Communications In Catalysis
Vol. 1, No. 2, 2018, pp.13-20
DOI: 10.22049/CIC.2018.26245.1020

Azarbaijan Shahid Madani University

Molecular iodine-catalyzed combinatorial library synthesis of 2-amino-3-cyano-4*H*-pyran derivatives at ambient temperature

Adeleh Moshtaghi Zonouz*, Davoud Moghani

Department of Chemistry, Faculty of Science, Azarbaijan Shahid Madani University, Tabriz, Iran.

*Corresponding author. Fax: +984134327541

E-mail address: adelehmz@yahoo.com

Received: 2018-05-20, Revised: 2018-08-31, Accepted: 2018-08-31

Abstract

An efficient and simple synthesis of some 2-amino-3-cyano-4*H*-pyran derivatives was developed via the one-pot and three-component reaction of aldehydes, ethyl acetoacetate, and malononitrile in the presence of ammonium acetate at room temperature using catalytic amount of iodine. The key advantages of this method are the easy access to various substituted 2-amino-3-cyano-4*H*-pyran derivatives, short reaction times and high yields.

Keywords: 2-Amino-3-cyano-4*H*-pyrans, One-pot reaction, Multi-component reaction, Molecular iodine

Introduction

2-Amino-4*H*-pyran derivatives represent an important class of compounds. They are often used in cosmetics and pigments, and utilized as potentially biodegradable agrochemicals [1-3]. Polyfunctionalized 4*H*-pyrans also constitute a structural unit of many natural products [4, 5] and biologically interesting compounds which possess various pharmacological activities, such as antiallergic [6], antitumor [7], and antibacterial [8-12]. 4*H*-Pyran derivatives are also potential calcium channel antagonists [13] which are structurally similar to biologically active 1,4-dihydropyridines (1,4-DHPs).

Generally, 2-amino-4-aryl-3-cyano-4*H*-pyrans are synthesized by the cyclization of arylidenemalononitriles and active methylene compounds in the presence of organic bases such as piperidine [14], pyridine [15], triethylamine [16, 17]. Most of these methods involve the use of volatile solvents and require longer reaction time (~ 2 h) and present with the difficulty in recovering the catalyst. Recently, one-pot synthesis of these compounds has been reported using Mg/La mixed oxide [18] and MgO [19, 20] as the basic catalyst. Also, SiO_2 NP-catalyzed (silica nanoparticles, SiO_2 NPs) one-pot synthesis of 4*H*-pyran derivatives has been reported [21]. More recently, we reported the multicomponent synthesis of 2-amino-4*H*-pyran derivatives in aqueous medium [22-24].

Thus, in view of the importance of this class of compounds, the development of a simple, efficient and versatile method for the preparation of 2-amino substituted 4*H*-pyrans is an active area of research and there is a scope for further improvement towards milder reaction conditions and higher product yields.

In recent years, the use of molecular iodine as an inexpensive, non-toxic, and readily available catalyst for various organic transformations to afford the corresponding products in excellent yields has received considerable attention. The mild Lewis acidity associated with iodine has enhanced its usage in organic synthesis to realize several organic transformations using stoichiometric levels to catalytic amounts. Owing to numerous advantages associated with this eco-friendly element, iodine has been explored as a powerful catalyst for various organic transformations [25-28].

All these facts prompted us to use catalytic amount of molecular iodine in the multi-component reaction for a combinatorial synthesis of ethyl 2-amino-4-aryl-3-cyano-6-methyl-4*H*-pyran-3-carboxylates **2a-l** under ambient conditions.

