

A Novel And Facile Synthesis of 2-(Cyclohexylamino)- 6,7-Dihydro-3-Aryl Benzofuran-4(5h)-Ones By One-Pot Three –Component Reaction

Bitā BAGHERNEJAD¹, Rahim HEKMATSHOAR^{1*}, Majid M. HERAVI¹

¹ *Department of Chemistry, School of Science, Alzahra University, Vanak, Tehran, Iran*

Received: 19/03/2010 Revised: 29/06/2010 Accepted: 01/07/2010

ABSTRACT

A simple and efficient synthesis of 2-(cyclohexylamino)-6,7-dihydro-3-aryl benzofuran-4(5H)-ones derivatives was achieved via a one-pot three –component reaction of cyclohexylisocyanide, aldehydes, and dimedone or 1,3-cyclohexanedione in DMF for 2 hr with good yields.

Keywords: Cyclohexyl isocyanide, dimedone, 1,3- cyclohexanedione, one-pot three –component reaction

1. INTRODUCTION

Benzofuranone is one of the most important heterocycles with widespread occurrence in nature [1]. Possessing a variety of biological activities, they are used as pharmaceutical, flavor, insecticidal, and fish antifeedant agent [2]. Their important biological activities and usefulness as synthetic intermediates of natural products have prompted a search for better methods of synthesis of benzofuranones. Although a number of synthetic methods [3] for the preparation of them have been reported, simple and efficient approaches still remain scarce. In recent years, multicomponent reactions (MCRs) have become important tools in modern preparative synthetic chemistry because these reactions increase the efficiency by combining several operational steps without any isolation of intermediates or change of the

conditions [4,5] and MCRs have recently emerged as valuable tools in the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds [6-8]. In 1921, Passerini⁹ pioneered the use of isocyanides and successfully developed a three-component synthesis of α -acyloxycarboxamides by reaction of a carboxylic acid, an aldehyde, and an isonitrile [10]. However, the most important breakthrough came in 1959 when Ugi described a four-component synthesis of α -acylamino amides from an aldehyde, an amine, an acid and an isocyanide [11,12]. This reaction, named later Ugi (Ugi 4CR or U-4CR) has become a widely investigated transformation during the past decade, in conjunction with technologies such as high throughput screening and combinatorial chemistry [13-19]. The ability of an isonitriles to undergo easy alkyl addition with a nucleophile and an electrophile under mild conditions has made them popular reactants

*Corresponding author, e-mail: rhekmatu@yahoo.com.

for the development of novel MCRs [20] Isocyanides [21] regarded for many years as compounds with unpleasant odors and with very few chemical and pharmaceutical applications, are now looked upon as useful synthons, attributed primarily to the renaissance of the isocyanide- based multicomponent reactions [13,22] In connection with our recent interest aimed at the development of efficient protocols for the preparation of biological active heterocycles [23] we herein report an efficient one-pot three component synthesis of 2-(cyclohexylamino)-6,7-dihydro-3-arylbenzofuran-4(5H)-ones in good yields (Figure 1).

2. EXPERIMENTAL

All products were characterized by mp, IR, ^1H NMR and GC/MS. Melting points were measured by using the capillary tube method with an Electrothermal 9200 apparatus. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX Advance spectrometer at 500 and 125 MHz, respectively, in CDCl_3 as solvent. IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network Mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel 60 F254, was used to monitoring the progress of reactions. All products were characterized by their spectra and physical data.

2.1. Typical procedure for Preparation of 2-(cyclohexylamino)-6,7-dihydro-3-aryl benzofuran-4(5H)one:

To a magnetically stirred solution of 1,3-cyclohexandione or dimedone (1mmol) and benzaldehydes (1 mmol) in DMF (5 mL) was added cyclohexyl isocyanide (0.11 g, 1mmol) and refluxing was continued for 2 h. The solvent was removed and the residue was washed with diethyl ether and then crystallized from CH_2Cl_2 : EtOH (1:2) to give the product. The dried product thus obtained showed a single spot on TLC (ethylacetate-hexane 1:3) and was pure enough for all analytical purposes.

