Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7497–7499

Synthesis of 1-aminoimidazolidin-4-one and 1-aminoimidazolidin-2-one based compounds: an interesting divergence in methodology

Benjamin E. Blass,* Keith Coburn, Neil Fairweather, Andrew Fluxe, Steve Hodson, Chris Jackson, John Janusz, Wenlin Lee, Jim Ridgeway, Ron White and Shengde Wu

Procter and Gamble Pharmaceuticals, Health Care Research Center, 8700 Mason Montgomery Road, Mason, OH 45040, United States

Received 21 June 2006; accepted 9 August 2006
Available online 1 September 2006

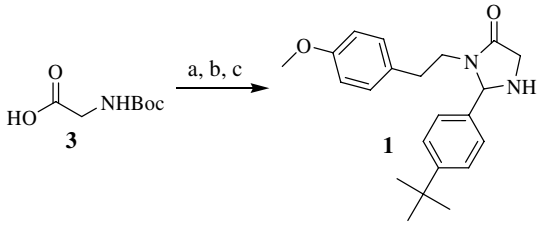
Abstract—An examination of the methods required for the amination of 2- and 4-imidazolidinones is described.

Imidazolidinones constitute a class of heterocyclic compounds with wide ranging biological activities. The 2-imidazolidinone and 4-imidazolidinone scaffolds can be found in compounds with CCR3 and 5-HT_{2c} receptor antagonists activity,[1] angiogenic,[2] and antibacterial[3] properties, and in phosphodiesterase inhibitors.[4] We recently became interested in both of these scaffolds as part of our ongoing efforts to explore diverse chemical space for drug discovery. We were particularly interested in the preparation of the aza analogs of both of these structures, as very few examples have been reported to date. The majority of the literature in this area is focused on aminohydantoins. Further, the direct aminations of the parent 2- and 4-imidazolidinones have not been reported to date, nor have the reduction of the corresponding *N*-nitroso compounds.

We chose to explore the methods for amination of these compounds with two simple model systems (**1** and **2**), both of which could be prepared from readily available materials. Thus, for the preparation of **1**, *N*-Boc glycine (**3**) was converted to the amide via EDCI coupling with the 4-methoxyphenethyl amine. Deprotection with TFA, followed by condensation with 4-*tert*-butyl benzaldehyde in the presence of cesium carbonate provided **1** (Scheme 1).

Preparation of the 2-imidazolidinone **2** was slightly more complicated. 4-*tert*-Butyl benzaldehyde (**4**) was converted to the nitro alkene, which readily underwent a Michael condensation with 4-methoxyphenethyl amine. Reduction with zinc dust to the diamine,[5] followed by cyclization with carbonyldiimidazole provided **2**, the second test substrate (Scheme 2).

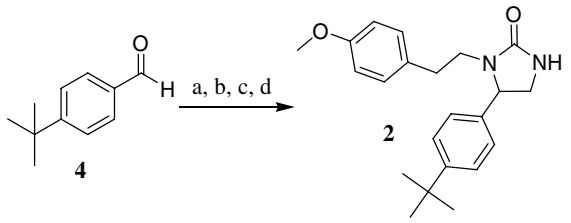
Our initial investigations focused on the amination of the 2-imidazolidinones. Nitrosation of this scaffold was readily accomplished by treatment of **2** with sodium nitrite in glacial acetic acid at room temperature. Reduction to the desired product, **5**, was then accomplished with the addition of zinc dust at 8–15 °C (83%, Scheme 3).[6] Control of the temperature during the zinc addition was critical to maintain selectivity and avoid formation of the original starting material, **2**, via N–N bond reduction.



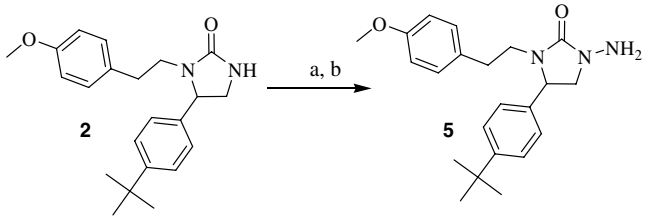
Scheme 1. Reagents and conditions: (a) EDCI, 4-OMe phenethylamine, CH_2Cl_2, (b) TFA/CH_2Cl_2 1/1, (c) 4-*t*-butylbenzaldehyde, Cs_2CO_3, MeOH, 60 °C.

