Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 49 (2008) 296–299

An efficient synthesis of N-arylated, orthogonally protected racemic aspartates

Guanglin Luo,* Ling Chen, Rita Civiello and Gene M. Dubowchik

Department of Chemistry, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT, USA

Received 6 February 2007; revised 8 November 2007; accepted 9 November 2007
Available online 17 November 2007

Abstract—A brief and efficient synthesis of variously N-arylated racemic aspartates has been achieved by two consecutive reactions in one-pot, in which imine or equivalent, formed in situ from various anilines and ethyl glyoxylate, reacted with the Reformatsky reagent, *tert*-butyl 2-bromozinc acetate. Notably the two esters are orthogonally protected for the convenience of further derivatization.

N-Aryl-α-amino acids are common pharmacophores in a number of medicinally important agents. Many of their derivatives, including non-nucleoside reverse transcriptase inhibitor Opaviraline **1**,[1] insulin sensitizer Farglitazar **2**,[2] anticoagulant factor Xa inhibitor **3**,[3] and platelet aggregation inhibitor GP IIb/IIIa antagonist Lotrafiban (SB-214857) **4**,[4] shown in Figure 1, possess a wide range of biological activities.

One of our recent medicinal chemistry programs required an efficient method of accessing various *N*-aryl aspartic acid derivatives as intermediates for further elaboration at two acid or ester functional groups. Our first thought was a direct coupling of various aryl bromides with aspartic acid or esters. N-Arylation of amino acids or esters was initially achieved by Ma using a copper-catalyzed coupling reaction of aryl halides and amino acids or esters (CuI and K_2CO_3 in dimethylacetamide).[5] However, these conditions were only successful for amino acids bearing hydrophobic side groups (exemplified by valine, phenylalanine, and proline) and failed for those with hydrophilic substituents (glutamic acid, serine, or glycine). Later, intra-molecular N-arylation of an aspartic acid derivative for the synthesis of **4** was achieved under these conditions.[6] Conditions were further developed by Hayes substituting K_2CO_3 with tetrabutylammonium hydroxide to effect N-arylation of aspartic acid in acceptable yield.[7] The key to success was the formation of a soluble salt in dimethylacetamide, dimethylformamide, or acetonitrile. Recently this transformation was achieved with water as solvent, albeit with low yield (32%) in the case of aspartic acid.[8] Our initial attempt to utilize these conditions failed in cases of more complicated, functionalized bromides. What is more, these coupling reactions use commercial

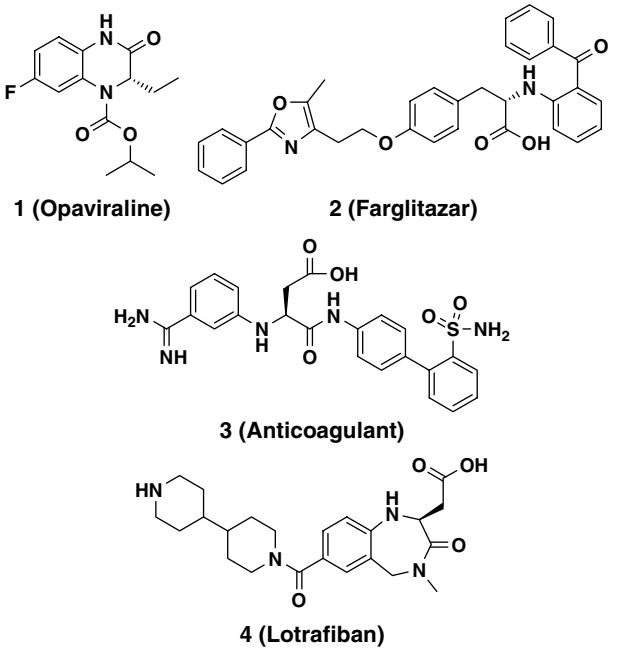
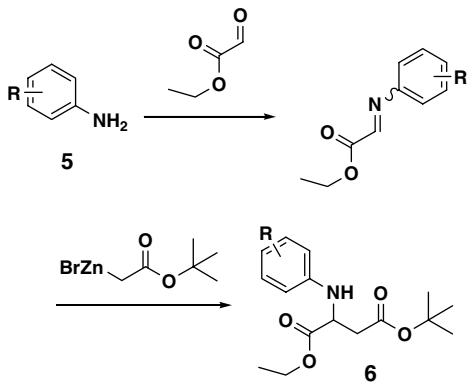


Figure 1. Selected biologically active N-arylated aminoacids.