2.2. Selected physical data

2-(cyclohexyl amino) 6,7-dihydro-3-phenyl benzofuran-4(5H)-one (4a): mp 143°C. IR (KBr) (ν_{max} , cm^{-1}): 1660 (C=O), 3350 (N-H). ^1H NMR (CDCl_3 , 500 MHz) δ_{H} (ppm): 1.10-2.25 (10H, m), 2.09 (2H, m), 2.40 (2H, t, J=6.9), 3.29 (2H, t, J=6.9), 4.07 (CH-N, m), 5.82 (NH, s), 7.41-7.85 (5H,m). ^{13}C NMR (CDCl_3 , Me_4Si) δ_{C} (ppm): 22.91, 25.07 (2CH₂), 25.13, 26.07, 30.11 (2CH₂), 41.08, 53.22, 105.66, 110.24, 120.07, 121.31, 125.45, 129.14, 131.66, 142.14, 145.61, 170.07 (C-O), 186.29 (C=O). GC/MS: 309 (M⁺).

2-(cyclohexyl amino)-6,7-dihydro-3-(4-chlorophenyl)-benzofuran-4(5H)-one (4b): Mp. 168 °C. IR (KBr) (ν_{max} , cm^{-1}): 1670 (C=O), 3300 (N-H). ^1H NMR (CDCl_3 , 500 MHz) δ_{H} (ppm): 1.14-2.3 (10H, m), 2.21 (2H, m), 2.82 (2H, t, J=7.2), 3.43 (2H, t, J=7.2), 4.15 (CH-N, m), 5.91 (NH, s), 7.44 (2H,d, J=7.9), 7.82 (2H,d, J=7.9). ^{13}C NMR (CDCl_3 , Me_4Si) δ_{C} (ppm):

23.22, 25.15 (2CH₂), 25.70, 26.13, 33.16 (2CH₂), 41.42, 53.33, 110.21,

120.35, 123.45 (arom. and 2CH), 135.17 (arom. and 2CH), 137.10, 142.24, 144.81 (C-Cl), 170.55 (C-O), 187.31 (C=O). GC/MS: 343 (M⁺).

2-(cyclohexyl amino)-6,7-dihydro-3-(4-bromophenyl)-benzofuran-4(5H)-one (4d): Mp. 148 °C. IR (KBr) (ν_{max} , cm^{-1}): 1668 (C=O), 3345 (N-H). ^1H NMR (CDCl_3 , 500 MHz) δ_{H} (ppm): 1.13-2.17 (10H, m), 2.19 (2H, m), 2.86 (2H, t, J=7.1), 3.39 (2H, t, J=7.1), 4.05 (CH-N, m), 5.98 (NH, s), 7.45 (2H,d, J=7.9), 7.79 (2H,d, J=7.9). ^{13}C NMR (CDCl_3 , Me_4Si) δ_{C} (ppm): 22.82, 26.05 (2CH₂), 25.66, 26.03, 33.32 (2CH₂), 41.68, 52.88, 110.01, 120.15, 122.45 (arom. and 2CH), 133.19 (arom. and 2CH), 136.19, 141.23, 144.71 (C-Cl), 170.43 (C-O), 186.91 (C=O). GC/MS: 388 (M⁺).

2-(cyclohexylamino)-6,7-dihydro-3-(4-methoxyphenyl)-benzofuran-4(5H)-one (4e): Mp. 169 °C. IR (KBr) (ν_{max} , cm^{-1}): 1666 (C=O), 3324 (N-H). ^1H NMR (CDCl_3 , 500 MHz) δ_{H} (ppm): 1.10-2.11 (10H, m), 2.31 (2H, m), 2.77 (2H, t, J=7.0), 3.35 (2H, t, J=7.0), 4.01 (CH-N, m), 5.43 (3H, s), 5.87 (NH, s), 7.26 (2H,d, J=7.9), 7.77 (2H,d, J=7.9). ^{13}C NMR (CDCl_3 , Me_4Si) δ_{C} (ppm): 23.11, 25.12 (2CH₂), 25.66, 26.02, 33.46 (2CH₂), 41.31, 52.99, 110.97, 120.08, 123.21 (arom. and 2CH), 134.83 (arom. and 2CH), 136.90, 142.14, 144.92 (C-Cl), 170.61 (C-O), 185.84 (C=O). GC/MS: 339 (M⁺).

