Beilstein Journal of Organic Chemistry

Facile synthesis of benzothiadiazine 1,1-dioxides, a precursor of RSV inhibitors, by tandem amidation/ intramolecular aza-Wittig reaction

Krishna C. Majumdar*§ and Sintu Ganai

Full Research Paper

Open Access

Address:
Department of Chemistry, University of Kalyani, Kalyani 741235, W.B India

Email:
Krishna C. Majumdar* - kcm@klyuniv.ac.in

* Corresponding author
§ Tel.: +91-33-2582 8750; Fax: +91-33-2582 8282

Keywords:
benzothiadiazine-3-one 1,1-dioxide; 3-ethoxy-1,2,4-benzothiadiazine 1,1-dioxide; intramolecular aza-Wittig reaction; sultam

Beilstein J. Org. Chem. **2013,** *9,* 503–509.
doi:10.3762/bjoc.9.54

Received: 03 December 2012
Accepted: 07 February 2013
Published: 08 March 2013

Associate Editor: P. R. Hanson

Abstract

Reaction of *o*-azidobenzenesulfonamides with ethyl carbonochloridate afforded the corresponding amide derivatives, which gave 3-ethoxy-1,2,4-benzothiadiazine 1,1-dioxides through an intramolecular aza-Wittig reaction. The reaction was found to be general through the synthesis of a number of benzothiadiazine 1,1-dioxides. Acid-catalyzed hydrolysis of 3-ethoxy-1,2,4-benzothiadiazine 1,1-dioxides furnished the 2-substituted benzothiadiazine-3-one 1,1-dioxides in good yields and high purity, which is the core moiety of RSV inhibitors.

Introduction

Sultams have gained popularity in the scientific community especially among synthetic and medicinal chemists, because this basic moiety is present in many natural products and biologically active substances [1-8]. Especially, benzothiadiazine-3-one 1,1-dioxide and its derivatives possess potential activity, including hypoglycemic [9], anticancer and anti-HIV activity [10-13], and also serve as selective antagonists of CXR_2 [14]. 2-Substituted-2*H*-1,2,4-benzothiadiazine-3(4*H*)one 1,1-dioxides showed varying degrees of sedative and hypotensive activities [15]. A number of benzothiadiazine 1,1-dioxide derivatives have recently been reported that display potent activity [16-22], including hypoglycemic (**1**), anti-HIV (**2**), HIV-1 specific non-nucleoside reverse transcriptase inhibitor (**3**), sedative (**4**), and respiratory syncytial virus (RSV) inhibitory activity (**5**; Figure 1).

A literature search revealed that the 1,2,4-benzothiadiazine 1,1-dioxides are generally synthesized either by condensation of *o*-aminobenzenesulfonamides with urea at elevated temperature [23] or by the reaction of *o*-aminobenzenesulfonamide with isocyanates in DMF under reflux [24]. Although various approaches to the preparation of 1,2,4-benzothiadiazine 1,1-dioxide derivatives have been reported [25-32], the development of a simpler method for the synthesis of the 1,2,4-benzo-

