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Click Reaction for the Synthesis of Phenylmethylene Hydrations

Masoumeh Mortazi and Farahnaz K Behbahani*

Department of Chemistry, Karaj Branch, Islamic Azad University, Iran

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***Corresponding author:** Farahnaz K Behbahani, Department of Chemistry, Karaj Branch, Islamic Azad University, Karaj, Iran,
Email: farahnazkargar@yahoo.com

Abstract

Introduction: A simple method for preparing phenylmethylene hydrations is proposed based on a Knoevenagel Condensation using aromatic aldehydes and hydrations in the presence of ethanol amine in ethanol/water under reflux condition. The synthetic process is interesting and synthesized phenylmethylene hydantoins are new compounds.

Conclusion: In conclusion, we have developed an improved synthetic method for the synthesis of phenylmethylene hydrations in good-to-excellent yields in mild medium. This method has the advantages of good yields, mild reaction conditions, easy work-up, inexpensive reagents and being environmentally friendly over the existing procedures.

Keywords: Phenylmethylene Hydrations; Ethanol Amine; Aldehydes; Synthesis

Introduction

Imidazolidine-2, 4-diones, or hydantoins have been widely used in biological screenings resulting in numerous pharmaceutical applications. Indeed, many derivatives have been recognized as anti-convulsants [1] and antimuscarinics, [2] antiulcer and antiarrythmics, [3] antiviral, antidiabetics, [4] serotonin and fibrinogen receptor antagonists, [5] inhibitors of the glycine binding site of the NMDA receptor, [6] and antagonists of leukocyte cell adhesion acting as allosteric inhibitors of the protein–protein interaction [7]. Moreover, substituted hydantoins are important building blocks for the synthesis of non-natural amino acids both in raceme form by alkaline degradation [8] and in an enantioselective way by enzymatic resolution [9]. For this reason, there is a lot of interest in developing new strategies for a straightforward synthesis of selectively substituted hydantoins both in solution and in solid phase [10]. Also, hydantoins were considered good scaffolds for future design of tyrosine kinase inhibitors [11].

Ethanolamine is commonly called monoethanolamine or MEA in order to be distinguished from diethanolamine (DEA) and triethanolamine (TEA). Ethanolamine is the second-most-abundant head group for phospholipids, a substance found in biological membranes, and is also used in messenger molecules such as palmitoylethanolamide which has an effect on CB1 receptors [12]. MEA is used in aqueous solutions for scrubbing certain acidic gases. It is used as feedstock in the production of detergents, emulsifiers, polishes, pharmaceuticals, corrosion inhibitors, chemical intermediates [13,14]. For example, reacting ethanolamine with ammonia gives the commonly used chelating agent, ethylenediamine: [13] In pharmaceutical formulations, MEA is primarily used for buffering or preparation of emulsions. MEA can be used as pH regulator in cosmetics. Here we interest to develop a novel method for the synthesis of phenylmethylene hydrations using aromatic aldehydes and hydantoine in the presence of ethanolamine in water/ethanol under reflux conditions (Figure 1).

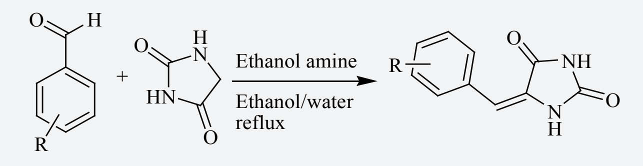
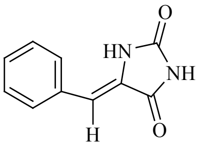
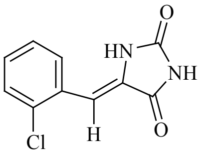
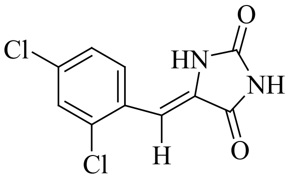
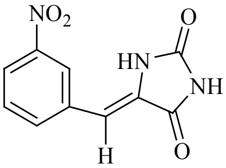
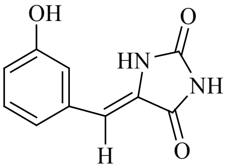
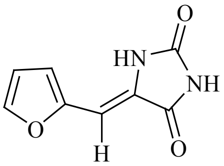
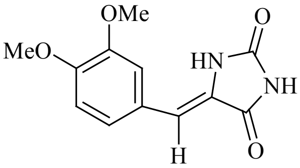


Figure 1.