Experimental

Typical procedure: Preparation of ethyl 2-amino-3-cyano-6-methyl-4-(2-methylphenyl)-4*H*-pyran-5-carboxylate *2j*

A 10 mL round-bottomed flask was charged with 2-methylbenzaldehyde **1j** (0.12 mL, 1 mmol), malononitrile (0.066 g, 1 mmol), ethyl acetoacetate (0.136 mL, 1 mmol), ammonium acetate (0.115 g, 1.5 mmol), iodine (0.038 g, 0.15 mmol) and a few drops of ethanol (5-6 drops). The mixture was then stirred at room temperature under an open atmosphere till the completion of reaction as indicated by TLC (Thin Layer Chromatography) (55 min). The precipitated solid was filtered, and washed with water. The crude product was recrystallized from ethanol to

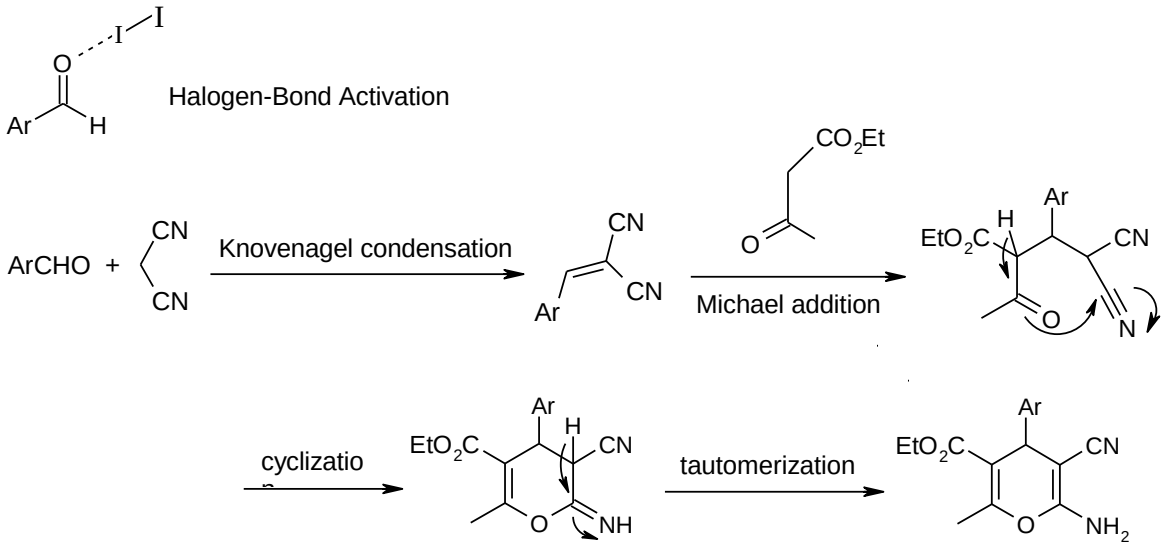
give **2j** as white crystals (0.229 g, 77 % yield). mp 140-141 °C; IR (KBr) $\overline{\nu}$ = 3426 (s), 3332 (s), 3202 (m), 2194 (s), 1690 (s), 1647 (m), 1608 (m), 1370 (m), 1259 (s), 1061 (s), 742 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 7.20 Hz, 3H, CH_3 ester), 2.38 (s, 3H, CH_3-6), 2.49 (s, 3H, CH_3), 3.98 (m, 2H, CH_2 ester), 4.51 (br, s, NH_2), 4.77 (s, 1H, C(4)-H), 7.10 (m, 4H, Ar-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.91 (CH_3 ester), 18.34 (CH_3-6), 19.27 (CH_3), 34.15 (C-4), 60.60 (CH_2 ester), 61.71 (C-3), 108.04 (C-5), 119.12 (CN), 126.59, 126.85 (C-4´, 5´), 127.87, 130.37 (C-3´, 6´), 135.21 (C-1´), 142.47 (C-2´), 157.02, 157.42 (C-2, 6), 165.91 (CO) ppm; MS (70 eV): m/z (%) = 298 (18.40) [M^+], 269 (13.89), 253 (6,69), 225 (8.35), 207 (100), 179 (28.92), 161 (15.53); ($C_{17}H_{18}N_2O_3$) Calcd.: C 68.44, H 6.08, N 9.39; found: C 68.65, H 5.98, N 9.20. X-ray data: CCDC 798881; $C_{17}H_{18}N_2O_3$, Mw = 298.33 g/mol, Triclini**c** P-1 (No. 2)**,** a = 8.563(2), b = 9.385(3), c = 10.605(3) Å, α= 106.41(3)˚, β = 101.11(4) ˚, γ = 102.90(3)˚, V = 766.4(4) $Å^3$, Z = 2, ρcalcd = 1.293 g/cm^3, μ(MoK_α) = 0.71069 Å), colorless, transparent, crystal dimensions = 0.40 × 0.48 × 0.72 mm, 3401 independent reflections.

