Tetrahedron Letters 52 (2011) 3234–3236

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Unprecedented formation of benzo[*d*][1,2,3,6]oxatriazocine derivatives via diazo-oxygen bond formation and synthesis of enantiomerically pure 1-alkyl benzotriazole derivatives

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ARTICLE INFO

Article history:
Received 26 January 2011
Revised 1 April 2011
Accepted 12 April 2011
Available online 18 April 2011

ABSTRACT

A series of amino acid-derived enantiomerically pure substituted benzo[*d*][1,2,3,6]oxatriazocine derivatives and 1-alkyl substituted benzotriazoles has been prepared by the diazotization of amino acid-derived benzo-fused alicycles. The first unprecedented diazo-oxygen bond formation in acidic medium led to an entirely new kind of substituted benzo[*d*][1,2,3,6]oxatriazocine heterocycles.

Over the past decades, the design and synthesis of medium ring heterocycles, having a ring size in the range of 7–11 with oxygen and nitrogen atoms, have drawn a lot of attention as a consequence of a wide variety of applications such as biologically active natural products,[1] drug candidates,[2] materials,[3] and for catalysis.[4] For example, the benzoxazocine ring is often present in many pharmaceutical agents.[5] Nefopam hydrochloride,[6] with a benzoxazocine ring is a non-narcotic analgesic drug having antidepressant activity.[7]

Benzotriazoles are also important structural motifs, having a wide range of biological activities, including antifungal,[8] antitumor,[9] anti-inflammatory,[10] antimicrobial,[11] and antidepressant.[12] In particular, 1-alkyl-benzotriazole derivatives are highly selective agonists for human orphan G-protein coupled receptor GPR109b.[13] Further, benzotriazole was found to be an efficient ligand for the Cu-catalyzed *N*-arylation of imidazoles.[14]

We have been working on the synthesis and biology of *S*-amino acid-based chiral heterocyles and natural product-like molecules.[15] Recently, we have published a new series of amino acid-derived benzoxazepine derivatives as an antitumor agent in breast cancer.[15c] In continuation of our studies in finding out the effect of ring size on antitumor activity, we decided to synthesize and evaluate a series of amino acid-derived benzoxazine derivatives. We planned to synthesize benzoxazines via tandem diazotization followed by intramolecular nucleophilic displacement of diazonium sulphate with amino acid-derived primary carbinol (Scheme 2).

S-amino acids **3a–e** were reacted with 1-flouro-2-nitrobenzene derivatives **1** and **2** in the presence of K_2CO_3 and dry DMF at 80 °C to furnish 2-nitro benzene protected amino acid derivatives which were converted to their methyl esters **4a–e** and **5** in the presence of $SOCl_2$ and MeOH (Scheme 1). Nucleophilic aromatic substitution of 2-nitro-fluoro benzene with amino acids occurs without any racemization.[15e] $LiBH_4$ reduction of **4a–e** and **5** gave carbinols **6a–e** and **7** in 80–90% yield. The alcohol of **6a–e** and **7** was protected with TBDMS group by using TBDMSiCl, imidazole in dry DCM to afford **8a–e** and **9** in good yield. Aromatic nitro group was reduced to amine by hydrogenolysis to provide TBDMS protected carbinol **10a–e** and **11** with 65–75% yield.

The final diazotization of the intermediates **10a–e**, **11** gave **12a–e**[16] and **13** (Scheme 2) by one-pot three step sequence, (i) diazotization of the aromatic amine (ii) TBDMS deprotection, and (iii) cyclization through diazo-oxygen (N=N–O) bond formation. Instead of benzoxazine, benzo[*d*][1,2,3,6]oxatriazocines were isolated.

Since the secondary amine of **A** is in conjugation with diazo group, it is less reactive than primary carbinol (Scheme 3). Thus, formation of benzotriazole does not take place (path *b*) (Fig. 1). Benzoxazines do not form through elimination of diazo group followed by subsequent attack of primary carbinol of **A** (path *c*). It is noted that the formation of benzo[*d*][1,2,3,6]oxatriazocines takes place through nucleophilic attack of primary carbinol on electrophilic diazo group (path *a*). To the best of our knowledge amino acid-derived chiral heterocycles containing diazo-oxygen bond are not reported in the literature.

With benzo[*d*][1,2,3,6]oxatriazocines in hand, synthesis of benzoxazine was attempted through thermal elimination of molecular nitrogen in **12a**. Thus, heating at 120 °C gave only recovery of starting materials perhaps due to strong double bond character in C–N=N–O of **12a**, (Scheme 4). After failure of thermal elimination of N_2, the free radical reaction of **12a** with Cu powder was attempted at 70 °C. Starting material was fully consumed without isolation of desired product. Further, one-pot diazotization of **10a** followed by heating at 70 °C in the presence of Cu powder afforded uncharacterized complex mixture.

