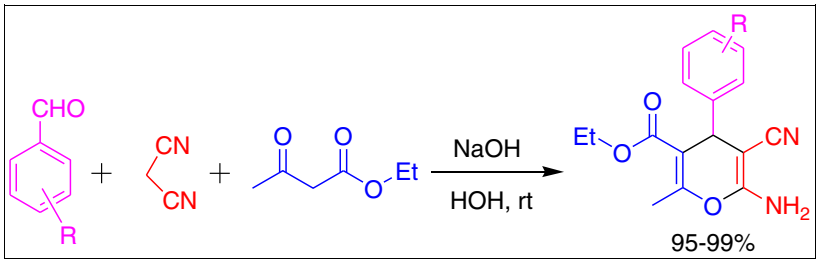
An Efficient, Multicomponent, One-pot Synthesis of Tetra Substituted Pyrans in Water

R. Pagadala, S. Maddila, and S. B. Jonnalagadda*

School of Chemistry & Physics, University of KwaZulu-Natal, Westville Campus, Chiltern Hills, Durban 4000, South Africa
*E-mail: jonnalagaddas@ukzn.ac.za

Additional Supporting Information may be found in the online version of this article.
Received June 27, 2013
DOI 10.1002/jhet.2125
Published online 00 Month 2014 in Wiley Online Library (wileyonlinelibrary.com).



A new and environmentally benign multi-component synthesis of tetra substituted 4*H*-pyran derivatives is developed via the one-pot reaction of an aromatic aldehyde, malononitrile, and 1,3-diketone in the presence of NaOH with water as the solvent at RT. The reaction is efficient and affords excellent yields of the products.

J. Heterocyclic Chem., **00,** 00 (2014).

INTRODUCTION

The heterocyclic synthesis is crucial, because heterocyclic derivatives occupy a central role in our increasingly technological society. Heterocyclic compounds have retained their prominence as an integral part of new drug discovery. Multicomponent reactions have proved to be powerful and efficient bond-forming tools in modern heterocyclic and medicinal chemistry [1]. The pharmaceutical industries. which continually search for new chemicals and drugs need to be cognizant of green solutions for their syntheses [2]. Water [3] and ionic liquids [4] have attracted attention as eco-friendly solvents for organic synthesis.

The synthesis of poly-functionalized 4*H*-pyrans is important as they represent key building blocks of several natural and synthetic heterocyclic compounds [5,6]. 4*H*-Pyrans are attractive to researchers because of their pharmacological and biological activities such as antitumor, antibacterial, antiviral, spasmolytic, antifungal, anti-inflammatory, and anti-anaphylactic properties [7–13]. Thus, in view of their wide utility, the synthesis of such compounds is an appealing challenge.

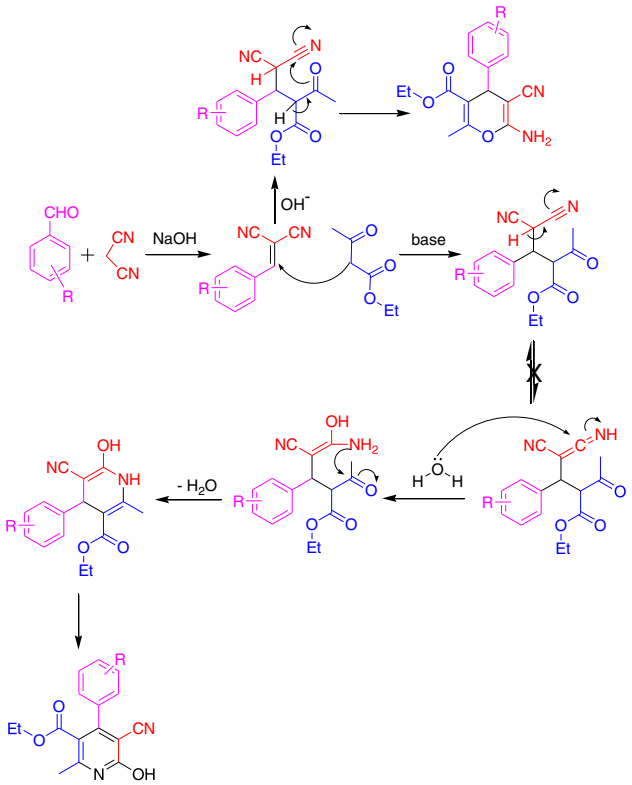
Of the many methods available for the synthesis of 4*H*-pyrans, the most widely used is the one-pot, three-component synthesis, catalyzed by metal oxides and mixed metal oxides [14–16], Cu(II) oxymetasilicate [17], organic bases [18], Baker's yeast [19], and ionic liquids [20]. However, many of the synthetic methods for 4*H*-pyrans reported so far suffer from one or more drawbacks. Most require prolonged reaction times, expensive catalysts, harsh reaction conditions, and tedious work-ups. Many of those provide moderate yields. Dong *et al.* have stated that some pyridines can only be obtained in the presence of ethanol/methanol [21]. There is still wide scope to develop new efficient, cost-effective and eco-sustainable methods for the synthesis of tetra substituted pyrans. To our knowledge, there are no similar reports in the literature on the synthesis of tetra-substituted 4*H*-pyrans.

