Tetrahedron Letters 54 (2013) 1364–1367

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient synthesis of pyrido-imidazodiazepinediones

Dominique P. Arama, Vincent Lisowski, Eliana Scarlata, Pierre Fulcrand, Ludovic T. Maillard, Jean Martinez, Nicolas Masurier *

Institut des Biomolécules Max-Mousseron (IBMM), UMR 5247, Universités Montpellier I et II, 15 Avenue Charles Flahault, 34093 Montpellier, France

ARTICLE INFO

Article history:
Received 21 November 2012
Accepted 21 December 2012
Available online 4 January 2013

Keywords:
Diazepinones
Friedel–Crafts acylation
Imidazo[1,2-*a*]pyridine
Polyfused heterocycles
Urea derivatives

ABSTRACT

We herein report the synthesis of a series of 12 optically pure 3,4-dihydro-1*H*-pyrido-[1′,2′:1,2]-imidazo[4,5-*d*][1,3]diazepine-2,5-diones, which form a new family of azaheterocycle-fused [1,3]diazepines. The key step of the synthesis consists in a selective C-acylation of 2-amino-imidazo[1,2-*a*]pyridine by various natural amino-acids, followed by an intracarbonylation reaction.

The diazepine scaffold is one of the classical examples of privileged structures, which has proved its effectiveness in a number of pharmaceutical drugs and still continues to attract much interest today in medicinal chemistry.[1,2] Aryldiazepine ring systems achieved popularity first in the 1960s with diazepam as the first orally active benzo[1,4]diazepinone anxiolytic by interaction with GABA receptor. This scaffold was further shown to interact with multiple receptor types with high affinity[3] and has been used in the design of enzyme inhibitors[4–7] and protein–DNA interaction inhibitors.[8] Beyond benzo[1,4]diazepines, [1,4]diazepines fused with various heterocyclic ring systems such as imidazole,[9–14] indole,[15] pyrrole,[16] pyridine,[17] pyrazole,[18,19] thiophene,[20–23] etc. have been investigated.

Among the different classes of diazepines, the [1,3]diazepines have been studied to a minor extent although their representatives (benzo-, thiazolo-, and imidazo-fused) exhibit various biological activities including cytotoxic,[24] anti-HIV,[25] AMP deaminase inhibitor,[26] anti-HCV,[27] lymphocyte-specific kinase (Lck) inhibitors.[28] The [1,3]diazepin-2-one scaffold can also be found in natural products[29] or in synthetic compounds with pharmacological activities, like calcitonin gene-related peptide (CGRP) receptor antagonists,[30] dopamine D2 partial agonists,[31] or HIV protease inhibitors[32] (Fig. 1). Therefore, development of new fused [1,3]diazepin-2-one scaffolds, incorporating an urea moiety in the diazepine core could be of interest to access new bioactive compounds.

We recently reported the synthesis of an original series of optically pure imidazopyrido[1,3]diazepin-5-ones.[33] The key step of the synthesis is a Friedel–Crafts acylation at the C-3 position of the easily accessible 2-amino-imidazo[1,2-*a*]pyridine.[34,35] In continuation of this study, we describe herein the synthesis of imidazo[1,2-*a*]pyridine-based [1,3]diazepin-2,5-diones (target compounds **1**, Fig. 1).

The synthesis of target compounds **1** was envisioned from 2-amino-imidazo[1,2-*a*]pyridine **3,** according to the strategy depicted in Scheme 1. Imidazo[1,2-*a*]pyridine (IP), an aza analog of

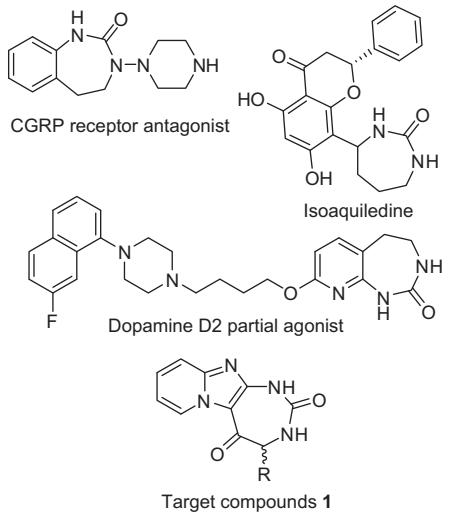
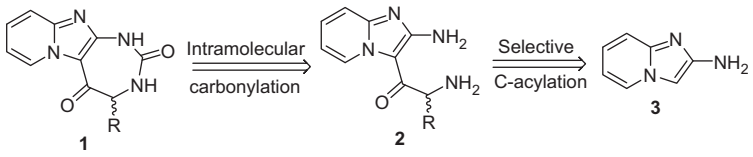


Figure 1. Representative examples of [1,3]diazepin-2-ones.