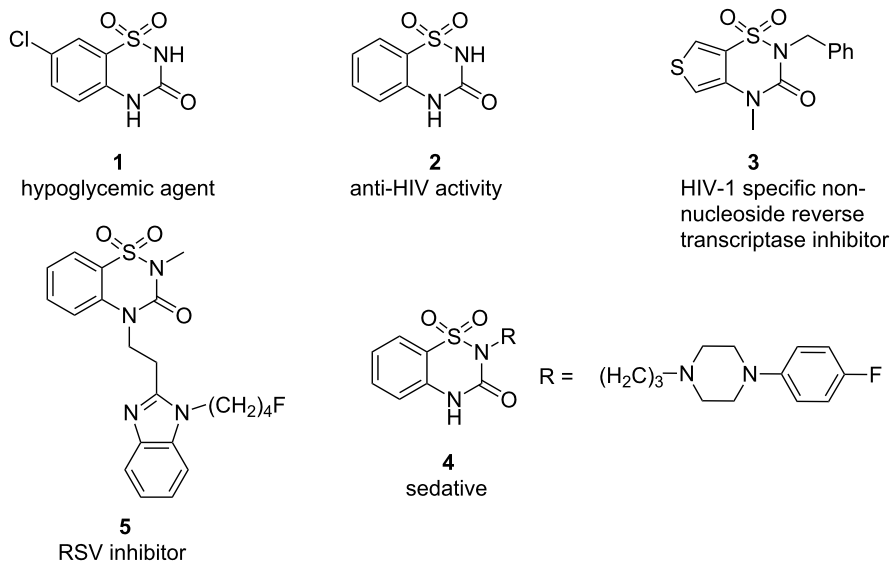


Figure 1: Biologically active 1,2,4-benzothiadiazine 1,1-dioxide derivatives.

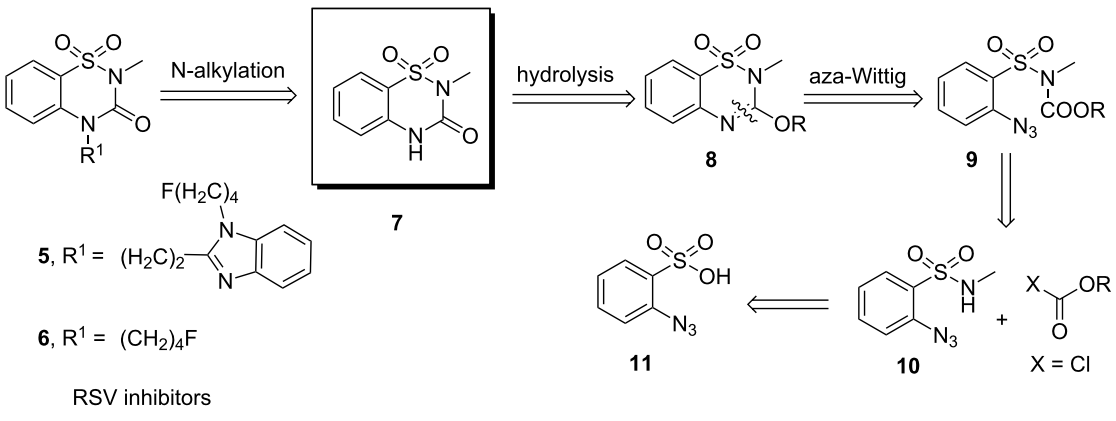
thiadiazine 1,1-dioxide moiety is still desirable because of their biological significance.

The aza-Wittig reaction is employed for the construction of C=N, N=N and S=N double bonds in various heterocycles and heterocycle-containing natural products [33-43]. Recently, we have synthesized asymmetrically substituted piperazine-2,5-dione derivatives using the intramolecular aza-Wittig reaction [44]. In continuation of our earlier work [45-51], we have undertaken a study to synthesize 1,2,4-benzothiadiazine 1,1-dioxide derivatives using an intramolecular aza-Wittig reaction as the key step. Herein we report our results.

Retrosynthetic analysis of the RSV inhibitors **5** and **6** relied on benzothiadiazine-3-one 1,1-dioxide **7**, which can easily be obtained by simple hydrolysis of the benzothiadiazine 1,1-dioxide derivative **8**. Construction of this six-membered sultam **8** was thought to be achieved by intramolecular aza-Wittig reaction of the *o*-azido derivative **9**. The following retrosynthetic analysis led us to the starting material *o*-azidobenzenesulfonic acid (**11**) for the synthesis of the intermediate **10** necessary for the synthesis of RSV inhibitors (Scheme 1).