Keywords: Ethyl glyoxylate; Imine; *N*-Aryl aspartate; Reformatsky reagent.
* Corresponding author. Tel.: +1 230 677 6640; fax: +1 203 677 7702; e-mail: guanglin.luo@bms.com

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.11.060



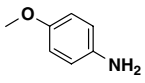
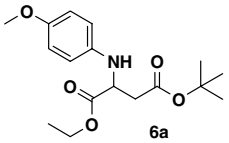
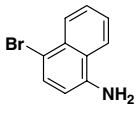
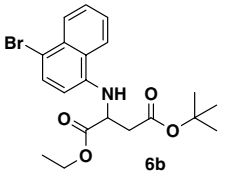
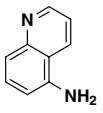
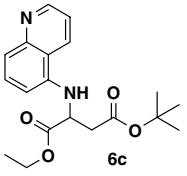
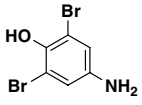
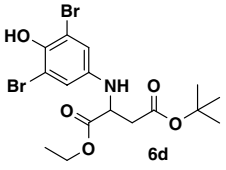
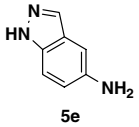
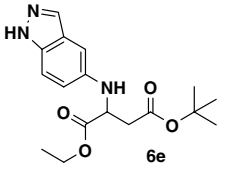
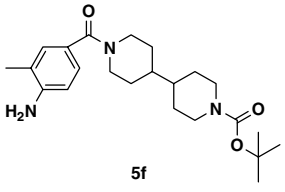
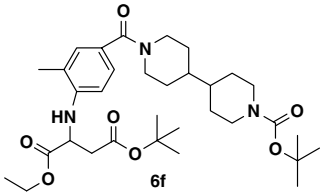
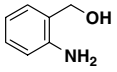
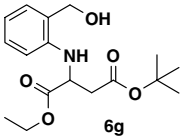
Scheme 1. Proposed synthesis of N-arylated aspartates.

aspartic acid or the dimethyl ester as starting materials and further steps are required to differentiate the two acid or ester groups as we require.

Another useful amino ester N-arylation method was developed by Lam,[9] in which arylboronic acids reacted with α-amino esters using $Cu(OAc)_2$ as a catalyst. Compared to the CuI-catalyzed coupling reaction, the advantage of this method is minimum racemization of the amine chiral center. Again, in the case of aspartate, differentiation of 2 equiv esters is needed and availability of a variety of arylboronic acids is limited.

With the aim of differentiating the ester groups from the beginning, we envisioned a simple reaction sequence, in

Table 1. Conversion of anilines **5** to *N*-aryl aspartates **6**

Entries	Aniline **5**	Imine synthesis method	Product **6**	Yield[a] (%)
1	 **5a**	A	 **6a**	82
2	 **5b**	B	 **6b**	83
3	 **5c**	B	 **6c**	82
4	 **5d**	A	 **6d**	65
5	 **5e**	C	 **6e**	65
6	 **5f**	B	 **6f**	85
7	 **5g**	B	 **6g**	91

[a] Isolated yield of pure compound for two steps.