Results and Discussion

To generalize this reaction to a library synthesis, hydration was treated with various aldehydes using ethanolamine in ethanol/water which successfully yielded the corresponding phenylmethylene hydantoines (Table 1). As shown in Table 1, in all cases, phenylmethylene hydantoines were obtained in good-to-excellent yields. In the present procedure, aromatic aldehyde carrying electron-withdrawing substituents in benzene ring reacted faster than those of possessing electron-donating groups. The longer reaction times were observed for the substrates bearing electron-donating groups (Table 1). The present method was convincingly superior to the reported methods with respect to yield, reaction time, simplicity and safety.

Table 1: Synthesis of Phenylmethylene hydrations using ethanolamine.

Entry	Aldehyde	Product	Time (h)	Yields%	Mp (°C)
1	Benzaldehyde		7.0	83	232-227
2	2-Chlorobenzaldehyde		3.5	88	270-275
3	2,4-Dichlorobenzaldehyde		2.0	89	285-281
4	3-Nitrobenzaldehyde		2.5	88	272-267
5	3-Hydroxybenzaldehyde		3.0	87	322-316
6	Furfural		2.5	89	232-226
7	3,4-Dimethoxybenzaldehyde		5.0	84	290-273

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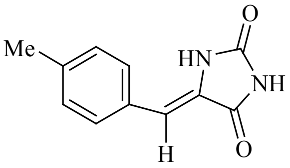
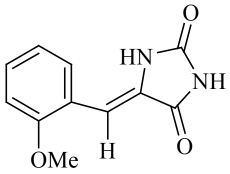
8	4-Methylbenzaldehyde		5.5	83	287-284
9	4-Methoxylbenzaldehyde		4.5	85	255-243

Experimental

a. Preparation of phenyl ethylene hydrations General procedure: Hydration (10 mmol, 1.0 g) was dissolved in 10 mL H2O while heating at 70 °C on oil bath with continuous stirring. After complete dissolution, the pH was adjusted to 7.0 using saturated $NaHCO_3$ solution. The temperature was then raised to 90 °C after the addition of 0.9 mL ethanolamine (0.015 mmol, 0.9 mL). A solution of aldehyde (10 mmol in 2–5 mL EtOH) was added drop wise with continuous stirring. The reaction was kept under reflux for approximately 2-7 h. The reaction was monitored by TLC every hour after a yellow or white precipitate is formed. After complete depletion of the starting material, the mixture was cooled and the precipitate was filtered and washed with $EtOH/H_2O$ (1:5) before recrystallization from EtOH. Reaction yield range from 80-90%, based on the nature of the used aldehyde.