* Corresponding author. Tel.: +33 4 11 75 96 42; fax: +33 4 11 75 96 41.
E-mail address: nicolas.masurier@univ-montp1.fr (N. Masurier).

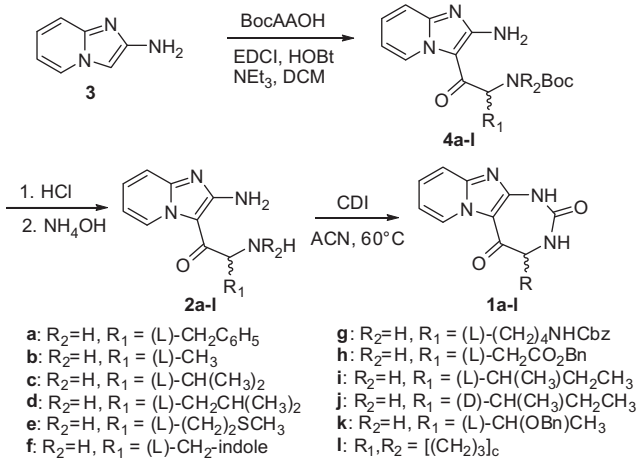
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.12.087



Scheme 1. Retrosynthetic approach for the synthesis of target compounds **1**.

indole, is known to be an electron-rich aromatic ring with particular reactivity at C-3 position for aromatic substitution.[36,37] This C-3 position can be easily acylated (vs amine acylation) by a selective Friedel–Crafts acylation, by simple carboxylic acid activation of amino acid derivatives, leading to diamines **2**.[33] Subsequent intracarbonylation of appropriate diamines **2** could lead to urea derivatives **1**.

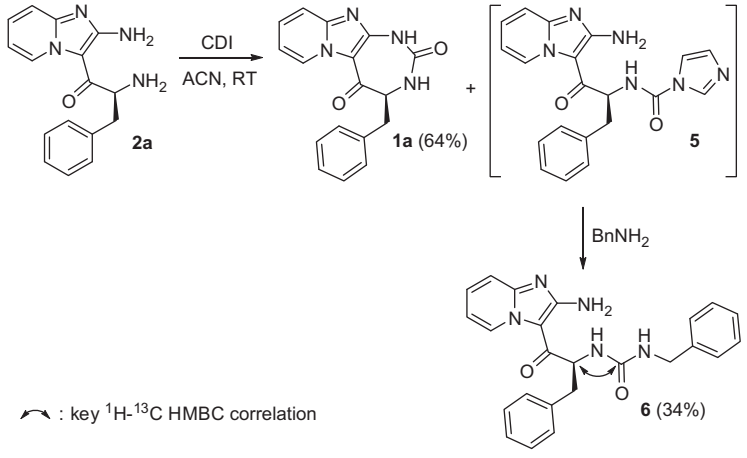
2-Amino-IP **3** was synthesized according to our previously described procedure.[33] Intermediate **3** was selectively acylated at C-3 position using a set of *N*-Boc-protected amino acids (Scheme 2). Natural amino acids bearing alkyl (Ala, Val, Ile), aromatic (Phe, Trp), sulfur-containing (Met), alcohol-containing (Thr), acid-containing (Asp), base-containing (Lys) side chains, and the cyclic amino acid (Pro) were examined. Activation of the N-protected amino acid was performed using EDCI/HOBT in DCM at room temperature. Reactions were monitored by TLC on alumina oxide with DCM/EtOH (99:1 v/v) as eluent and by HPLC. Each crude **4** was purified by chromatography on neutral alumina oxide.[38] For all used amino-acids, C-3 addition compounds **4a–l** were obtained in good to high yields (64–97%). N-addition side-products were only detected as traces by LC–MS in accordance with previous results.[33] After Boc removal by HCl treatment, the resulting hydrochloride salt was neutralized with aqueous ammonia and the solution was extracted with chloroform. 2-Amino-3-acyl-imidazo[1,2-*a*]pyridines **2a–l** were isolated without further purification.