Results and Discussion

In the efforts to develop an efficient and environmentally benign methodology for the synthesis of 2-amino substituted 4*H*-pyrans (**2**), we initiated our studies through a three-component reaction between benzaldehyde **1a** (1 mmol), ethyl acetoacetate (1 mmol), and malononitrile (1 mmol) in a few drops of ethanol at room temperature. No reaction was observed. Then ammonium acetate (1.5 mmol), as a basic catalyst, was added to the reaction mixture. After 2 hours, only 24% of product **2a** was obtained after recrystallization of the crude product from ethanol. Despite using a high quantity of ammonium acetate, 1,4-dihydropyridine was not detected as the product. We also carried out the reaction at refluxing temperature in ethanol for thermal decomposition of ammonium acetate to ammonia which can enhance the formation of pyridine rather than the pyran; again, in this case the pyran derivative was formed rather than the pyridine derivative. To improve the product yield, based on the literature survey [27], iodine was used in catalytic amount (15 mol%) and the reaction was carried out under similar conditions. To our surprise, a significant improvement in the yield of product **2a** (91%) was observed. The reaction was also carried out under similar conditions in the presence of catalytic amount of iodine without using ammonium acetate, but no reaction was observed. Using ammonium acetate and iodine are complementary to each other, because when ammonium acetate was used as a basic catalyst, low yield of pyran products was obtained (<25%), and when the reaction was carried out under similar conditions in the presence of catalytic amount of iodine without using ammonium acetate, no reaction was observed. Hence, the presence of one chemical enhances the effects of the second, and therefore, ammonium acetate and iodine have a synergistic effect in this methodology. In this case ammonium acetate acts as a basic catalyst, and the acidity of iodine

makes it capable of binding with the aldehyde carbonyl oxygen, thereby increasing the reactivity of the parent carbonyl compounds.

Thus halogen-bond activation mode [29, 30] is proposed for this iodine-catalyzed reaction. This mode of activation can catalyze both Knovenagel condensation and Michael addition reactions (Scheme 1).



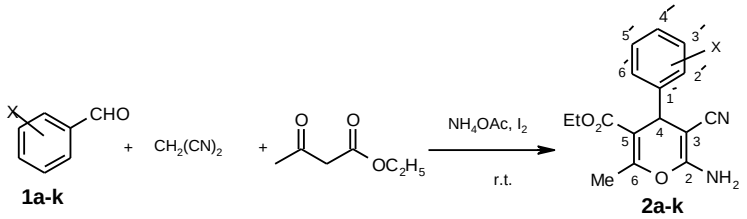
Scheme 1**.** Proposed mechanism for the formation of products **2**

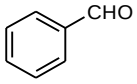
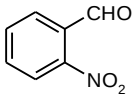
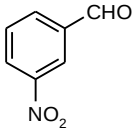
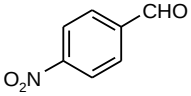
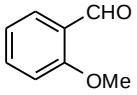
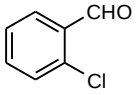
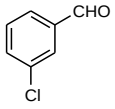
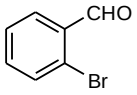
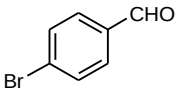
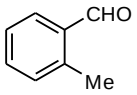
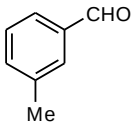
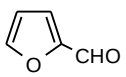
The improved conditions were then applied to a range of aldehyde substrates. Both electron-poor and electron-rich aldehydes were well tolerated. The results with different aldehydes are depicted in table 1. It was evident that different aromatic aldehydes with ethyl acetoacetate and malononitrile could be converted to the corresponding products in good to excellent yields in the presence of ammonium acetate and catalytic amount of iodine (15 mol%) at room temperature. The structure of **2j** was determined by X-ray crystallographic study [31]. Figure 1 shows the structure and the atomic numbering scheme used for the compound **2j**.