* Corresponding author. Tel.: +1 513 403 9685; fax: +1 513 622 4296; e-mail: bblass2@fuse.net

0040-4039/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2006.08.022

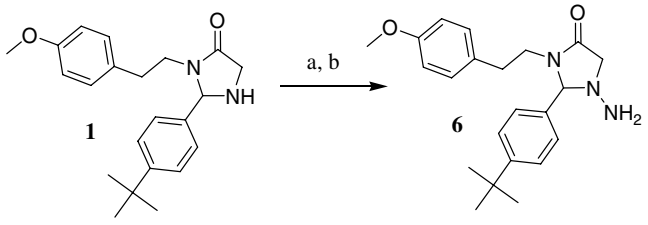


Scheme 2. Reagents and conditions: (a) CH_3NO_2, NH_4OAc, AcOH, reflux, (b) 4-OMe phenethylamine, THF, rt, (c) Zn, HCl, EtOH, (d) CDI, DMF, 50 °C.



Scheme 3. Reagents and conditions: (a) $NaNO_2$, AcOH, 25 °C, (b) AcOH, Zn, 8–15 °C.

We then turned our attention to the 4-imidazolidinone scaffold. While the nitrosation of **1** was accomplished using similar conditions to the 2-imidazolidinone scaffold, we were surprised to discover that reduction to the amine was far more difficult. In our hands, the zinc/acetic acid method employed for the reduction of the 2-nitroso-2-imidazolidinone was not selective in the 4-imidazolidinone series. The only product observed in the 4-imidazolidinone class was the original starting material, **1**, a result of reduction of the N–N bond. Similar results were observed with palladium on carbon and hydrogen, palladium on alumina and hydrogen, and titanium trichloride. Further, tin chloride in a variety of solvents, both with and without microwave irradiation, left the nitroso compound unchanged. Similar results were observed with sodium borohydride, sodium cyanoborohydride, and even lithium aluminum hydride.[7] All of these procedures have been previously reported to be effective in the reduction of various nitroso compounds without concomitant reduction of the N–N bond. To our surprise, the only conditions that produced reasonable quantities of the desired 1-amino-imidazolidin-4-one (**6**) was reduction with zinc dust in the presence of ammonium chloride at 80 °C for 10 min with microwave irradiation (72%, Scheme 4).[8]



Scheme 4. Reagents and conditions: (a) $NaNO_2$, AcOH, MeOH, 0 °C, (b) Zn, NH_4Cl, MeOH.

The interesting difference in selectivity between these two apparently similar ring systems is not easily explained. One could argue that the 4-imidazolidinone ring system contains a basic nitrogen that may be protonated under acidic conditions, thus activating the N–N bond to reductive cleavage. However, reports in the literature of successful, selective reduction of other *N*-nitroso systems to the corresponding *N*-amino compound suggest that protonation alone cannot explain the difference reported here. The empirical observation that hydride reagents fail to produce the desired product, **6**, and that hydrogenation conditions are not selective for nitroso reduction versus N–N bond cleavage is also a surprising and unexplained result.

In summary we have developed a method for the preparation of the previously unknown 1-amino imidazolidin-4-one and 1-aminoimidazolidin-2-one based structures from the parent imidazolidinone core in good yield. We have further demonstrated that the nature of the reductive conditions employed is critical to the successful formation of the desired products.

References and notes

1. (a) Hudkins, R. L.; Zulli, A. L.; Reddy, D. R.; Gingrich, D. E.; Tao, M.; Becknell, N. C.; Diebold, J. L.; Underiner, T. L. U.S. Patent 2005143442, 2005; (b) Goodacfre, C. J.; Bromidge, L. P.; Clapham, D.; King, F. D.; Lovell, P. J.; Allen, M.; Campbell, L. P.; Holland, V.; Riley, G. J.; Starr, K. R.; Trail, B. K.; Wood, M. D. *Biorg. Med. Chem. Lett.* **2005**, *15*, 4989–4993.
2. Gong, L.; Wilhelm, R. S. U.S. Patent 2005090504, 2005.
3. (a) Ochiai, H.; Watanabe, Y.; Murotani, Y.; Fukuda, H.; Yoshino, O.; Minami, S.; Hayashi, T.; Momonoi, K. GB 2233330, 1991; (b) Araujo, M. A.; Born, J.; Capela, R.; Casimiro, C.; Chambel, P.; Gomes, P.; Iley, J.; Lopes, F.; Morais, J.; Moreira, R.; Oliveira, E.; Rosario, V.; Vale, N. *J. Med. Chem.* **2005**, 888–892.
4. Godfrey, J. D., Jr.; Mueller, R. H.; Zahler, R. EP, 1989.
5. Mouhtaram, M.; Jung, L.; Stambach, J. F. *Tetrahedron* **1993**, *49*, 1391–1400.
6. *Preparation of* **5**: To a solution of 5-(4-*tert*-butylphenyl)-1-[2-(4-methoxyphenyl)ethyl]-2-imidazolidinone (6 g, 17 mmol) in glacial acetic acid (120 mL), is slowly added a solution of sodium nitrite (1.52 g, 22 mmol) in water (10 mL). After 30 min, the suspension is cooled to 8 °C, via a water–ice bath. Zinc (1 g) is added with a rise in temp to 15 °C. A second portion of zinc (1 g) is added at 8 °C, with a temp rise to 12 °C. The final addition of zinc (1.3 g, 50 mmol total) is made at 7.8 °C. The temp is allowed to rise slowly and the solution is allowed to stir at 12–17 °C for 1 h. The mixture is cooled in an ice-bath and is diluted with CH_2Cl_2 (60 mL) and water (25 mL). NH_4OH (175 mL) is added, keeping the temp $\leqslant$27 °C. The CH_2Cl_2 is separated, and the aqueous layer is washed with CH_2Cl_2 (2×75 mL). The combined organics are dried (Na_2SO_4), and evaporated to give a colorless oil. The oil is diluted with Et_2O (25 mL) and is cooled in an ice-bath. HCl in Et_2O (12 mL, 24 mmol) is slowly added. Hexanes (10 mL) is slowly added and the suspension is allowed to stir at room temp overnight. The suspension is filtered, washed with hexanes, to give the title compound. Yield: 5.7 g (83%). ^1H NMR (DMSO-d_6): δ 7.47 (d, $J = 8.1$ Hz, 2H), 7.33 (d, $J = 8.1$ Hz, 2H), 7.04 (d, $J = 8.4$ Hz, 2H), 6.82 (d, $J = 8.4$ Hz, 2H), 4.67

