Pergamon

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Tetrahedron Letters 44 (2003) 9111–9114

TETRAHEDRON LETTERS

Synthesis of C5-substituted imidazolines

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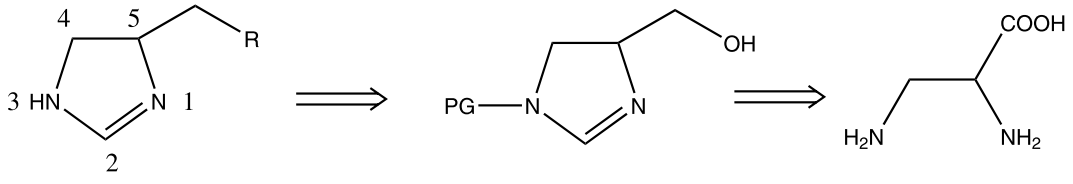
Received 1 August 2003; revised 2 October 2003; accepted 10 October 2003

Abstract—5-(Hydroxymethyl)-3-(*t*-butyloxycarbonyl)imidazoline **2** was prepared in four steps from 2,3-diaminopropionic acid in 72% overall yield. Mitsunobu reaction with a series of phenol derivatives gave the corresponding 5-(aryloxymethyl)-3-(*t*-butyloxycarbonyl)imidazolines **8a–l**. Phthalimide and *N*-benzyl trifluoroacetamide also reacted.

It has been established recently that some imidazoline-containing ligands have a high affinity for binding sites distinct from α-adrenoreceptors. Three discrete imidazoline receptors have been characterised,[1] and shown to be involved in several physiological regulations or pathological processes like hypertension.[2] They are being increasingly studied for their possible implication in human brain disorders such as depression,[3] Alzheimer's type dementia[4] and Parkinson's disease.[5] There is also some evidence for the implication of imidazoline receptors in the nervous regulation of blood pressure[6] and in insulin secretion control.[7] Thus for further biological evaluation, novel imidazoline derivatives are needed. Until now, many of the imidazolines reported were substituted at positions C2 and C5. We are interested in the development of a general method for the synthesis of C2-unsubstituted derivatives **1** bearing various side-chains at C5. Our plan was to use 5-(hydroxymethyl)imidazoline **2** as key intermediate to the target molecules **1** (Scheme 1).

5-(Methoxycarbonyl)imidazoline **5** was prepared in two steps from racemic 2,3-diaminopropionic acid **3** according to known procedures.[8,9] Attempted *N*-protection of **5** with chloroformates caused extensive degradation of the imidazoline ring (PG = methoxycarbonyl, benzyloxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl). On the other hand, Boc protection[10] was very efficient, giving 3-(*t*-butyloxycarbonyl)-5-(methoxycarbonyl)imidazoline **6**[11] in 86% yield (Scheme 2). Treatment of **6** with sodium borohydride afforded the desired alcohol **2**[12] with an overall yield of 72% for the four steps.

The instability of the imidazoline ring requires very mild conditions for further functionalization. Different methods for the substitution of the alcohol function of imidazoline **2** were unsuccessful. For instance, we were unable to form C–X or C–C bonds by nucleophilic substitution (after classical activation of the OH group by sulfonylation), or by organometallic coupling reactions[13] from the bromide **7** obtained in modest yield



1 **2** **3**

Scheme 1. General strategy (PG = protecting group).

Keywords: imidazoline; Mitsunobu reaction.
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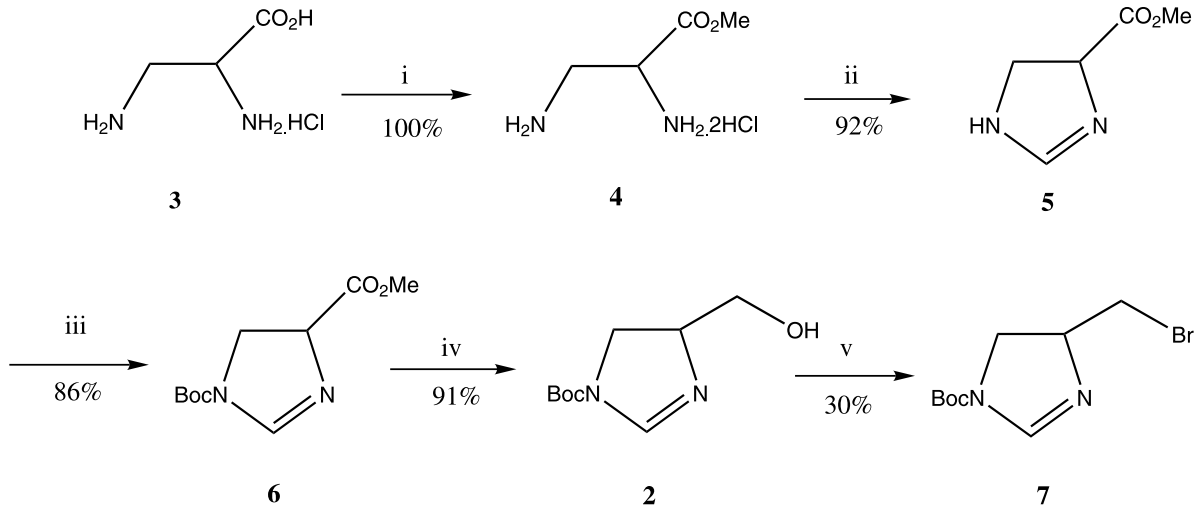
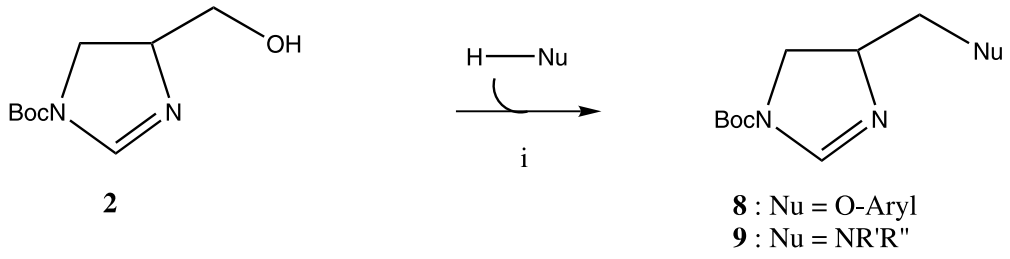
doi:10.1016/j.tetlet.2003.10.044