Selected bond distances and angles for compound **2j** are listed in tables 2 and 3 respectively.

The X-ray structural analysis of **2j** (Figure 1) shows that the 4*H*-pyran ring is in a flattened boat conformation, with the 4-aryl substituent in the pseudo axial position and orthogonal to the plane of the 4*H*-pyran ring. Moreover the methyl substituent in the phenyl ring lies on the same side as the C4-hydrogen on the 4*H*-pyran ring (synperiplanar, *sp*); thus crystal structure of compound **2j** shows the *sp* conformer. Also the carbonyl group ester is *trans* to the double bond of the 4*H*-pyran.

Table 1. Iodine-catalyzed three-component synthesis of 2-amino-4-aryl-3-cyano-4*H*-pyran derivatives[a].



Entry	Aldehyde	Time (min)	Product	Yield (%)	Mp (˚C)
1		110	**2a**	91[b]	190-192
2		45	**2b**	97[b]	177.5-178.5
3		55	**2c**	99[b]	187-188
4		75	**2d**	80[c]	175-176
5		90	**2e**	72[c]	196-197
6		25	**2f**	99[b]	191-192
7		70	**2g**	82[c]	180-180.5
8		35	**2h**	99[b]	183-184
9		100	**2i**	80[c]	180-181
10		55	**2j**	77[c]	140-141
11		65	**2k**	79[c]	176-177
12		45	**2l**	85[c]	203-204

[a]All reactions were conducted using aldehyde (1 mmol), ethyl acetoacetate (1 mmol), malononitrile (1 mmol), ammonium acetate (0.15 mmol), and molecular iodine (15 mol %) in a few drops of ethanol at room temperature. The structures of compounds **2a-l** were confirmed by the comparison of melting points and spectral data obtained in this study with those reported in the literature [22]. [b] Crude isolated yields. [c] After recrystallization.

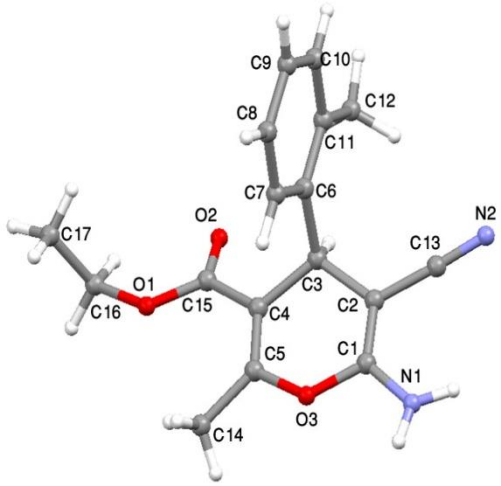


Figure 1. Crystal structure of ethyl 2-amino-3-cyano-6-methyl-4-(2-methylphenyl)-4*H*-pyran-5-carboxylate **2j**.

Table 2. Bond lengths (Å) of the compound $C_{17}H_{18}N_2O_3$.

