Synthesis of Amlodipine Using Aza Diels-Alder Reaction

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The 1,4-dihydropyridine Ca^{+2} channel blockers are clinically significant antihypertensive drugs and have been immensely valuable as molecular tools with which probe structural and functional aspects of Ca^{+2} channel function.[1,2]

Most of the 1,4-dihydropyridines were prepared by a procedure first described by Hantzsch[3] in 1882 shown in Scheme 1. This procedure is simple, and isolation of product is generally straightforward. However, it is well documented[4] that ortho-substituted benzaldehydes generally gave very low yields.

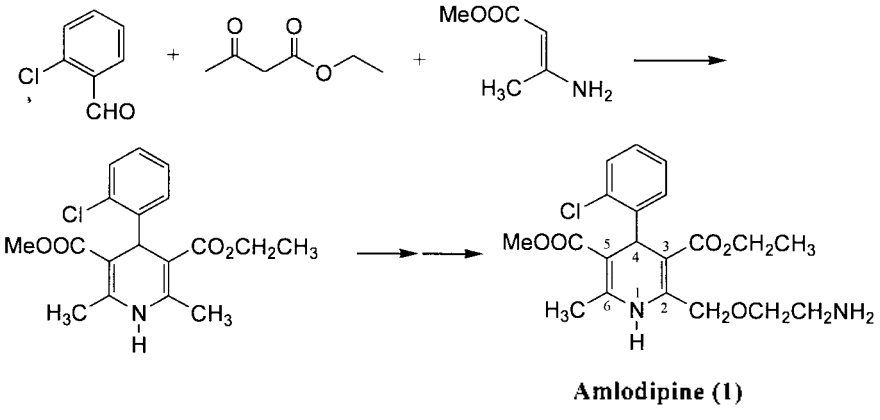
The aim of our work was to develop more efficient new protocol to 1,4-dihydropyridine frameworks. We have chosen Amlodipine (**1**)[5] with ortho-substituted phenyl ring because it is one of the most widely used drugs in 1,4-dihydropyridine family. Here we have described aza Diels-Alder reaction approach to construct highly substituted 1,4-dihydropyridine moiety focused on Amlodipine (**1**).

Results and Discussion

Reaction of ethyl acetoacetate with 2-chlorobenzaldehyde in benzene gave the Knoevenagel condensation product **2** in 70% yield. Formation of imine was accomplished from **2** by the reaction with benzylamine **3** in the presence of anhydrous magnesium sulfate. However, our several attempts to isolate imine were unsuccessful because of easy decomposition. Thus, aza Diels-Alder reaction was directly conducted without isolation of imine with methyl butynoate **4** as the dienophile in dry toluene at refluxing condition. Surprisingly, HPLC analysis of the crude products obtained from aza Diels-Alder reaction mixture containing unreacted starting materials showed highly regioselective (>50 : 1) formation of **5** over **6** with 45% yield. Our methodology provides a new way of assembling 1,4-dihydropyridine rings. As far as we know, this is the first example of aza Diels-Alder reaction approach for the formation of substituted 1,4-dihydropyridin rings. The structure of **5** was confirmed by comparing **5** with authentic sample synthesized from Hantzsch reaction (Scheme 1) followed by *N*-benzylation. Then side chain at C-2 in Amlodipine (**1**) was successfully introduced by using the established method of Pfizer company[6] as shown in Scheme 2.