Results and Discussion

Sulfonic acid **11** bearing an *o*-azido group [30] was converted into the corresponding sulfonyl chloride by treatment with oxalyl chloride followed by the reaction with appropriate amines to give the requisite 2-azido-*N*-substituted benzenesulfonamides **10a–i**. The sulfonamide **10b** was reacted with ethyl carbonochloridate to afford the corresponding amide derivative

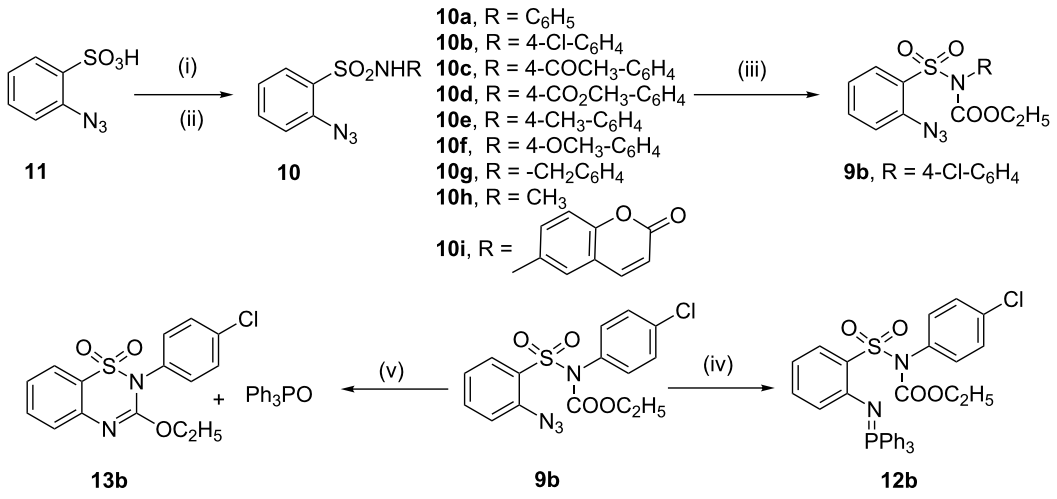


Scheme 1: Retrosynthesis analysis of RSV inhibitors.

9b required for our study. Initially, we turned our attention to the synthesis of a benzothiadiazine 1,1-dioxide derivative using substrate **9b** by intramolecular aza-Wittig reaction. To test this premise, **9b** was treated with triphenylphosphine in THF at room temperature, but no desired product was obtained, and only the intermediate iminophosphorane **12b** was isolated, even under reflux (Scheme 2).

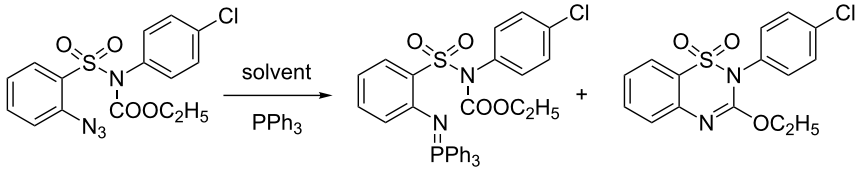
We next conducted a series of reactions with the replacement of the solvent THF by other solvents, such as toluene, CH_2Cl_2, and CH_3CN, but none of them afforded any cyclized product (Table 1, entries 2–4,). Then the reaction conditions were modified through the use of a higher-boiling-point solvent, i.e., *o*-dichlorobenzene (DCB). The reaction was successful at higher temperature, affording the desired cyclized product **13b** (54%) along with the by-product triphenylphosphine oxide (Table 1, entry 5).

Subsequently, we turned our attention to develop a simpler one-step procedure by heating the sulfonamide **10b** with ethyl carbonochloridate, Et_3N and PPh_3 in DCB at 135 °C for 6 h, which gave the cyclized product **13b** in 78% yield (Table 2, entry 1). The base Et_3N was then replaced by Cs_2CO_3 or K_2CO_3, but no better result was obtained (Table 2, entries 2 and 3). Only DIPEA gave 69% yield of the product (Table 2, entry 4). However, surprisingly the use of xylene as the solvent improved the yield of the cyclized product (Table 2, entry 5). The replacement of NEt_3 by DIPEA as the base also gave a similar



Scheme 2: Preparation of 3-ethoxy-1,2,4-benzothiadiazine 1,1-dioxide. Reagent and conditions: (i) $(COCl)_2$, DMF, CH_2Cl_2, reflux, 3 h; (ii) RNH_2, NaOAc, MeOH + water, 60 °C; (iii) $ClCO_2C_2H_5$, acetone, Et_3N, rt, 5 h; (iv) PPh_3, THF, reflux, 10 h; (v) PPh_3, DCB, 135 °C, 8 h.