N1-C1	1.3425 (19)	C3-C6	1.534 (2)
N2-C13	1.149 (2)	C4-C5	1.332 (2)
O1-C15	1.334 (2)	C4-C15	1.488 (2)
O1-C16	1.459 (2)	C5-C14	1.479 (3)
O2-C15	1.193 (2)	C6-C7	1.388 (2)
O3-C1	1.3624 (19)	C6-C11	1.390 (2)
O3-C5	1.3945 (17)	C7-C8	1.395 (2)
C1-C2	1.344 (2)	C8-C9	1.366 (3)
C2-C13	1.412 (2)	C9-C10	1.375 (3)
O1-C16	1.459 (2)	C10-C11	1.398 (2)
C2-C3	1.5181 (19)	C11-C12	1.497 (3)
C3-C4	1.504 (2)	C16-C17	1.430 (3)

Table 3. Bond angles (deg) of the compound $C_{17}H_{18}N_2O_3$.

C1-O3-C5	119.89 (12)	C7-C6-C11	119.40 (15)
N1-C1-C2	128.14 (15)	C7-C6-C3	118.67 (16)
N1-C1-O3	110.41 (14)	C11-C6-C3	121.82 (14)
C2-C1-O3	121.44 (12)	C6-C7-C8	120.58 (19)
C1-C2-C13	119.65 (13)	C9-C8-C7	120.04 (19)
C1-C2-C3	122.09 (13)	C8-C9-C10	119.78 (17)
C13-C2-C3	117.81 (14)	C9-C10-C11	121.3 (2)
C4-C3-C2	109.77 (13)	C6-C11-C10	118.92 (17)
C4-C3-C6	112.59 (12)	C6-C11-C12	121.87 (15)
C2-C3-C6	110.14 (12)	C10-C11-C12	119.20 (18)
C5-C4-C15	124.74 (15)	N2-C13-C2	177.34 (17)
C5-C4-C3	122.42 (13)	O2-C15-O1	122.96 (14)
C15-C4-C3	112.81 (14)	O2-C15-C4	121.94 (16)
C4-C5-O3	121.33 (14)	O1-C15-C4	115.10 (15)
C4-C5-C14	130.93 (14)	C17-C16-O1	110.85 (19)
O3-C5-C14	107.74 (14)		

Conclusion

In summary, the one-pot three-component reaction protocol developed in the present study offers a fast and an efficient method for the synthesis of 2-amino substituted 4*H*-pyrans at room temperature. The experimental procedure is simple and represents an attractive alternative to existing methods. This reaction protocol conforms to several green chemistry principles coupled with the potential for developing combinatorial libraries.

Supplementary material

Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Center (CCDC, No. 798881 for compound **2j**). The above-mentioned data may be obtained free of charge from the Director, CCDC, 12, Union Road, Cambridge CB2 1EZ [FAX +44 (1223) 336-033] or E - mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk.

Acknowledgements

The authors acknowledge the research office of Azarbaijan Shahid Madani University for financial support. We are also grateful to Dr. Michael Serafin from the institute of inorganic chemistry of the Giessen University for X-ray analysis.

References

[1] Ellis. G. P, Weissberger. A, Taylor. E.C, chem. Heterocyc. com. In Chromenes, Chromanes and Chromeones. Wiley: New York. 1977, P.13.

[2] Abdel Galil. F. M, Riad. B.Y, Sherif. S.M, Elnagdi. M. H, Chem. Lett. **1982,** 11, 1123.

[3] Hafez. E. A, Elnagdi. M.H, Elagamey. A. A, El-Taweel. F. A, Heterocyl., 1987,26, 903.

[4] Kuthan. J, Adv. Heterocycl. Chem, 1983, vol. 34, 145.

[5] Hatakeyama. S, Ochi. N, Numata. H, Takano. S. J, Chem. Soc. Chem. Commun, 1988,17, 1202.

[6] Witte. E. C, Neubert. P, Roesoh. A, Ger Offen. DE, 1986, 3427985.

[7] Wang. J , Liu. D, Zhang. Z. J, Shan. S, Han. X, Srinivasula. S.M, Croce. C. M, Alnemri. E.S, Huang. Z, Proc. Natl. Acad. Sci. U.S.A, 2000, 97, 7124.

[8] El-Saghier. A. M. M, Naili. M. B, Rammash. B. Kh, Saleh. N. A, Kreddan. K. M, Arkivoc xvi, 2007,83.