Scheme 2. Synthesis of the key intermediate. *Reagents and conditions*: (i): CH_3OH, $SOCl_2$; (ii) $HC(OMe)_3$, MeOH; (iii) Boc_2O, Et_3N, CH_2Cl_2; (iv) $NaBH_4$, *i*-PrOH; (v) NBS, PPh_3, $BaCO_3$.



Scheme 3. Mitsunobu reactions. *Reagents and conditions*: (i) DIAD, Ph_3P, THF, 20°C, 48 h.

by reacting alcohol **2** with *N*-bromosuccinimide and triphenylphosphine.[14] Finally, we found that the Mitsunobu reaction[15] could be easily performed with the key intermediate **2**. Thus, a mixture of triphenylphosphine and a dialkyl azodicarboxylate enabled the replacement of the hydroxyl group by various nucleophiles. For this Mitsunobu reaction, we found that the order of addition of reagents was crucial. Because the classical procedure failed to give the expected products (i.e. addition of diisopropyl azodicarboxylate to a mixture of alcohol, protonated nucleophile and triphenylphosphine), the betaine was preformed before the addition of a mixture of imidazoline **2** and nucleophile. The method was well exemplified with a series of phenols to furnish 5-(aryloxymethyl)-3-(*t*-butyloxycarbonyl)imidazoline compounds **8** (Scheme 3).[16] The reactions, listed in Table 1, were conducted in THF at 20°C for 48 h (Table 1, entries 1–12). Yields were moderate to good and increased with the acidity of the phenol. All products were characterized by the usual spectroscopic analyses.[17]

This reaction could also be applied to amine nucleophiles activated by electron-withdrawing groups. Phthalimide and *N*-benzyl trifluoroacetamide[18] gave the corresponding coupled products in good yields (Table 1, entries 13–14).

The reported strategy constitutes a novel general method for chemical modification of the sensitive C2-unsubstituted imidazolines. Only a few special syntheses have been previously disclosed;[19] some of them have quite broad scope, though they have not been applied to the preparation of imidazolines with C5-functionalized side-chains. Our method should be easily extendable to chiral precursors ((*R*)- or (*S*)-2,3-diaminopropionic acid).

Table 1. Yields of compounds **8** and **9**

Entry	Nu	Compd	Yield (%)
1	O-C_6H_5	**8a**	40
2	O-C_6H_4-4′-CH_3	**8b**	33
3	O-C_6H_4-4′-NO_2	**8c**	91
4	O-C_6H_4-2′-F	**8d**	92
5	O-C_6H_4-3′-F	**8e**	64
6	O-C_6H_4-4′-F	**8f**	88
7	O-C_6H_4-4′-CF_3	**8g**	80
8	O-C_6H_3-3′,5′-$(CF_3)_2$	**8h**	95
9	O-C_6H_4-4′-CN	**8i**	50
10	O-C_6H_4-4′-CO_2Me	**8j**	60
11	O-α-Naphthyl	**8k**	77
12	O-β-Naphthyl	**8l**	70
13	N-Phth	**9a**	59
14	N($COCF_3$)Bn	**9b**	75

After cleavage of the *N*-protecting group by treatment with iodotrimethylsilane in dichloromethane, the compounds were isolated in poor yields (30–50%), as fumarate salts from diethyl ether.[20] Biological evaluation was performed by determining the affinity of the compounds for the rat α_2 adrenoreceptor, the rat serotonine reuptake site and the rat adrenaline reuptake site by competition with [^{3}H] RX 821002, [^{3}H] paroxetine and [^{3}H] nisoxetine respectively.[3] No notable activity was found.