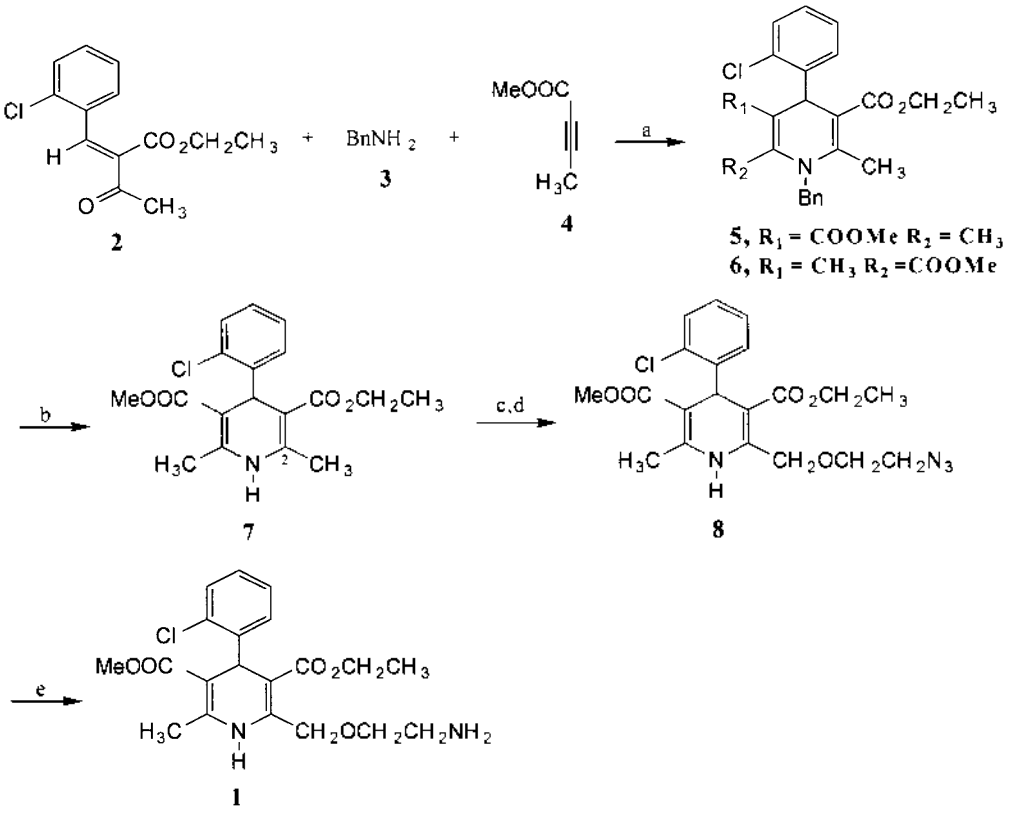
The 1,4-dihydropyridine product **5** was reacted with formic acid and Pd/C at refluxing condition to give **7** which was then brominated with pyridinium tribromide. According to literature,[7] only C-2 position was selectively brominated over 5 position. This brominated adduct was then coupled with 2-azidoethanol prepared from 2-bromoethanol and sodium azide in the presence of sodium hydride to afford **8** in two steps 66% yield. Finally, reduction of azido group with zinc dust to primary amine was accomplished to furnish Amlodipine (**1**).

In conclusion, a facile new synthetic route to Amlodipine (**1**) has been developed with overall 8% yield starting from 2-chlorobenzaldehyde. This highly useful protocol that may use as an alternative route will provide an efficient synthesis of Amlodipine. Also we are now exploring the other 1,4-dihydropyridine drugs bearing the different substituents at C-2,3,5, and 6 positions.



Amlodipine (1)

Scheme 1. Hantzsch condensation.



Scheme 2. [a]Reagents and conditions: (a) anhydrous $MgSO_4$, $PhCH_3$, reflux, 40 h, 45%; (b) 10% Pd/C, HCOOH, CH_3OH, reflux, 72 h, 74%; (c) $C_5H_5N^+HBr_3^-$, CH_2Cl_2, 0 °C; (d) $N_3CH_2CH_2OH$, NaH, ether, 0 °C; two steps 66%; (e) HCl, Zn dust, CH_3OH, rt, 52%.