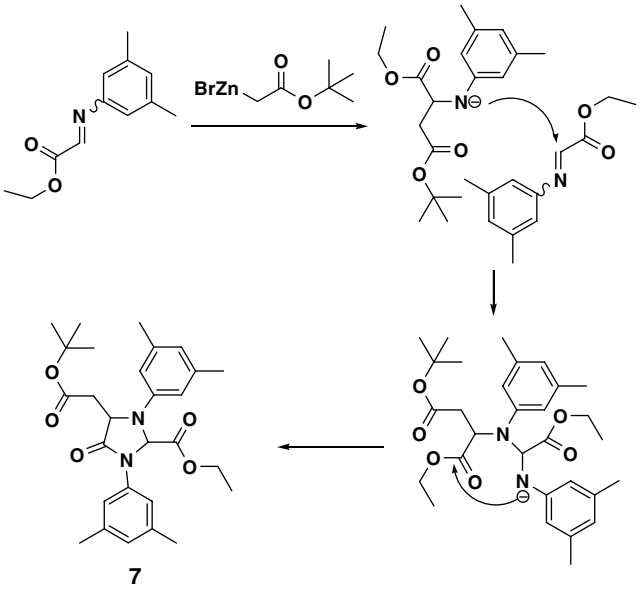
which imine intermediates formed in situ between ethyl glyoxylate and widely available anilines react with commercially available Reformatsky reagent *tert*-butyl bromozinc acetate, as shown in Scheme 1. Reaction of Reformatsky reagents with different electrophiles including imines have long been known in the literature.[10]

Our first attempt, using *p*-anisidine **5a** met with good success (Table 1, entry 1). Synthesis of the corresponding imine according to literature procedures with 4 Å molecular sieves as a dehydrating reagent,[11] followed by reaction with *tert*-butyl 2-bromozinc acetate,[12] afforded the desired aspartate **6a** in 82% yield after purification. In subsequent reactions with various aniline derivatives, it was found that imine formation was critical for the success of the subsequent reaction with the Reformatsky reagent. Various conditions for the formation of imines were then surveyed but not optimized among the aniline derivatives shown in Table 1.[13] Generally, analytical means (TLC, LCMS, or ^{1}H NMR) were taken to make sure that the formation of imines was sufficiently clean and complete.

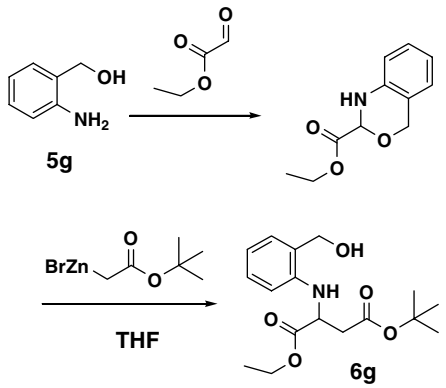
The crude imines generally reacted with the Reformatsky reagent very well to afford a variety of N-arylated aspartates as shown in Table 1.[14] It is noteworthy that an free phenol group (entry 4) or indazole NH group (entry 5) did not require protection as long as an extra equivalent of Reformatsky reagent was used. An aniline (**5f**)[15] with *ortho*-substitution, amide and BOC functional groups (entry 6) also proceeded smoothly to the desired product. However, when an insufficient amount of Reformatsky reagent was used, a new product could be formed. In the case of 3,5-dimethyl aniline, a highly substituted imidazolone **7** was formed (Scheme 2).[15] Presumably after the addition of Reformatsky reagent to the imine, the resulting N-centered anion could react with another equivalent of imine, when available, to generate a new aniline anion which attacks the ethyl ester to form the 5-membered ring imidazolone **7**.[15] No 6-membered ring product was observed. Compound **7** appeared to be a single diastereomer, though no rigorous efforts were attempted to assign relative stereochemistry.

Owing to the presence of a 2-hydroxymethyl substituent in **5g** (entry 7), the intermediate formed in the reaction sequence is most likely a 6-membered cyclic semi-aminal instead of imine (Scheme 3), reaction of which with *tert*-butyl 2-bromozinc acetate also proceeded well to afford **6g** in 91% yield. Compound **6g** or analogs can be converted to benzodiazepinones such as Lotrafiban **4** using known procedures.[7,16]