References

1. J C Thenmozhiyal, P T H Wong, W K Chui (2004) Anticonvulsant activity of phenylmethylene hydrations: a structure-activity relationship study. J Med Chem 47(6): 1527-1535.
2. (a) C W Bazil and T A Pedley (1998) Advances in the Medical treatment of epilepsy. Annu Rev Med 49: 135-162; (b) M S Luer (1998) Fosphenytoin. Neurol Res 20(2): 178-182.
3. (a) M Matsukura, Y Daiku, K Ueda, S Tanaka, T Igarashi, et al. (1992) Synthesis and Ant arrhythmic activity of 2,2-dialkyl-1’-(N-substituted amino alkyl)-spiro-(chroman-4,4’-imidazolidine)-2’,5’-diones. Chem Pharm Bull, Tokyo 40(7): 1823-1827; (b) J Knabe, J Baldauf, A Ahlhelm (1997) Racemates and Enantiomers of Basic, Substituted 5-phenylhydantoins, Synthesis and Anti-arrhythmic Action. Pharmazie 52(12): 912-9.
4. L Somsa k, L Kova cs, M To th, E O sz, L Szilagyi, et al. (2001) Synthesis of and a comparative study on the inhibition of muscle and liver glycogen phosphorylases by epimeric pairs of d-gluco- and d-xylopyranosylidene-spiro-(thio)hydantoins and N-(d-glucopyranosyl) amides. J Med Chem 44(17): 2843-2848.
5. (a) G P Moloney, A D Robertson, G R Martin, S MacLennan, N Mathews, et al. (1997) A novel series of 2,5-substituted tryptamine derivatives as vascular 5HT1B/1D receptor antagonists. J Med Chem 40(15): 2347-2362; (b) G P Moloney, G R Martin, N Mathews, A Milne, H Hobbs, et al. (1999) Synthesis and serotonergic activity of substituted 2, N-benzylcarboxamido-5-(2-ethyl-1-dioxoimidazolidinyl)-N, N-dimethyltryptamine derivatives: novel antagonists for the vascular 5-HT(1B)-like receptor. J Med Chem 42(14): 2504-2526.
6. M Jansen, H Potschka, C Brandt, W L Oscher, G Dannhardt (2003) Hydantoin-substituted 4,6-dichloroindole-2-carboxylic acids as ligands with high affinity for the glycine binding site of the NMDA receptor. J Med Chem 46(1): 64-73.
7. K Last Barney, W Davidson, M Cardozo, L L Frye, C A Grygon, et al. (2001) Binding site elucidation of hydantoin-based antagonists of LFA-1 using multidisciplinary technologies: evidence for the allosteric inhibition of a protein-protein interaction. J Am Chem Soc 123(24): 5643-5650.
8. J C Sutherland, G P Hess (2000) Synthesis of fluorinated amino acids. Nat Prod Rep 17(6): 621-631.
9. (a) C Syldatk, R M uller, M Siemann, K Krohn, F Wagner (1992) in Biocatalytic Production of Amino Acids and Derivatives, (ed J D Rozzell and F Wagner), Hanser, M unchen p. 75; (b) K Drauz, H Waldmann (1995) Enzyme Catalysis in Organic Synthesis, VCH, Weinheim p. 409.
10. Some very recent papers dealing with the synthesis of hydantoins: (a) T Miura, Y Mikano, M Murakami (2011) Org Lett 13: 3560; (b) G Baccolini, C Boga, C Delpivo, G Micheletti (2011) Tetrahedron Lett 52: 1713; (c) O A Attanasi, L De Crescentini, G Favi, S Nicolini, F R Perrulli, et al. (2011) Org Lett 13: 353; (d) I A Hashmi, A Aslam, K Ali Syed, A Vigar uddin, I A Firdous (2010) Synth Commun 40: 2869; (e) M Gao, Y Yang, Y D Wu, C Deng, W M Shu, et al. (2010) Org Lett 12: 4026; (f) S M Dumbris, D J Diaz, L Mc Elwee White (2009) J Org Chem74: 8862.
11. Jemal A, Rebecca Siegel R, Ward E, Hao Y, Xu J, et al. (2008) Cancer statistics. CA Cancer J Clin 58(2): 71-96.
12. Calignano A, La Rana G, Piomelli D (2001) Antinociceptive activity of the endogenous fatty acid amide, palmitylethanolamide. European Journal of Pharmacology 419 (2-3): 191-8.
13. Klaus Weissermel, Hans Jürgen Arpe, Charlet R Lindley, Stephen Hawkins (2003) Oxidation Products of Ethylene. Industrial Organic Chemistry. Wiley VCH pp. 159-161.
14. Carrasco F (2009) Ingredients Cosméticos. Diccionario de Ingredientes Cosméticos 4ª Ed pp. 306.

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