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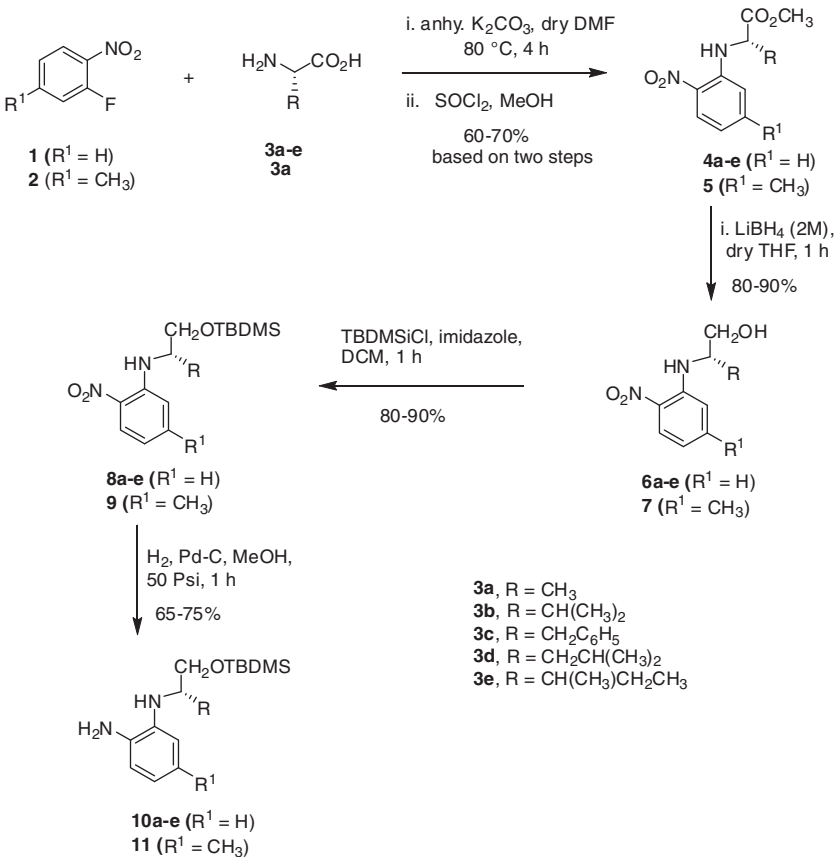
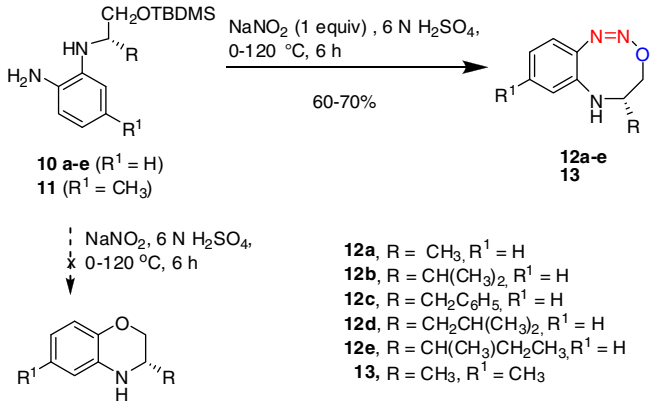
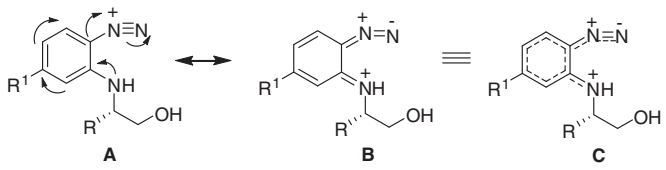
doi:10.1016/j.tetlet.2011.04.049



Scheme 1. Preparation of intermediates **10a-e**, **11**.



Scheme 2. Synthesis of benzo[*d*][1,2,3,6]oxatriazocines derivatives.



Scheme 3. Resonance structure of **A** and resonance hybrid.