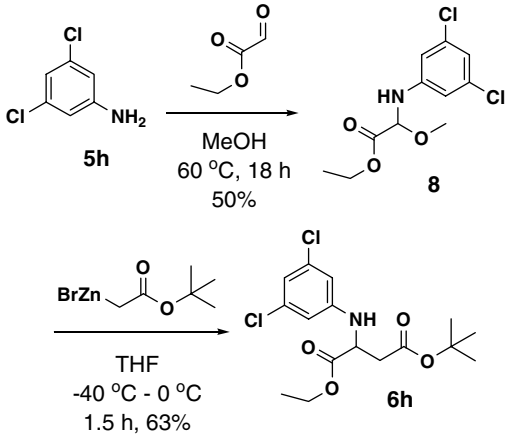
Inspired by the success with the putative semi-aminal intermediate in Scheme 3, we were interested in proceeding through semi-aminal adducts with methanol instead of imines which are sometimes unstable, especially when the aniline is electron-deficient. The formation of one successful methanol semi-aminal had been described in the literature.[17] In the case of 3,5-dichloroaniline (**5h**) from which formation of the imine was not successful, a stable intermediate **8** was obtained in ca. 50% isolated yield (Scheme 4).[15] Reaction of **8** with *tert*-butyl 2-bromozinc acetate went well to afford the desired



Scheme 2. Formation of a densely substituted imidazolone.



Scheme 3. Proposed semi-aminal intermediate.



Scheme 4. Proposed semi-aminal intermediate and reaction.

product **6h** in 63% yield (Scheme 4).[15] However, though stable and identifiable, the formation of methanol semi-aminals was not always achievable. For example, the dianilino-aminal was found to be the major product in the case of simple aniline.

In summary, a very short and facile racemic synthesis has been achieved for N-arylated aspartates through an imine or semi-aminal intermediate in one-pot. More critically, the two acid groups were orthogonally protected as ethyl and *tert*-butyl esters, which could be deprotected under basic and acid conditions, respectively.

Acknowledgment

The authors are grateful to Dr. John E. Macor for his constant support and encouragement.

Supplementary data

Supplementary data (analytical data including copies of ^{1}H and ^{13}C NMR spectra for compounds **5f**, **6a**–**6h**, **7** and **8**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.060.