Scheme 2. Synthesis of 3,4-dihydro-1*H*-pyrido[1′,2′:1,2]imidazo-[4,5-*d*][1,3]diazepine-2,5-diones **1a–l**.

To study the experimental conditions of [1,3]diazepin-2,5-diones **1** formation, diamine derivative **2a** was first reacted with 1,1′-carbonyldiimidazole (CDI) in acetonitrile at room temperature (Scheme 3). Compound **1a** was isolated in 64% yield, but the LC–MS analysis of the crude revealed the presence of another compound, which was assumed to be the reaction intermediate **5** (Scheme 3). The electrospray mass spectrum showed a molecular ion at *m*/*z* 375 corresponding to the addition of one imidazocarbonyl moiety on compound **2a**. However, attempts to isolate this intermediate failed. In order to identify the site of carbonylation, compound **2a** was reacted with CDI in acetonitrile. After 2 h, 1 equiv of benzylamine was added, to trap intermediate **5**. Compound **6** was isolated in 34% yield after purification by chromatography on neutral alumina oxide (Scheme 3). The ^{1}H–^{13}C HMBC analysis of **6** showed a correlation between the CH_{α} of the phenylalanine residue (5.20 ppm) and the urea carbonyl signal (158.9 ppm), which unambiguously proved the N-activation position. This result confirmed that the aromatic amine in position 2 of the IP nucleus still remained moderately reactive, as it was already observed for the Friedel–Crafts acylation reaction.

To optimize the cyclization reaction, compound **2a** was reacted with CDI at 60 °C for 2 h and compound **1a** was isolated in good yield (78%). Under these conditions, no trace of compound **5** was detected by the LC–MS analysis. Thus, the scope of the reaction was extended to other 2-amino-3-acylimidazo[1,2-*a*]pyridines **2b–l**.[39] Conversion of diamines **2b–l** was quantitative as proved by HPLC monitoring and the urea derivatives **1b–l** were easily isolated by filtration in 40–99% yields (Table 1).



Scheme 3. Cyclization study at room temperature.

Table 1
Synthesized compounds **1a–l**

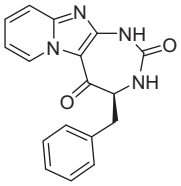
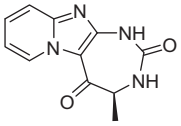
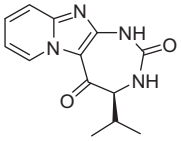
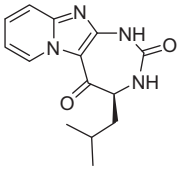
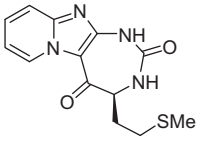
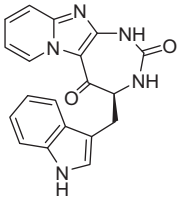
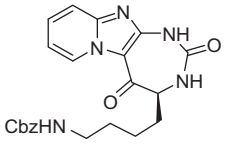
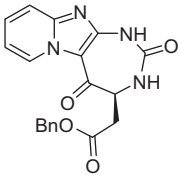
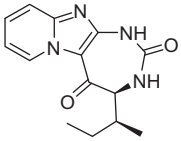
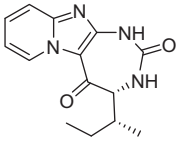
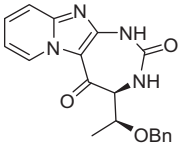
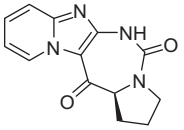
Compounds	Structure	Yield (%)
1a		78
1b		93
1c		60
1d		86
1e		68
1f		89
1g		56
1h		62
1i		53
1j		60

Table 1 (*continued*)

Compounds	Structure	Yield (%)
1k		40
1l		99

In summary, we have developed a practical sequence for the synthesis of the IP-fused [1,3]diazepine-2,5-dione heterocyclic scaffold. From an initial C-3 acylation of 2-aminoIP by Boc-amino acids and after removal of the amino protecting group, the diamines were engaged in an intramolecular carbonylation to access a library of 12 urea compounds in 40−99% overall yields. In light of the remarkable biological activities of diazepine derivatives, these unusual heterocycle fused [1,3]diazepines are currently under investigation for their pharmacological potentialities.

Supplementary data

Supplementary data (including ^{1}H and ^{13}C NMR data for all new derivatives) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.087.