2-(cyclohexyl amino)-6,6-dimethyl-6,7-dihydro-3-phenyl benzofuran-4(5H)-one (6a): Mp. 150 °C. IR (KBr) (ν_{max} , cm^{-1}): 1667 (C=O), 3322 (N-H). ^1H NMR (CDCl_3 , 500 MHz) δ_{H} (ppm): 1.09 (6H, s), 1.16-2.18 (10H, m), 2.31 (2H, s), 2.47 (2H, s), 4.17 (CH-N, m), 5.77 (NH, s), 7.39-7.79 (5H, m). ^{13}C NMR (CDCl_3 , Me_4Si) δ_{C} (ppm): 22.33, 25.28 (2CH₂), 25.89 (2CH₂), 28.15 (2CH₃), 31.13, 35.51, 53.29, 67.72, 105.67, 110.29, 120.87, 121.29, 125.64, 129.75, 131.17, 142.12, 145.84, 170.45 (C-O), 186.88 (C=O). GC/MS: 337 (M⁺).

2-(cyclohexyl amino)-6,6-dimethyl-6,7-dihydro-3-(4-chlorophenyl) benzofuran-4(5H) one (6b): Mp. 178 °C. IR (KBr) (ν_{max} , cm^{-1}): 1660 (C=O), 3320 (N-H). ^1H NMR (CDCl_3 , 500 MHz) δ_{H} (ppm): 1.12 (6H,s), 1.14-2.14 (10H, m), 2.29 (2H, s), 2.80 (2H, s), 4.14 (CH-N), 5.49 (NH, s), 7.46 (2H,d, J=8.2), 7.83 (2H,d, J=8.2). ^{13}C NMR (CDCl_3 , Me_4Si) δ_{C} (ppm): 23.20, 24.16 (2CH₂), 27.17 (2CH₂), 28.15 (2CH₃) 34.41, 38.24, 53.21, 58.22, 100.21 (CH-N), 122.41 (arom. and 2CH), 135.51 (arom. and 2CH), 137.17, 142.46, 145.11, 146.62 (C-Cl), 171.45 (C-O), 186.31 (C=O). GC/MS: 371 (M⁺).

2-(cyclohexyl amino)-6,6-dimethyl-6,7-dihydro-3-(4-bromophenyl) benzofuran-4(5H) one (6d): Mp. 172 °C. IR (KBr) (ν_{max} , cm^{-1}): 1663 (C=O), 3342 (N-H). ^1H NMR (CDCl_3 , 500 MHz) δ_{H} (ppm): 1.10 (6H,s), 1.17-2.31 (10H, m), 2.47 (2H, s), 2.92 (2H, s), 4.27 (CH-N, m), 5.64 (NH, s), 7.37 (2H,d, J=8.2), 7.81 (2H,d, J=8.2). ^{13}C NMR (CDCl_3 , Me_4Si) δ_{C} (ppm): 23.39, 24.25 (2CH₂), 27.31 (2CH₂), 28.28 (2CH₃) 34.38, 38.33, 53.28, 58.37, 100.94 (CH-N), 123.34 (arom. and 2CH), 135.19 (arom. and 2CH), 137.73,

142.18, 145.67, 147.28 (C-NO₂), 170.55 (C=O), 187.39 (C=O). GC/MS: 416 (M⁺).