References and notes

1. Prince, W.; Moore, K.; Cass, L.; Dallow, N.; Jones, A.; Kleim, J.-P.; Mutch, P.; St. Clair, M. *Antiviral Res.* **1999**, *41*, 2 (Abs. 49).
2. (a) Henke, B. R.; Blanchard, S. G.; Brackeen, M. F.; Brown, K. K.; Cobb, J. E.; Collins, J. L.; Harrington, W. W., Jr.; Hashim, M. A.; Hull-Ryde, E. A.; Kaldor, I.; Kliewer, S. A.; Lake, D. H.; Leesnitzer, L. M.; Lehmann, J. M.; Lenhard, J. M.; Orband-Miller, L. A.; Miller, J. F.; Mook, R. A., Jr.; Noble, S. A.; Oliver, W., Jr.; Parks, D. J.; Plunket, K. D.; Szewczyk, J. R.; Willson, T. M. *J. Med. Chem.* **1998**, *41*, 5020–5036; (b) Liu, K. G.; Smith, J. S.; Ayscue, A. H.; Henke, B. R.; Lambert, M. H.; Leesnitzer, L. M.; Plunket, K. D.; Willson, T. M.; Sternbach, D. D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2385–2388.
3. Juraszyk, H.; Dorsch, D.; Mederski, W.; Tsaklakidis, C.; Barnes, C.; Gleitz, J. W.O. Patent 0230880, 2002.
4. (a) Miller, W. H.; Ku, T. W.; Ali, F. E.; Bondinell, W. E.; Calvo, R. R.; Davis, L. D.; Erhard, K. F.; Hall, L. B.; Huffman, W. F.; Keenan, R. M.; Kwon, C.; Newlander, K. A.; Ross, S. T.; Samanen, J. M.; Takata, T. D.; Yuan, C. *Tetrahedron Lett.* **1995**, *36*, 9433–9436; (b) Samanen, J. M.; Ali, F. E.; Barton, L. S.; Bondinell, W. E.; Burgess, J. L.; Callahan, J. F.; Calvo, R. R.; Chen, W.; Chen, L.; Erhard, K.; Feuerstein, G.; Heys, R.; Hwang, S.-M.; Jakas, D. R.; Keenan, R. M.; Ku, T. W.; Kwon, C.; Lee, C.-P.; Miller, W. H.; Newlander, K. A.; Nichols, A.; Parker, M.; Peishoff, C. E.; Rhodes, G.; Ross, S.; Shu, A.; Simpson, R.; Takata, D.; Yellin, T. O.; Uzsinskas, I.; Venslavsky, J. W.; Yuan, C.-K.; Huffman, W. F. *J. Med. Chem.* **1996**, *39*, 4867–4870.
5. Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459–12467.
6. Ma, D.; Xia, C. *Org. Lett.* **2001**, *3*, 2583.
7. Clement, J.-B.; Hayes, J. F.; Sheldrake, H. M.; Sheldrake, P. W.; Wells, A. S. *Synlett* **2001**, 1423–1427.
8. Lu, Z.; Twieg, R. J. *Tetrahedron Lett.* **2005**, *46*, 2997–3001.
9. Lam, P. Y. S.; Bonne, D.; Vincent, G.; Clark, C. G.; Combs, A. P. *Tetrahedron Lett.* **2003**, *44*, 1691–1694.
10. For a review; see: Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press LLC, 1996, pp 207–236.
11. Manhas, M. S.; Ghosh, M.; Bose, A. K. *J. Org. Chem.* **1990**, *55*, 575–580.
12. *tert*-Butyl 2-bromozinc acetate (0.50 M in THF) was commercially available from Reike Metals, Inc.
13. Conditions for the formation of imines: *Method A*: Approximately 1.1:1 ratio of ethyl glyoxylate (50% toluene solution) and **5** (4.0 mmol) in CH_2Cl_2 (10 ml) with 4 Å M.S. till completion, then filtered and concentrated; *Method B*: Approximately 1:1 ratio of ethyl glyoxylate (50% toluene solution) and **5** (2.0 mmol) in benzene (20 ml) was refluxed for 18 h (or till completion) followed by concentration; *Method C*: Approximately 1.1:1 ratio of ethyl glyoxylate (50% toluene solution) and **5** (2.0 mmol) in THF (6 ml) with anhydrous $MgSO_4$ till completion, then filtered and concentrated.
14. General procedures for the synthesis of **6**: Intermediate imine (2.0 mmol) was redissolved in anhydrous THF (8 ml) and cooled at 0 °C or −20 °C under nitrogen. 1.1 or 2.2 (for entries 4, 5 and 7) equiv of *tert*-butyl 2-bromozinc acetate (0.50 M in THF) was quickly added to the stirring solution of **6**. (A reverse addition could also be utilized). The reaction was usually complete within 2 h. After quenching with NH_4Cl solution, the mixture was extracted with EtOAc three times. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography to afford **6**. All analytical data for the new compounds were documented in Supplementary data.
15. See Supplementary data.
16. (a) Ku, T. W.; Ali, F. E.; Barton, L. S.; Bean, J. W.; Bondinell, W. E.; Burgess, J. L.; Callahan, J. F.; Calvo, R. R.; Chen, L.; Eggleston, D. S.; Gleason, J. G.; Huffman, W. F.; Hwang, S. M.; Jakas, D. R.; Karash, C. B.; Keenan, R. M.; Kopple, K. D.; Miller, W. H.; Newlander, K. A.; Nichols, A.; Parker, M. F.; Peishoff, C. E.; Samanen, J. M.; Uzinskas, I.; Venslavsky, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 8861–8862; (b) Andews, I. P.; Atkins, R. J.; Badham, N. F.; Bellingham, R. K.; Breen, G. F.; Carey, J. S.; Etridge, S. K.; Hayes, J. F.; Hussain, N.; Morgan, D. O.; Share, A. C.; Smith, S. A. C.; Walsgrove, T. C.; Wells, A. S. *Tetrahedron Lett.* **2001**, *42*, 4915–4917.
17. Chen, B.-C.; Zhao, R.; Bednarz, M. S.; Wang, B.; Sundeen, J. E.; Barrish, J. C. *J. Org. Chem.* **2004**, *69*, 977–979.