References and notes

1. Sternbach, L. H. *J. Med. Chem.* **1979**, *22*, 1–7.
2. Hunt, J. T.; Ding, C. Z.; Batorsky, R.; Bednarz, M.; Bhide, R.; Cho, Y.; Chong, S.; Chao, S.; Gullo-Brown, J.; Guo, P.; Kim, S. H.; Lee, F. Y. F.; Leftheris, K.; Miller, A.; Mitt, T.; Patel, M.; Penhallow, B. A.; Ricca, C.; Rose, W. C.; Schmidt, R.; Slusarchyk, W. A.; Vite, G.; Manne, V. *J. Med. Chem.* **2000**, *43*, 3587–3595.
3. Bolli, M. H.; Marfurt, J.; Grisostomi, C.; Boss, C.; Binkert, C.; Hess, P.; Treiber, A.; Thorin, E.; Morrison, K.; Buchmann, S.; Bur, D.; Ramuz, H.; Clozel, M.; Fischli, W.; Weller, T. *J. Med. Chem.* **2004**, *47*, 2776–2795.
4. Churcher, I.; Williams, S.; Kerrad, S.; Harrison, T.; Castro, J. L.; Shearman, M. S.; Lewis, H. D.; Clarke, E. E.; Wrigley, J. D. J.; Beher, D.; Tang, Y. S.; Liu, W. S. *J. Med. Chem.* **2003**, *46*, 2275–2278.
5. Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S. *J. Med. Chem.* **1988**, *31*, 2235–2246.
6. Evans, B. E.; Bock, M. G.; Rittle, K. E.; DiPardo, R. M.; Whitter, W. L.; Veber, D. F.; Anderson, P. S.; Freidinger, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4918–4922.
7. Micale, N.; Vairagoundar, R.; Yakovlev, A. G.; Kozikowski, A. P. *J. Med. Chem.* **2004**, *47*, 6455–6458.
8. Rodriguez, I. B.; Procopio, J. R.; Hernandez, L. H.; Fresenius, Z. *Anal. Chem.* **1987**, *328*, 117–119.
9. Hosmane, R. S.; Bhan, A.; Karpel, R. L.; Siriwardane, U.; Hosmane, N. S. *J. Org. Chem.* **1990**, *55*, 5882–5890.
10. Daly, J. W.; Hide, I.; Bridson, P. K. *J. Med. Chem.* **1990**, *33*, 2818–2821.
11. Hosmane, R. S.; Bhan, A. *J. Heterocycl. Chem.* **1990**, *27*, 2189–2196.
12. Bridson, P. K.; Weirich, T. P. *J. Heterocycl. Chem.* **1988**, *25*, 1179–1182.
13. Ivanov, E. I. *Khim. Geterotsikl. Soedin.* **1998**, 828–831.
14. Ivanov, E. I.; Kalayanov, G. D.; Yaroshchenko, I. M. *Khim. Geterotsikl. Soedin.* **1990**, 997–998.
15. Garcia, C. *J. Heterocycl. Chem.* **1973**, *10*, 51–53.
16. Funke, C.; Es-Sayed, M.; De Meijere, A. *Org. Lett.* **2000**, *2*, 4249–4251.
17. Boojamra, C. G.; Burow, K. M.; Thompson, L. A.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 1240–1256.
18. Baraldi, P. G.; Manfredini, S.; Periotto, V.; Simoni, D.; Guarneri, M.; Borea, P. A. *J. Med. Chem.* **1985**, *28*, 683–685.

