CH^1 of chromene), 7.70 (s, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 17.08 (Me), 30.59 (CH_2), 41.11 (CH_2NH), 52.07 (OMe), 53.65 (CH_2N), 62.71 (CH^{13a}), 96.93 (C^{6a} of chromene), 106.11 (C^{14}), 117.03 (CH^4 of chromene), 118.75 (C^{14b} of chromene), 123.26 (CH^2 of chromene), 129.81 (CH of chromene[1]), 131.56 (CH^3 of chromene), 136.43 (C^{14a} of chromene), 152.30 (C^{4a} of chromene), 161.17 (C^7), 162.90 (COOMe), 167.32 (COO), 171.93 (CONH). MS (EI, 70 eV): *m*/*z* (%) = 354 [M^+] (3), 167 (11), 149 (53), 104 (13), 83 (15), 81 (10), 76 (10), 71 (26), 70 (24), 69 (28), 67 (12), 57 (93), 56 (20), 55 (57), 43 (100), 42 (18), 41 (92).Anal. Calcd for $C_{19}H_{18}N_2O_5$ (354.36): C, 64.40; H, 5.12; N, 7.91. Found: C, 66.50; H, 4.90; N, 6.92.