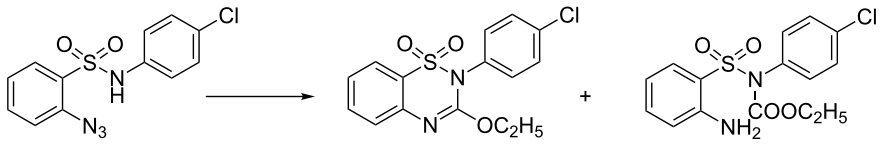
Table 1: Summary of the intramolecular aza-Wittig reactions.[a]



Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1[c]	THF	reflux	6	0
2[c]	toluene	120 °C	8	0
3[c]	CH_2Cl_2	reflux	8	0
4[c]	CH_3CN	reflux	6	0
5	DCB	135 °C	8	54

[a]All the reactions were carried out with 1 equiv **9b** and 1.5 equiv PPh_3; [b]isolated yields of **13b**; [c]only **12b** was separated.

Table 2: Summary of the intramolecular aza-Wittig reactions in a one-pot fashion.[a]



10b **13b** **14b**

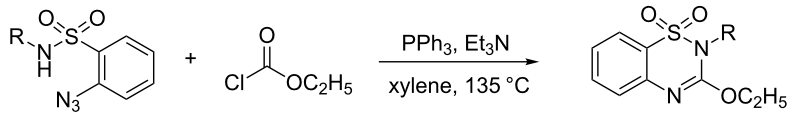
Entry	Solvent	Base	Temp (°C)	Time (h)	Yield (%)[b]
1	DCB	Et_3N	135 °C	6	78
2	DCB	K_2CO_3	135 °C	8	<30
3	DCB	Cs_2CO_3	135 °C	8	46
4	DCB	DIPEA	135 °C	6	69
5	**xylene**	**Et_3N**	**135 °C**	**6**	**94**
6	xylene	DIPEA	135 °C	6	92
7[c]	xylene	Et_3N	150 °C	6	5
8	xylene	–	135 °C	10	0

[a]All the reactions were carried out with 1 equiv **10b**, 1.5 equiv $ClCO_2Et$, 2 equiv base, and 1.5 equiv PPh_3; [b]isolated yields of **13b**; [c]a smaller amount of **13b** was isolated than the major product **14b**.

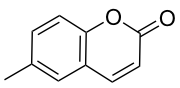
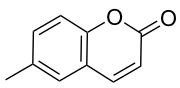
yield of the product (Table 2, entry 6). The decomposition of the iminophosphorane intermediate into the corresponding amine derivative **14b** was found to occur at higher temperature (150 °C) producing a low yield of the cyclized product (Table 2, entry 7). The reaction did not occur at all in the absence of a base (Table 2, entry 8). The observations are summarized in Table 2.

It is notable that xylene appears to be a suitable solvent for this reaction. We then carried out the reactions with a variety of substrates **10a–i** under the optimized conditions (ethyl carbonochloridate, PPh_3, Et_3N, xylene at 135 °C) in order to generalize the method, and the results are summarized in Table 3. The reactions of all the substrates having electron-deficient R-substituents at the 2-position proceeded smoothly,

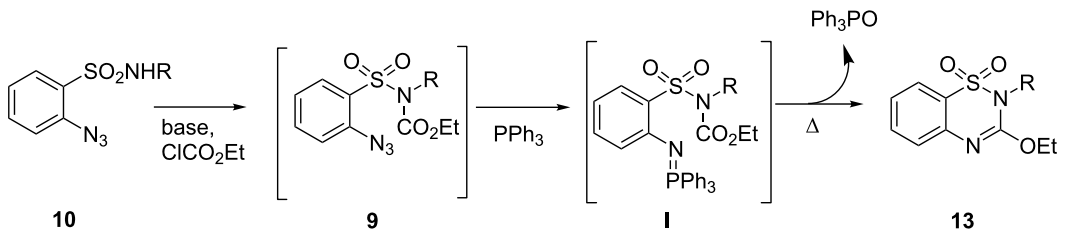
Table 3: Generalization of intramolecular aza-Wittig reaction.[a]