2-(cyclohexyl amino)-6,6-dimethyl-6,7-dihydro-3-(4-methoxyphenyl) benzofuran-4(5H) one (6e): Mp. 157 °C. IR (KBr) (ν_{\max} , cm⁻¹): 1658 (C=O), 3340 (N-H). ¹HNMR (CDCl₃, 500 MHz) δ_{H} (ppm): 1.07 (6H,s), 1.12-2.29 (10H, m), 2.27 (2H, s), 2.91 (2H, s), 4.19 (CH-N, m), 5.27 (3H, s), 5.55 (NH, s), 7.36 (2H,d, J=8.2), 7.74 (2H,d, J=8.2). ¹³C NMR (CDCl₃, Me₄Si) δ_{C} (ppm): 23.27, 24.44 (2CH₂), 27.71(2CH₂), 28.42 (2CH₃) 34.48, 38.27, 53.66, 55.61, 58.22, 100.28 (CH-N), 123.12 (arom. and 2CH), 135.08 (arom. and 2CH), 137.97, 142.66, 146.07, 148.07 (C-NO₂), 170.51 (C=O), 186.72 (C=O). GC/MS: 367 (M⁺).

3. RESULTS AND DISCUSSION

2-(Cyclohexylamino)- 6,7-dihydro benzofuran-4(5H)-ones were obtained by cyclohexyl isocyanide,

aldehydes, and dimedone or 1,3- cyclohexanedione in DMF for 2 h (Figure 1) in good yields (Table 1). The effect of temperature was studied by carrying out the reactions at different temperatures. The yields of reactions increased as the reaction temperature was raised. From these results, it was decided that refluxing temperature would be the best one for all reactions. The reaction proceeds very cleanly under reflux condition and free of side products.

The scope of the reaction respect to the aldehyde component was examined. As shown in Table 1, aromatic aldehydes containing both electron donating or withdrawing groups gave excellent yields.

In order to demonstrate the merit of the present work, we studied the results of the synthesis of these compounds in the presence of KHSO₄ or H₁₄[NaP₅W₃₀O₁₁₀] as catalysts, but they do not affect the reaction times and yield of products.

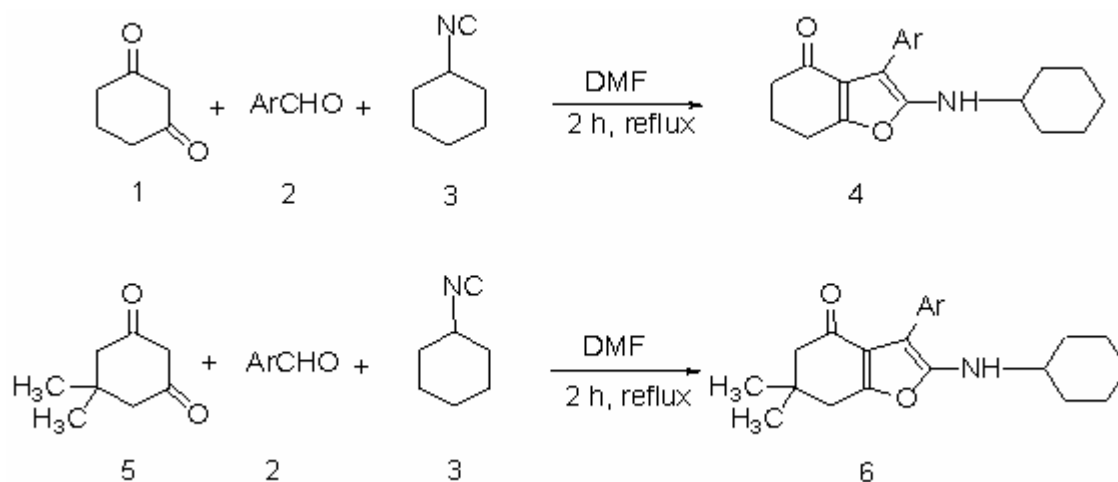


Figure 1. The reaction mechanism for the synthesis of 2-(Cyclohexylamino)- 6,7-dihydro benzofuran-4(5H)-ones

A reasonable mechanism for this reaction is suggested in Figure 2. The first step may involve a condensation reaction of 1,3-cyclohexanedione with the aromatic

aldehyde and further cyclohexylisocyanide attack to this intermediate to give the product.