[9] Kumar. R. R, Perumal. S, Senthilkumar. P, Yogeeswari. P, Sriram. D, Bioorg. Med. Chem. Lett, 2007,17, 6459.

[10] Fairlamb. I. J. S, Marrison. L. R, Dickinson. J. M, Lu. F.J, Schmidt. J. P, Bioorg. Med. Chem.2004,12, 4285.

[11] Aytemir. M. D, Erol, D. D, Hider. R. C, Özalp. M, Turk, J. Chem, 2003, 27, 757.

[12] Kidwai. M, Saxena. S, Khan. M. K. R, Thukral. S. S, Bioorg. Med. Chem. Lett, 2005,15, 4295.

[13] Suarez. M, Salfran. E, Verdecia. Y, Ochoa. E, Alba. L, Martin. N, Martinez. R, Quinteiro. M, Seoane. C, Novoa. H, Blaton. N, Peeters. O. M, De Ranter. C, Tetrahedron, 2002,

[14] 58, 953.

[15] Martin. N, Pascual. C, Seoane. C, Soto. J. L, Heterocyce.1987,26, 2811.

[16] Harb. A. F, Hesien. A. M, Metwally. S. A, Elnagdi. M. H, Liebigs Ann. Chem,1989, 585.

[17] Zayed. S. E, Abou Elmaged. E. I, Metwally. S. A, Elnagdi, M. H,

Collect. Czech. Chem. Commun.1991, 56, 2175.

[18] Elnagdi. M. H, Adbel-Motaleb. R. M, Mustafa. M. J, Heterocycl. Chem, 1987,24, 1677.

[19] Seshu Babu. N, Pasha. N, Venkateswara Roa. K. T, Sai Prasad. P. S, Lingaiah. N, Tetrahedron Lett,2008,49, 2730.

[20] Kumar. D, Reddy. V. B, Mishra. B. G, Rana. R. K, Nadagouda. M. N, Varma. R. S, Tetrahedron, 2007, 63, 3093.

[21] Kumar. D, Reddy, V. B, Sharad. Sh, Dube. U, Kapur. S, Eur. J. Med. Chem, 2009,44, 3805.

[22] Banerjee. S, Horn. A, Khatri. H, Sereda, G, Tetrahedron Lett, 2011,52, 1878.

[23] Moshtaghi. Z. A, Eskandari. I, Moghani. D, Chem. Sci. Trans, 2012, 1, 91.

[24] Moshtaghi. Z. A, Eskandari. I, Khavasi. H. R, Tetrahedron Lett, 2012, 53, 5519.

[25] Moshtaghi. Z. A, Moghani. D, Okhravi. S, Current Chem. Lett, 2014, 3, 71.

[26] Zolfigol. M. A, Salehi. P, Khorramabadi-zad. A, Shayegh. M, J. Mol. Catal. A, 2007, 261, 88.

[27] Yadav. J. S, Reddy. B. V. S, Rao. C, Reddy. V. M, J. Synthesis, 2003,247.

[28] Bhosale. R. S, Magar. Ch. V, Solanke. K. S, Mane. S. B, Choudhary. S. S, Pawar. R. P, Synth. Commun, 2007,37, 4353.

[29] Ko. S, Sastry. M. N. V, Lin. C, Yao. C. F, Tetrahedron Lett, 2005,46, 5771 references therein.

[30] Von der Heiden. D, Bozkus. S, Klussmann. M, Breugst. MJ, Org. Chem, 2017, 82 (8), 4037.

[31] Breugst. M, Von der Heiden. D, Chem. Eur. J, 2018, 24, 9187.

[32] (a) Sheldrick. G.M, SHELXS-86, Program for the Solution of Crystal Structures, Universität Göttingen, (b) Sheldrick. G.M, SHELXL-1986,93, Program for Crystal Structure Refinement, Universität Göttingen, 1993.