10 **13**

Entry	*o*-azidosulfonamide	Time (h)	Product	Yield (%)[b]
1	**10a**, R = C_6H_5	8	**13a**, R = C_6H_5	90
2	**10b**, R = 4-Cl-C_6H_4	6	**13b**, R = 4-Cl-C_6H_4	94
3	**10c**, R = 4-$COCH_3$-C_6H_4	6	**13c**, R = 4-$COCH_3$-C_6H_4	92
4	**10d**, R = 4-CO_2CH_3-C_6H_4	6	**13d**, R = 4-CO_2CH_3-C_6H_4	95
5	**10e**, R = 4-CH_3-C_6H_4	7	**13e**, R = 4-CH_3-C_6H_4	80
6	**10f**, R = 4-OCH_3-C_6H_4	7	**13f**, R = 4-OCH_3-C_6H_4	83
7	**10g**, R = -$CH_2C_6H_5$	7	**13g**, R = -$CH_2C_6H_5$	87
8	**10h**, R = CH_3	7	**13h**, R = CH_3	79
9	**10i**, R = 	6	**13i**, R = 	89

[a]Reaction conditions: Compound **10** (1 mmol), $ClCO_2C_2H_5$ (1.5 mmol), Et_3N (2 mmol) and PPh_3 (1.5 mmol) were heated at 135 °C in xylene; [b]isolated yields of compound **13**.

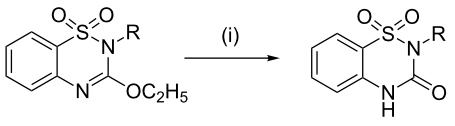


Scheme 3: Rationalization of the formation of compound **13**.

providing excellent yields, whereas the substrates having electron-donating R-substituents gave lower yields.

The proposed mechanism for the formation of the products **13** may involve amidation of SO_2NH_2 by the reaction of nucleophilic sulfonamide **10** with ethyl carbonochloridate in the presence of Et_3N to form the intermediates **9**, which may then undergo intramolecular aza-Wittig reaction via the formation of iminophosphorane intermediate **I**. We isolated iminophosphorane intermediate **12b** from the reaction with **10b** at room temperature. In the presence of heat the iminophosphorane intermediate **I** leads to the formation of the product 3-ethoxy-1,2,4-benzothiadiazine 1,1-dioxide **13** (Scheme 3). However, in all other cases we did not carry out the reactions at room temperature for isolation of the intermediates.

We have also demonstrated the conversion of the products **13** to the 2-substituted benzothiadiazine-3-one 1,1-dioxide **15** by hydrolysing **13** with ethanolic HCl. The benzothiadiazine-3-one 1,1-dioxide derivatives **15c,e,h** were obtained in excellent yields from the compounds **13c,e,h** (Scheme 4). These 2-substituted benzothiadiazine-3-one 1,1-dioxides may further be alkylated at the 4-position with suitable halides to yield the RSV inhibitors **5** and **6** by using the reported [13] procedure.



13c, R = 4-$COCH_3$-C_6H_4
13e, R = 4-CH_3-C_6H_4
13h, R = CH_3

15c, R = 4-$COCH_3$-C_6H_4, Yield: 94%
15e, R = 4-CH_3-C_6H_4, Yield: 96%
15h, R = CH_3, Yield: 97%

Scheme 4: Preparation of benzothiadiazine-3-one 1,1-dioxide derivatives by acid-catalyzed hydrolysis; reagents and conditions: 50 mg of compound **13**, 1 mL HCl, 4 mL ethanol, 80 °C, 4 h.

Previously, Jung and Khazi [52] reported the synthesis of the benzothiadiazine 1,1-dioxide moiety from the reaction of *o*-aminobenzenesulfonamide with the costlier triphosgene, whereas in our case the synthesis of benzothiadiazine 1,1-dioxide derivatives was achieved from *o*-azidobenzenesulfonamides and required cheaper ethyl carbonochloridate as the reagent.