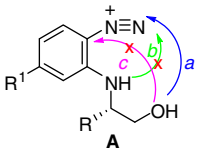
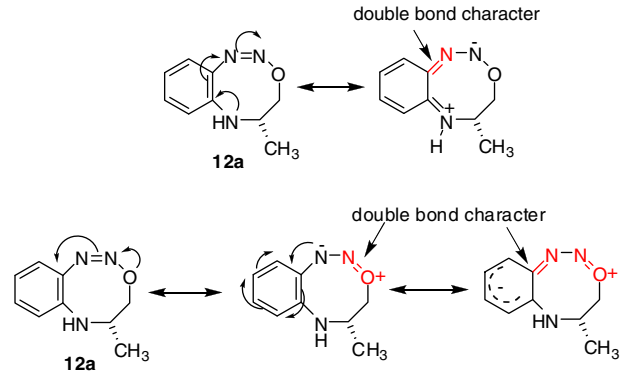
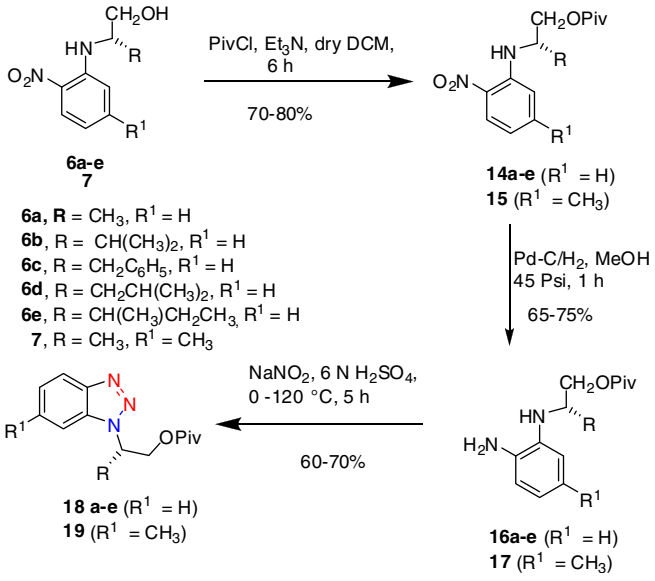


Figure 1. Primary carbinol is more reactive than secondary amine.



Scheme 4. Double bond character of C–N=N–O bond.

The formation of **12a–e** and **13** takes place through the reaction of free primary carbinol on diazo group (Scheme 2). To prevent the N=N–O bond formation as well as to facilitate the nucleophilic secondary amine attack, primary carbinols **6a–e, 7** were protected with acid stable pivaloyl group in the presence of pivaloyl chloride, triethyl amine in dry DCM to provide **14a–e** and **15** in 70–80% yield (Scheme 5). Aromatic nitro groups of **14a–e, 15** were converted to



Scheme 5. Synthesis of 1-alkyl benzotriazoles derivatives.

amine by hydrogenolysis to afford pivaloyl protected amino carbinols **16a–e** and **17** in 65–75% yield. Then aromatic amines **16a–e** and **17** were diazotised in the presence of $NaNO_2$ (1 equiv), 6 N·H_2SO_4 to provide amino acid-derived 1-alkyl substituted enantiomerically pure benzotriazole derivatives **18a–e** and **19** with good yield through formation of (N–N=N) bond.

In conclusion, we have reported an unprecedented diazo-oxygen (N=N–O) bond formation which led to an entirely new kind of benzo[*d*][1,2,3,6]oxatriazocines via one-pot three step sequence, (i) diazotisation (ii) TBDMS deprotection, and (iii) cyclization. We have also synthesized amino acid-derived 1-alkyl benzotriazole derivatives via diazotization of **16a–e** and **17** through diazo-nitrogen (N=N–N) bond formation. Although diazo-nitrogen bond formation is known,[17] diazo-oxygen bond formation in acidic medium is not reported in the literature.

Acknowledgements

Authors thank the Department of Science and Technology (DST), New Delhi, India for financial support. KS and SB thank CSIR for the fellowships.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.049.