(t, $J = 7.8$ Hz, 1H), 3.87 (t, $J = 7.8$ Hz, 1H), 3.71 (s, 3H), 3.55 (m, 1H), 3.34 (t, $J = 8.1$ Hz, 1H), 2.64 (m, 5H), 1.29 (s, 9H). MS ($M+H^+$) 368.

7. (a) Toure, B. B.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 8429–8436; (b) Lunn, G.; Sansone, E. B.; Keefer, L. K. *J. Org. Chem.* **1984**, *49*, 3470–3473; (c) Klager, K.; Wilson, E. M.; Helmkamp, G. K. *J. Ind. Eng. Chem.* **1960**, *52*, 119–120; (d) Henry, E.; Creger, P. L. *J. Am. Chem. Soc.* **1960**, *82*, 4634–4638; (e) Feliu, A. L. *J. Labelled Compd. Radiopharm.* **1988**, *25*, 1245–1254.
8. *Preparation of* **6**. Step 1, 3-(4-methoxyphenethyl)-2-(4-*tert*-butylphenyl)-1-nitrosoimidazolidin-4-one: To a solution of 3-(4-methoxyphenethyl)-2-(4-*tert*-butylphenyl)imidazolidin-4-one (2.77 g, 7.87 mmol) in MeOH (30.0 mL) at 0 °C is added acetic acid (1.10 mL) followed by the dropwise addition of a solution of sodium nitrite (0.83 g, 11.96 mmol) in H_2O (2.50 mL). The reaction mixture is stirred with warming to rt for a total of 18 h. The reaction mixture is neutralized with $NaHCO_3$, extracted with EtOAc, and dried. Evaporation of the EtOAc yielded 2.25 g of the crude product. MS ($M+H^+$) 382. The material was then used without further purification. Step 2, 3-(4-methoxyphenethyl)-1-amino-2-(4-*tert*-butylphenyl)imidazolidin-4-one: To a solution of crude 3-(4-methoxyphenethyl)-2-(4-*tert*-butylphenyl)-1-nitrosoimidazolidin-4-one (0.90 g, 2.36 mmol) in MeOH (13.0 mL) is added zinc (0.76 g, 11.69 mmol) and a saturated solution of NH_4Cl (8.0 mL). The reaction mixture is irradiated in the microwave for 10 min at 80 °C followed by dilution with CH_2Cl_2 and H_2O. The CH_2Cl_2 was separated, dried, and evaporated to yield 0.62 g (71%) of the crude product that does not require further purification. ^1H NMR (CD_3OD) δ 7.48 (d, 2H, $J = 8.3$ Hz), 7.37 (d, 2H, $J = 8.3$ Hz), 6.96 (d, 2H, $J = 8.6$ Hz), 6.81 (d, 2H, $J = 8.5$ Hz), 4.75 (s, 1H), 3.78 (d, 1H, $J = 11.5$ Hz), 3.75 (s, 3H), 3.57 (m, 1H), 3.35 (d, 2H, $J = 12$ Hz), 2.74 (m, 2H), 2.47 (m, 1H), 1.35 (s, 9H). MS ($M+H^+$) 368.