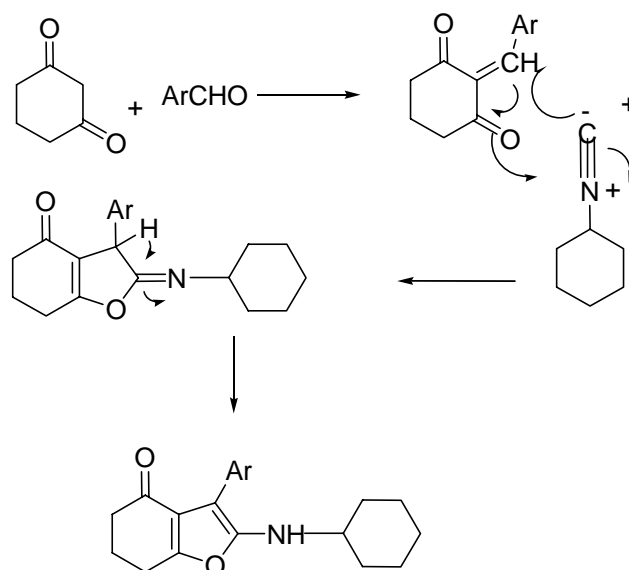


Figure 2. Proposed reaction mechanism in the presence of KHSO_4 or $\text{H}_{14}[\text{NaP}_5\text{W}_{30}\text{O}_{110}]$ as catalysts

Table 1. Synthesis of 4(5H) benzofuranones with different aldehydes

Entry	Substrate	Ar	Product	Time (min)	Yield(%) ^a
1	1	C_6H_5	4a	60	95
2	1	4-Cl- C_6H_4	4b	40	96
3	1	4- NO_2 - C_6H_4	4c	40	95
4	1	4-Br- C_6H_4	4d	40	95
5	1	4- CH_3O - C_6H_4	4e	80	96
6	5	C_6H_5	6a	60	93
7	5	4-Cl- C_6H_4	6b	40	95
8	5	4- NO_2 - C_6H_4	6c	40	94
9	5	4-Br- C_6H_4	6d	40	94
10	5	4- CH_3O - C_6H_4	6e	80	95

^aYields were provided by GC.

In conclusion, we have achieved an efficient process for the synthesis of biologically interesting functionalized benzofuran-4(5H)-one derivatives, starting from readily available and inexpensive reagents. The advantages of the present procedure are relatively short reaction times, simplicity of operation and work-up, and high yields of products which makes it a useful alternative to existing methods.

4. REFERENCES

- [1] Dean, F.M., "Advances in Heterocyclic Chemistry"; Katritzky, A.R., Ed.; *Academic*; New York ; 30: 167-238 (1982)
- [2] Nakanishi, K., "Natural Products Chemistry"; *Kodansha*; Tokyo, (1974).
- [3] Strenbach, D.D., Rossana, D.M., "Intramolecular diels-alder reactions of the furan diene: substituent and solvent effects", *Tetrahedron Lett.*, 23: 303(1982).
- [4] Jung, M.E., Street, L., "Synthetic studies on the avermectins: substituent effects on intramolecular Diels-Alder reactions of N-furfurylacrylamides and further reactions of the cycloadducts", *J. Am. Chem. Soc.*, 106: 8327 (1984).
- [5] Best, W.M., Wege, D., "Intramolecular diels-alder reactions of benzyne application to the total synthesis of mansonone E", *Tetrahedron Lett.*, 22: 4877 (1981).
- [6] Zhu, J., Bienayme, H., "Multicomponent Reactions", *Wiley-VCH*, Weinheim, (2005).