References and notes

1. Reviews: (a) Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125; (b) Maier, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073; (c) Evans, P. A.; Holmes, B. *Tetrahedron* **1991**, *47*, 9131; (d) Lindstrom, U. M.; Somfai, P. *Chem. Eur. J.* **2001**, *7*, 94; (e) Bieraugel, H.; Jansen, T. P.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Org. Lett.* **2002**, *4*, 2673; (f) Derrer, S.; Davies, J. E.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2957; (g) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 44.
2. (a) Taunton, J.; Collins, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10412; (b) Murray, P. J.; Kranz, M.; Ladlow, M.; Taylor, S.; Berst, F.; Holmes, A. B.; Keavey, K. N.; Jaxa-Chamiec, A.; Seale, P. W.; Stead, P.; Upton, R. J.; Croft, S. L.; Clegg, W.; Elsegood, M. R. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 773.
3. (a) Sanchez-Quesada, J.; Ghadiri, M. R.; Bayley, H.; Braha, O. *J. Am. Chem. Soc.* **2000**, *122*, 11757; (b) Bong, D. T.; Clark, T. D.; Granja, J. R.; Ghadiri, M. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 988.
4. Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481.
5. Neogi, A.; Majhi, T. P.; Mukhopadhyay, R.; Chattopadhyay, P. *J. Org. Chem.* **2005**, 2307–2314.
6. *The Merck Index*; Budavari, S., Ed., twelveth ed.; Merck Rahway: NJ, 1996. p 1105 and references cited therein.
7. Klohs, M. W.; Draper, M. S.; Petracek, F. J.; Ginzel, K. H.; Re, O. N. *Arzneim. Forsch. (Drug Res.)* **1972**, *22*, 132.
8. Rezaei, Z.; Khabnadideh, S.; Pakshir, K.; Hossaini, Z.; Amiri, F.; Assadpour, E. *Eur. J. Med. Chem.* **2009**, *44*, 3064–3067.
9. Al-Soud, Y. A.; Al-Masoudi, N. A.; Ferwanah, Abd El-R. S. *Bioorg. Med. Chem.* **2003**, *11*, 1701–1708.
10. Dawood, K. M.; Abdel-Gawad, H.; Rageb, E. A.; Ellithey, M.; Mohamed, H. A. *Bioorg. Med. Chem.* **2006**, *14*, 3672–3680.
11. Swamy, S. N.; Basappa, B.; Sarala, G.; Priya, B. S.; Gaonkar, S. L.; Prasad, J. S.; Rangappa, K. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 999–1004.
12. Kane, J. M.; Dudley, M. W.; Sorensen, S. M.; Miller, F. P. *J. Med. Chem.* **1988**, *31*, 1253.
13. Semple, G.; Skinner, P. J.; Cherrier, M. C.; Webb, P. J.; Sage, C. R.; Tamura, S. Y.; Chen, R.; Richman, J. G.; Connolly, D. T. *J. Med. Chem.* **2006**, *49*, 1227–1230.

(a). Chandrasekhar, S.; Seenaiah, M.; Rao, Ch. L.; Reddy, Ch. R. *Tetrahedron* **2008**, *64*, 11325–11327. and references therein; (b) Verma, A. K.; Singh, J.; Sankar, V. K.; Chaudhary, R.; Chandra, R. *Tetrahedron Lett.* **2007**, *48*, 4207–4210.

15. (a) Mishra, J. K.; Panda, G. *Synthesis* **2005**, 1881; (b) Mishra, J. K.; Panda, G. *J. Comb. Chem.* **2007**, *9*, 321; (c) Samanta, K.; Chakravarti, B.; Mishra, J. K.; Dwivedi, S. K. D.; Nayak, L. V.; Choudhry, P.; Bid, H. K.; Konwar, R.; Chattopadhyay, N.; Panda, G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 283; (d) Mishra, J. K.; Samanta, K.; Jain, M.; Dikshit, M.; Panda, G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 244; (e) Samanta, K.; Panda, G. *Org. Biomol. Chem.* **2010**, *8*, 2823.
16. *General experimental procedure for the synthesis of* ***12a–e*** *and* ***13****:* The compounds **10a–e** and **11** were dissolved in 5 mL 6 N·H_2SO_4, then the solution was cooled at 0 °C, followed by addition of ice-cooled aq solution of $NaNO_2$ (1 equiv.). It was refluxed for 6 h at 120 °C and was neutralized with aq $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and dried over anhydrous sodium sulphate. The solvent was removed under vacuum and the crude product was then purified by chromatography over silica gel with eluent chloroform/methanol (9.2:0.8) to afford the title compound **12a–e** and **13**. Spectra of **12a:** IR (neat, cm^{-1}): 3420, 3021, 2366, 1216, 768; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, 1H, J = 8.4 Hz), 7.50 (d, 1H, J = 8.3 Hz), 7.41–7.36 (m, 1H), 7.23–7.18 (m, 1H), 4.91–4.85 (m, 1H), 4.26–4.19 (m, 1H), 4.08–4.04 (m, 1H), 3.21 (bs, 1H), 1.61 (d, 3H, J = 6.9 Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 145.5, 133.2, 127.2, 124.0, 119.6, 109.7, 65.8, 57.3, 16.8 ppm; MS (ESI): m/z 178 $[M+H]^+$; Anal. Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71%; Found: C, 61.11; H, 6.20; N, 23.63%.
17. Kale, R. R.; Prasad, V.; Hussain, H. A.; Tiwari, V. K. *Tetrahedron Lett.* **2010**, *51*, 5740–5743.