Experimental Section

Preparation of 5. Benzylamine (0.7 g, 6.6 mmol) was added dropwise over 10 min to a solution of **2** (1.5 g, 6.0 mmol) and dry $MgSO_4$ (2.0 g) in freshly distilled ether (10.0 mL) at 0 °C under N_2. This resulting mixture was stirred at room temperature for 1 h. After 1 h, a solution of methyl butynoate (0.59 g, 6.0 mmol) in dry toluene (40.0 mL) was added at room temperature. The reaction mixture was heated to 110 °C for 40 h. The solution was allowed to cool to room temperature, then filtered. After removing the solvent, the residue was recrystallized in EtOAc to give title compound **5** as pale yellow needle (1.19 g). m.p. 118-123 °C; ^{1}H NMR[8] ($CDCl_3$, 300 MHz) δ 7.38-7.17, 7.08-7.02 (m, 9H, aromatics), 5.49 (s, 1H, 4H), 4.89 (s, 2H, -NC<u>H</u>$_2$Ph), 4.09 (m, 2H, -CO$_2$<u>C</u>H$_2$CH$_3$), 3.62 (d, 3H, J = 1.2 Hz, -CO$_2$<u>C</u>H$_3$), 2.36 (d, 3H, J = 2.0 Hz, 2-CH$_3$), 2.34 (d, 3H, J = 2.0 Hz, 5-CH$_3$), 1.19 (m, 3H, -CO$_2$CH$_2$<u>C</u>H$_3$); IR (KBr) ν 1680, 1700, 2920, 3040 cm^{-1}. Anal. Calcd for $C_{25}H_{26}ClNO_4$: C, 68.25; H, 5.96; N, 3.18. Found: C, 68.45; H, 5.89; N, 3.21.

Amlodipine (1). To a solution of **8** (300 mg, 0.69 mmol) in methyl alcohol (50.0 mL) at room temperature was added 3N HCl (67.0 mL). Zinc dust (3.0 g) was added to this reaction mixture over 10 min. This resulting mixture was stirred at room temperature for 10 min. The solution was filtered with celite and concentrated under reduced pressure. This acidic residue was washed with toluene (30.0 mL), neutralized with ammonia water, extracted with methylene chloride (3 × 30.0 mL). Organic layer was rinsed with brine and water, dried over anhydrous $MgSO_4$, filtered and concentrated to give crude product. This crude product was purified by column chromatography with 10% EtOAc in hexane to give amlodipine (147 mg). m.p. 178-180 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37-6.98 (m, 4H, aromatics), 5.38 (s, 1H, 4H), 4.73 (dd, 2H, J = 16.6, 16.6 Hz, -<u>C</u>H$_2$OCH$_2$CH$_2$NH$_2$), 4.02 (m, 2H, -CO$_2$<u>C</u>H$_2$CH$_3$), 3.76 (t, 2H, J = 4.9 Hz, -CH$_2$O<u>C</u>H$_2$CH$_2$NH$_2$), 3.59 (s, 3H, -CO$_2$<u>C</u>H$_3$), 2.96 (t, 2H, J = 4.9 Hz, -CH$_2$OCH$_2$<u>C</u>H$_2$NH$_2$), 2.33 (s, 3H, 5-CH$_3$), 2.05 (br, 2H, -CH$_2$OCH$_2$CH$_2$<u>N</u>H$_2$), 1.16 (m, 3H, -CO$_2$CH$_2$<u>C</u>H$_3$); IR (KBr) ν 1490, 1685, 3470 (br) cm^{-1}. Anal. Calcd for $C_{20}H_{25}ClN_2O_5$: C, 58.75; H, 6.16; N, 6.85. Found: C, 58.88; H, 6.19; N, 6.87.

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References

1. Triggle, D. J.; Lang, D. A.; Janis, R. A. *Med. Res. Rev.* **1989**, *9*, 123.
2. Goldmann, S.; Stoltefuss, J. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1559.
3. Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1.
4. Hinkel, L. E.; Ayling, E. E.; Morgan, W. H. *J. Chem. Soc.* **1931**, 1835.
5. 2-[(2-Aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine.
6. Campbell, S. F. *US. Pat. 4,572,909*. **1986**.
7. Sircar, I.; Anderson, K. R. *Tetrahedron Lett.* **1988**, *29*, 6835.
8. De Koning, A. J.; Budzelaar, P. H. M.; Brandsma, L.; De Bie, M. J. A.; Boersma, J. *Tetrahedron Lett.* **1980**, *21*, 2105.