- [7] Litvinov, V.P., "Multicomponent cascade heterocyclisation as a promising route to targeted synthesis of polyfunctional pyridines", *Russ. Chem. Rev.*, 72: 69 (2003).
- [8] Ugi, I., Dömling, A., Hörl, W., "Multicomponent Reactions", *Endeavour*, 18: 115 (1994).
- [9] Tietze, L.F., Modi, A., "Multicomponent domino reactions for the synthesis of biologically active natural products and drugs", *Med. Res. Rev.*, 20: 304 (2000).
- [10] Ugi, I., Dömling, A., Werner, B., "Since 1995 the new chemistry of multicomponent reactions and their libraries, including their heterocyclic chemistry", *J. Heterocycl. Chem.*, 37: 647 (2000).
- [11] Passerini, M., "Passerini Reaction", *Gazz Chim. Ital.*, 52: 432 (1992).
- [12] Cristau, P.; Vors, J. P.; Zhu., "Rapid synthesis of cyclopeptide alkaloid-like para-cyclophanes", *J. QSAR Comb. Sci.*, 25: 519 (2006).
- [13] Ugi, I., Meyr, R., Fetzer, U., Steinbrückner, C., "Versuche mit Isonitrilen", *Angew. Chem.*, 71: 386 (1959).
- [14] Ugi, I., Steinbrückner, C., "Über ein neues Kondensations-Prinzip", *Angew. Chem.*, 72: 267 (1960).
- [15] Murakami, M., "New Catalyzed Three-Component Cycloadditions for the Synthesis of Eight-Membered Carbocycles", *Angew. Chem. Int. Ed.* 42: 718 (2003).
- [16] Bienayme, H., Hulme, C., Oddon, G., Schmitt, P., "Maximizing synthetic efficiency: Multi-component transformations lead the way", *Chem. Eur. J.*, 6: 3321 (2000).
- [17] Dömling, A., "Recent advances in isocyanide-based multicomponent chemistry", *Curr. Opin. Chem. Biol.*, 6: 306 (2002).
- [18] Hulme, C., Gore, V., "Multi-component Reactions: Emerging Chemistry in Drug Discovery" "From Xylocain to Crixivan", *Curr. Med. Chem.*, 10: 51 (2003).
- [19] Orru, R. V. A., De Greef, M., "Recent Advances in Solution-Phase Multicomponent Methodology for the Synthesis of Heterocyclic Compounds", *Synthesis*, 1471 (2003).
- [20] Balme, G., Bossharth, E., Monteiro, N., "Pd-Assisted Multicomponent Synthesis of Heterocycles", *Eur. J. Org. Chem.* 21: 4101 (2003).
- [21] Wangelin, J.C., Neumann, A., Gordes, H., Klaus, D., Strübing, S., Beller, D.M., "Multicomponent Coupling Reactions for Organic Synthesis: Chemoselective Reactions with Amide-Aldehyde Mixtures", *Chem. Eur. J.*, 9: 4286 (2003).
- [22] Dömling, A., Ugi, I., "Multicomponent Reactions with Isocyanides", *Angew. Chem. Int. Ed.* 39, 3168 (2000).
- [23] Marcaccini, S., Torroba, T., "The use of isocyanides in heterocyclic synthesis. A review", *Org. Prep. Proced. Int.*, 25: 141 (1993).
- [24] Ugi, I., Lohberger, S., Karl, R., "In Comprehensive Organic Synthesis," Trost, B. M. Fleming, I., Eds.; *Pergamon*: New York,; 2 (4-6): 1083 (1993).
- [25] Bamoharram, F.F., Heravi, M.M., Roshani, M., "Catalytic Method for Synthesis of Aspirin by a Green, Efficient and Recyclable Solid Acid Catalyst (Preyssler's Anion) at Room Temperature", *J. Chin. Chem. Soc.*, 54: 1017 (2007).
- [26] Heravi, M.M., Bakhtiari, K., Oskooie, H.A., "Communication: KHSO₄ Supported onto Bentonite, A Versatile Reagent for Aromatization of Hantzsch 1,4-Dihydropyridines", *J. Chin. Chem. Soc.*, 54, 579 (2007).
- [27] Heravi, M.M., Oskooie, H. A., Baghernejad, B., "Facile, Regioselective and Green Synthesis of Ortho-nitrophenoles Using NaNO₂, KHSO₄", *J. Chin. Chem. Soc.*, 54:767 (2007).