Conclusion

In conclusion, we have developed a simple and efficient method for the synthesis of 3-ethoxybenzothiadiazine 1,1-dioxide and benzothiadiazine-3-one 1,1-dioxide derivatives starting from an easy precursor, by the application of an intramolecular aza-Wittig reaction. The reaction procedure is very simple and gives good to excellent yields of the products. This benzothiadiazine-3-one 1,1-dioxide can further be alkylated at the 4-position, following a literature procedure, to give the bioactive RSV inhibitors.

Supporting Information

Supporting Information File 1

Experimental part.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-54-S1.pdf]

Acknowledgements

We thank CSIR (New Delhi) and DST (New Delhi) for financial assistance. S.G. is grateful to CSIR (New Delhi) for his research fellowships, and K.C.M. is thankful to UGC (New Delhi) for a UGC Emeritus fellowship. We also thank DST (New Delhi) for providing the Bruker NMR (400 MHz), the Perkin-Elmer CHN Analyser, and the FTIR and UV–vis spectrometers.

References

1. Majumdar, K. C.; Mondal, S. *Chem. Rev.* **2011,** *111,* 7749–7773. doi:10.1021/cr1003776
2. Bernotas, R. C.; Dooley, R. J. *Tetrahedron* **2010,** *66,* 2273–2276. doi:10.1016/j.tet.2010.01.092
3. Zhou, A.; Rayabarapu, D.; Hanson, P. R. *Org. Lett.* **2009,** *11,* 531–534. doi:10.1021/ol802467f
4. Jiménez-Hopkins, M.; Hanson, P. R. *Org. Lett.* **2008,** *10,* 2223–2226. doi:10.1021/ol800649n