Acknowledgements

This work was generously supported by l'Institut de Recherches Servier (France) and the Fonds National de la Recherche Scientifique (FNRS, Belgium). We thank A. Dekoker-Malengreau and B. Clamot for technical assistance. J.M.-B. is a senior research associate of the FNRS.

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11. Spectral data for **6**: ^{1}H NMR (500 MHz, $CDCl_3$); δ 1.43 (9H, s, $(CH_3)_3C$), 3.72 (4H, m, H-4 and CH_3O), 3.83 (1H, dd, $J=7.7$, 4.6 Hz, H-4′), 4.73 (1H, dd, $J=10.0$, 7.8 Hz, H-5), 7.46 (1H, broad s, H-2). ^{13}C NMR (125 MHz, $CDCl_3$); δ 27.9, 45.6, 52.3, 68.7, 82.4, 149.5, 150.2, 170.8. MS *m*/*z* (EI) 228, 169, 155, 127, 69.
12. Spectral data for **2**: ^{1}H NMR (500 MHz, $CDCl_3$); δ 1.51 (9H, s, $(CH_3)_3C$), 3.56 (5H, m, H-4, H-4′ and CH_2OH), 4.30 (1H, m, H-5), 7.56 (1H, broad s, H-2). Anal. calcd for $C_9H_{16}N_2O_3$: C, 53.08; H, 8.05; N, 13.99; found: C, 53.22; H, 7.99; N, 13.67.
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16. **General procedure**: Triphenylphosphine (1.5 equiv.) dissolved in tetrahydrofuran (100 mg/mL) was cooled to 0°C. Diisopropyl azodicarboxylate (1.5 equiv.) was added and the mixture was allowed to stir for 10 min before adding compound **2** (1 equiv.) and phenol (1.5 equiv.) (or amine derivative) dissolved in tetrahydrofuran (100 mg/mL). The mixture was stirred at room temperature for 48 h. By adding a small amount of diisopropyl ether, after solvent evaporation, triphenylphosphine oxide precipitated. After filtration, the crude mixture was purified by preparative MPLC (SiO_2: 15–40 μ; P = 100–110 kg/cm^2; UV: 245 nm; CH_2Cl_2/*i*-PrOH, 98/2).
17. Spectral data for **8c**: ^{1}H NMR (500 MHz, $CDCl_3$); δ 1.52 (9H, s, $(CH_3)_3C$), 3.62 (1H, dd, $J=10.4$, 7.3, H-4), 3.80 (1H, dd, $J=10.4$, 10.4, H-4′), 4.06 (1H, dd, $J=9.8$, 6.4, CH_2O), 4.24 (1H, dd, $J=9.8$, 4.6, CH_2O), 4.59 (1H, dddd, $J=7.3$, 10.4, 6.4, 4.6, H-5), 6.97 (2H, d, $J=9.6$, Ar-H), 7.55 (1H, broad s, H-2), 8.18 (2H, d, $J=9.6$, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$); δ 28.1, 46.1, 66.2, 70.2, 82.6, 114.6, 125.7, 142.0, 150.0 (C-2), 163.4 (CO not visible). MS *m*/*z* (EI) $M^+ = 321$, 266, 222. IR (cm^{-1}) 3054, 1719, 1617, 1594, 1385, 1344.
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20. **Typical procedure**: *t*-Boc protected imidazoline **1** (173 mg, 0.63 mmol) was dissolved in dichloromethane (3 mL) under a nitrogen atmosphere. Trimethylsilyl iodide (134 μL, 0.94 mmol) was added dropwise and the solution was stirred for 5 h at room temperature. Methanol (1 mL)

was added and the stirring was continued for an additional hour. The solvents were evaporated under reduced pressure and the residue was taken up in a mixture of aqueous sodium bicarbonate (10%, 5 mL) and dichloromethane (5 mL). The organic phase was separated and the aqueous phase was extracted further by dichloromethane (2×5 mL). The pooled organic extracts were dried with potassium carbonate and evaporated under reduced pressure. The oily residue (80 mg) was dissolved in diethyl ether (5 mL) and treated with fumaric acid (73 mg, 0.63 mmol) dissolved in diethyl ether (10 mL). The off-white solid which formed was filtered and dried over vacuum (78 mg, 42% yield, mp: 94°C). Analytical data for 5-phenoxymethyl-imidazoline, fumarate: ^{1}H NMR (300 MHz, DMSO-d_6); δ 3.55 (1H, dd, H-4), 3.80 (1H, dd, H-4′), 4.05 (2H, d, O-CH_2), 4.45 (1H, m, H-5), 6.50 (2H, s, HC=CH), 6.95 (2H, d, H-*ortho*), 7.00 (1H, t, H-*para*), 7.30 (2H, t, H-*meta*), 8.00 (1H, s, H-2). IR (KBr, cm^{-1}): 3300-2300 (OH, NH_2^+), 1700–1560 (C=O), 1659-1590 (C=C, C=N). Anal. calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58; found: C, 57.33; H, 5.52; N, 9.57.