19. Lee, J. Y.; Kim, Y. C. *ChemMedChem* **2009**, *4*, 733–737.
20. Brouillette, Y.; Lisowski, V.; Fulcrand, P.; Martinez, J. *J. Org. Chem.* **2007**, *72*, 2662–2665.
21. Brouillette, Y.; Martinez, J.; Lisowski, V. *J. Org. Chem.* **2009**, *74*, 4975–4981.
22. Brouillette, Y.; Sujol, G.; Martinez, J.; Lisowski, V. *Synthesis* **2009**, 389–394.
23. Brouillette, Y.; Verdie, P.; Martinez, J.; Lisowski, V. *Synlett* **2008**, 2360–2364.
24. Rotas, G.; Natchkebia, K.; Natsvlishvili, N.; Kekelidze, M.; Kimbaris, A.; Varvounis, G.; Mikeladze, D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3220–3223.
25. Lam, P. Y.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Chang, C. H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson-Viitanen, S. *Science* **1994**, *263*, 380–384.
26. Bookser, B. C.; Kasibhatla, S. R.; Appleman, J. R.; Erion, M. D. *J. Med. Chem.* **2000**, *43*, 1495–1507.
27. El-Subbagh, H. I.; Hassan, G. S.; El-Azab, A. S.; Abdel-Aziz, A. A. M.; Kadi, A. A.; Al-Obaid, A. M.; Al-Shabanah, O. A.; Sayed-Ahmed, M. M. *Eur. J. Med. Chem.* **2011**, *46*, 5567–5572.
28. Takayama, T.; Umemiya, H.; Amada, H.; Yabuuchi, T.; Koami, T.; Shiozawa, F.; Oka, Y.; Takaoka, A.; Yamaguchi, A.; Endo, M.; Sato, M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 112–116.
29. Chen, S. B.; Gao, G. Y.; Leung, H. W.; Yeung, H. W.; Yang, J. S.; Xiao, P. G. *J. Nat. Prod.* **2001**, *64*, 85–87.
30. Boehringer Ingelheim Pharma GmbH & Co. KG, Eur. Pat. Appl. EP 2065382 A1, 2009.
31. Magano, J.; Acciacca, A.; Akin, A.; Collman, B. M.; Conway, B.; Waldo, M.; Chen, M. H.; Mennen, K. E. *Org. Process Res. Dev.* **2009**, *13*, 555–566.
32. Gupta, S. P.; Babu, M. S. *Bioorg. Med. Chem.* **1999**, *7*, 2549–2553.
33. Masurier, N.; Aruta, R.; Gaumet, V.; Denoyelle, S.; Moreau, E.; Lisowski, V.; Martinez, J.; Maillard, L. T. *J. Org. Chem.* **2012**, *77*, 3679–3685.
34. Hamdouchi, C.; De Blas, J.; Ezquerra, J. *Tetrahedron* **1999**, *55*, 541–548.
35. Hamdouchi, C.; Sanchez, C.; Ezquerra, J. *Synthesis* **1998**, 867–872.
36. Masurier, N.; Moreau, E.; Lartigue, C.; Gaumet, V.; Chezal, J. M.; Heitz, A.; Teulade, J. C.; Chavignon, O. *J. Org. Chem.* **2008**, *73*, 5989–5992.
37. Chaubet, G.; Maillard, L. T.; Martinez, J.; Masurier, N. *Tetrahedron* **2011**, *67*, 4897–4904.
38. *General procedure for the synthesis of 2-amino-3-acyl-imidazo[1,2-a]pyridines* ***4a–l****:* To a suspension of 0.5 g of trifluoro-*N*-imidazo[1,2-*a*]pyridin-2-yl-acetamide[33] (2.18 mmol) in 9 mL of aqueous 5 N sodium hydroxide solution was added 0.5 mL of THF. The solution was stirred at 40 °C for 2 h. The solution was extracted with dichloromethane (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was dissolved in 20 mL of dichloromethane and 2.4 mmol of BocAAOH (1.1 equiv), 325 mg (2.4 mmol, 1.1 equiv) of HOBt, 460 mg (2.4 mmol, 1.1 equiv) of EDCI, and 334 μL of triethylamine (243 mg, 2.4 mmol, 1.1 equiv) were added at 0 °C. The solution was stirred at rt for 4 h. The solution was then washed with saturated $NaHCO_3$ solution (2 × 50 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was concentrated in vacuo. The residue was purified by chromatography (Al_2O_3, DCM/EtOH 99/1 v/v) to offer **4a**–**l**.
39. *General procedure for the synthesis of 1,3-diazepine-2,5-diones* ***1a–l****.* A solution of 150 mg of compound **4a–l** in 3 mL of 12 N hydrochloric acid was stirred a room temperature for 1 h. The solution was treated with 28% aqueous ammonia solution and then extracted with chloroform (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was concentrated in vacuo to lead compounds **2a–l**, which were used in the next step without further purification. To a solution of the appropriate diamine **2a–l** in 5 mL of acetonitrile was added 1.1 equiv of carbonyldiimidazole (CDI). The solution was stirred at 60 °C until completion of the reaction (HPLC monitoring). After cooling to rt, the precipitate was collected by filtration, washed with diethylether, and dried in vacuo to give **1a–l**.