5. Supuran, C. T.; Casini, A.; Scozzafava, A. *Med. Res. Rev.* **2003,** *23,* 535–558. doi:10.1002/med.10047
6. Hanessian, S.; Sailes, H.; Therrien, E. *Tetrahedron* **2003,** *59,* 7047–7056. doi:10.1016/S0040-4020(03)00919-0
7. Dauban, P.; Dodd, R. H. *Tetrahedron Lett.* **2001,** *42,* 1037–1040. doi:10.1016/S0040-4039(00)02214-0
8. Drews, J. *Science* **2000,** *287,* 1960–1964. doi:10.1126/science.287.5460.1960
9. Wales, J. K.; Krees, S. V.; Grant, A. M.; Vikroa, J. K.; Wolff, F. W. *J. Pharmacol. Exp. Ther.* **1968,** *164,* 421–432.
10. Scozzofava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Med. Chem.* **2003,** *10,* 925–953. doi:10.2174/0929867033457647
11. Casini, A.; Scozzafava, A.; Mastrolorenco, A.; Supuran, C. T. *Curr. Cancer Drug Targets* **2002,** *2,* 55–75. doi:10.2174/1568009023334060
12. Scozzafava, A.; Casini, A.; Supuran, C. T. *Curr. Med. Chem.* **2002,** *9,* 1167–1185. doi:10.2174/0929867023370077
13. Arranz, E. M.; Díaz, J. A.; Ingate, S. T.; Witvrouw, M.; Pannecouque, C.; Balzarini, J.; De Clercq, E.; Vega, S. *Bioorg. Med. Chem.* **1999,** *7,* 2811–2822. doi:10.1016/S0968-0896(99)00221-7
14. Wang, Y.; Busch-Petersen, J.; Wang, F.; Ma, L.; Fu, W.; Kerns, J. K.; Jin, J.; Palovich, M. R.; Shen, J.-K.; Burman, M.; Foley, J. J.; Schmidt, D. B.; Hunsberger, G. E.; Sarau, H. M.; Widdowson, K. L. *Bioorg. Med. Chem. Lett.* **2007,** *17,* 3864–3867. doi:10.1016/j.bmcl.2007.05.011
15. Hayao, S.; Stryker, W.; Phillips, B.; Fujimori, H.; Vidrio, H. *J. Med. Chem.* **1968,** *11,* 1246–1248. doi:10.1021/jm00312a601
16. Khelili, S.; Kihal, N.; Yekhlef, M.; de Tullio, P.; Lebrun, P.; Pirotte, B. *Eur. J. Med. Chem.* **2012,** *54,* 873–878. doi:10.1016/j.ejmech.2012.05.011
17. de Tullio, P.; Servais, A.-C.; Fillet, M.; Gillotin, F.; Somers, F.; Chiap, P.; Lebrun, P.; Pirotte, B. *J. Med. Chem.* **2011,** *54,* 8353–8361. doi:10.1021/jm200786z
18. Francotte, P.; Goffin, E.; Fraikin, P.; Lestage, P.; van Heugen, J.-C.; Gillotin, F.; Danober, L.; Thomas, J.-Y.; Chiap, P.; Caignard, D.-H.; Pirotte, B.; de Tullio, P. *J. Med. Chem.* **2010,** *53,* 1700–1711. doi:10.1021/jm901495t
19. Pirotte, B.; de Tullio, P.; Nguyen, Q.-A.; Somers, F.; Fraikin, P.; Florence, X.; Wahl, P.; Hansen, J. B.; Lebrun, P. *J. Med. Chem.* **2010,** *53,* 147–154. doi:10.1021/jm9010093
20. Francotte, P.; de Tullio, P.; Goffin, E.; Dintilhac, G.; Graindorge, E.; Fraikin, P.; Lestage, P.; Danober, L.; Thomas, J.-Y.; Caignard, D.-H.; Pirotte, B. *J. Med. Chem.* **2007,** *50,* 3153–3157. doi:10.1021/jm070120i
21. Combrink, K. D.; Gulgeze, H. B.; Thuring, J. W.; Yu, K.-L.; Civiello, R. L.; Zhang, Y.; Pearce, B. C.; Yin, Z.; Langley, D. R.; Kadow, K. F.; Cianci, C. W.; Li, Z.; Clarke, J.; Genovesi, E. V.; Medina, I.; Lamb, L.; Yang, Z.; Zadjura, L.; Krystal, M.; Meanwell, N. A. *Bioorg. Med. Chem. Lett.* **2007,** *17,* 4784–4790. doi:10.1016/j.bmcl.2007.06.065
22. Boverie, S.; Antoine, M.-H.; Somers, F.; Becker, B.; Sebille, S.; Ouedraogo, R.; Counerotte, S.; Pirotte, B.; Lebrun, P.; de Tullio, P. *J. Med. Chem.* **2005,** *48,* 3492–3503. doi:10.1021/jm0311339
23. Girard, Y.; Atkinson, J. G.; Rokach, J. *J. Chem. Soc., Perkin Trans. 1* **1979,** 1043–1047. doi:10.1039/P19790001043
24. Chern, J.-W.; Ho, C.-P.; Wu, Y.-H.; Rong, J.-G.; Liu, K.-C.; Cheng, M.-C.; Wang, Y. *J. Heterocycl. Chem.* **1990,** *27,* 1909–1915. doi:10.1002/jhet.5570270712
25. Cherepakha, A.; Kovtunenko, V. O.; Tolmachev, A.; Lukin, O. *Tetrahedron* **2011,** *67,* 6233–6239. doi:10.1016/j.tet.2011.06.063
26. Hirota, S.; Sakai, T.; Kitamura, N.; Kubokawa, K.; Kutsumura, N.; Otani, T.; Saito, T. *Tetrahedron* **2010,** *66,* 653–662. doi:10.1016/j.tet.2009.11.064
27. Yang, D.; Liu, H.; Yang, H.; Fu, H.; Hu, L.; Jiang, Y.; Zhao, Y. *Adv. Synth. Catal.* **2009,** *351,* 1999–2004. doi:10.1002/adsc.200900101
28. Rolfe, A.; Hanson, P. R. *Tetrahedron Lett.* **2009,** *50,* 6935–6937. doi:10.1016/j.tetlet.2009.09.090
29. Hirota, S.; Kato, R.; Suzuki, M.; Soneta, Y.; Otani, T.; Saito, T. *Eur. J. Org. Chem.* **2008,** 2075–2083. doi:10.1002/ejoc.200701131
30. Blackburn, C.; Achab, A.; Elder, A.; Ghosh, S.; Guo, J.; Harriman, G.; Jones, M. *J. Org. Chem.* **2005,** *70,* 10206–10209. doi:10.1021/jo051843h
31. Su, W.; Cai, H.; Yang, B. *J. Chem. Res.* **2004,** 87–88. doi:10.3184/030823404323000936
32. Makino, S.; Nakanishi, E.; Tsuji, T. *J. Comb. Chem.* **2003,** *5,* 73–78. doi:10.1021/cc020056k
33. Xie, H.; Yuan, D.; Ding, M.-W. *J. Org. Chem.* **2012,** *77,* 2954–2958. doi:10.1021/jo202588j
34. Zhong, Y.; Wang, L.; Ding, M.-W. *Tetrahedron* **2011,** *67,* 3714–3723. doi:10.1016/j.tet.2011.03.056
35. Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. *Tetrahedron* **2007,** *63,* 523–575. doi:10.1016/j.tet.2006.09.048
36. Cossío, F. P.; Alonso, C.; Lecea, B.; Ayerbe, M.; Rubiales, G.; Palacios, F. *J. Org. Chem.* **2006,** *71,* 2839–2847. doi:10.1021/jo0525884
37. Palacios, F.; Aparicio, D.; Rubiales, G.; Alonso, C.; de los Santos, J. M. *Curr. Org. Chem.* **2006,** *10,* 2371–2392. doi:10.2174/138527206778992716
38. Eguchi, S. *Top. Heterocycl. Chem.* **2006,** *6,* 113–156. doi:10.1007/7081_022
39. Cassidy, M. P.; Özdemir, A. D.; Padwa, A. *Org. Lett.* **2005,** *7,* 1339–1342. doi:10.1021/ol0501323
40. Snider, B. B.; Zhon, J. *J. Org. Chem.* **2005,** *70,* 1087–1088. doi:10.1021/jo048131w
41. Gil, C.; Bräse, S. *Chem.–Eur. J.* **2005,** *11,* 2680–2688. doi:10.1002/chem.200401112
42. Alajarín, M.; Sánchez-Andrada, P.; Vidal, A.; Tovar, F. *J. Org. Chem.* **2005,** *70,* 1340–1349. doi:10.1021/jo0482716
43. Fresneda, P. M.; Molina, P. *Synlett* **2004,** 1–17. doi:10.1055/s-2003-43338
44. Majumdar, K. C.; Ray, K.; Ganai, S. *Synlett* **2010,** 2122–2124. doi:10.1055/s-0030-1258519
45. Majumdar, K. C.; Ganai, S.; Sinha, B. *Tetrahedron* **2012,** *68,* 7806–7811. doi:10.1016/j.tet.2012.07.040
46. Majumdar, K. C.; Ganai, S.; Nandi, R. K.; Ray, K. *Tetrahedron Lett.* **2012,** *53,* 1553–1557. doi:10.1016/j.tetlet.2012.01.015
47. Majumdar, K. C.; Ganai, S.; Nandi, R. K. *New J. Chem.* **2011,** *35,* 1355–1359. doi:10.1039/c1nj20121b
48. Majumdar, K. C.; Ganai, S.; Chattopadhyay, B.; Ray, K. *Synlett* **2011,** 2369–2373. doi:10.1055/s-0030-1260312
49. Majumdar, K. C.; Ganai, S. *Synlett* **2011,** 1881–1887. doi:10.1055/s-0030-1260975
50. Majumdar, K. C.; Ray, K.; Ganai, S.; Ghosh, T. *Synthesis* **2010,** 858–862. doi:10.1055/s-0029-1218610
51. Majumdar, K. C.; Ray, K.; Ganai, S. *Synthesis* **2010,** 2101–2105. doi:10.1055/s-0029-1218763
52. Khazi, I. A.; Jung, Y.-S. *Lett. Org. Chem.* **2007,** *4,* 423–428. doi:10.2174/157017807781467641