RESULTS AND DISCUSSIONS

Our studies were aimed at developing new selective and eco-friendly approaches for the preparation of heterocyclic compounds. In this communication, we report a simple and environmentally compatible method to synthesize 4*H*-pyrans under moderate conditions in good yields with water as the solvent. As a part of this, we embarked on the synthesis of 4*H*-pyrans under alkaline conditions with water as the solvent. The optimization of the reaction conditions, including the quantity of base, reaction medium, and nature of base were investigated, and the results are summarized in Table 1. The described method accommodated a wide spectrum of three-component reactions with good to excellent yield of the target compounds.

To generalize our methodology, several pyrans **4a–i** were synthesized. Reactions were carried out simply by reacting various substituted benzaldehydes **2a** (1.0 equiv.), malononitrile **3** (1.0 equiv.), and 1, 3-diketone **1** (1.0 equiv.) in the presence of aqueous NaOH at RT (Scheme 1). All the synthesized compounds were characterized and confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra. Compounds **4a**, **4h**, and **4i** were further identified by ^{15}N-NMR (GHSQC) to confirm the presence

of the $-NH_2$ group in their structure. The reaction mechanism may tentatively be visualized to occur via a tandem sequence of the reactions depicted in the reaction schemes in Mechanism 1.



Mechanism 1. Plausible reaction mechanism for the synthesis of tetra-substituted 4*H*-pyrans.

Interestingly, all the reactions are clean, and the products were obtained with simple workup, filtration, and washing with water. As the purity of the product was high, no further recrystallization was required except for **4b** and **4e**, which were further purified by column chromatography. The yields of the products are presented in Table 2.

This study describes an efficient approach for the synthesis of substituted pyrans by using NaOH in aqueous conditions. Water plays an important role in the three-component oriented synthesis of substituted 4*H*-pyrans, because the hydrogen bonds formed facilitate the dual activation of both electrophile and nucleophiles. Hence, water has enhanced characteristics relative to organic solvents for the synthesis of the pyrans reported here.

CONCLUSION

In conclusion, for the first time, we report a novel and one-pot tandem method involving a three-component system for synthesizing a series of tetra-substituted 4*H*-pyrans by using NaOH as catalyst in water. Our method has many advantages over the existing procedures, such as elimination of organic solvents, high yields, simple work-up, cost-effectiveness, non-toxic catalyst, and no column-chromatography requirement in most cases. In this procedure, no organic solvent is used except as an eluent in TLC.

EXPERIMENTAL

General remarks. All chemicals used were reagent grade and were used as received without further purification. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 25°C at 400 and 100 MHz (Bruker Avance, Switzerland) instrument respectively, using TMS as internal standard. Chemical shifts are given in parts per million (ppm). The FT-IR spectroscopy of samples were carried out on a Perkin Elmer (Maryland, US) Precisely 100 FT-IR spectrometer in the 400–4000 cm^{-1} region. Liquid chromatography–mass spectrometry (LCMS) mass spectra were recorded on a Mass Spectrometry and Proteomics Center low resolution mass spectrometer operating at 70 eV. Elemental analyses were carried out using a Perkin-Elmer CHNS Elemental Analyzer model 2400. Melting points are uncorrected and were recorded on a hot stage melting point apparatus Ernst Leitz Wetzlar, Germany. Reactions were monitored, and the purity of products was checked out on TLC on aluminum-backed plates coated with Kieselgel 60 F254 silica gel, visualizing the spots under UV light and iodine chamber.

General experimental procedure for the synthesis of 4*H*-Pyran. Water (5 mL) was added to the solution containing freshly distilled benzaldehyde (1.0 mmol), malononitrile (1.0

Table 1

Optimization of reaction conditions of the multicomponent reactions.

Entry	Product No.	Base	Amount (equiv.)	Solvent	Time (h)	Yield [a](%)
1	4a	NaOH	2.0	H_2O	8.0	65.0
2	4a	NaOH	4.0	H_2O	4.0	99.0
3	4a	TEA	4.0	H_2O	4.0	20.0
4	4a	K_2CO_3	4.0	CH_2Cl_2	8.0	0.0
5	4a	K_2CO_3	4.0	DMF	8.0	0.0
6	4a	K_2CO_3	4.0	H_2O	8.0	50.0
7	4a	TEA	4.0	CH_2Cl_2	6.0	0.0
8	6a	TEA	4.0	DMF	6.0	0.0

[a]Isolated yields.

Scheme 1. Synthesis of tetra-substituted 4*H*-pyran (**4a–i**) derivatives via a three-component coupling of ethylacetoacetate (**1**), substituted aromatic aldehydes (**2a–i**), and malononitrile (**3**).

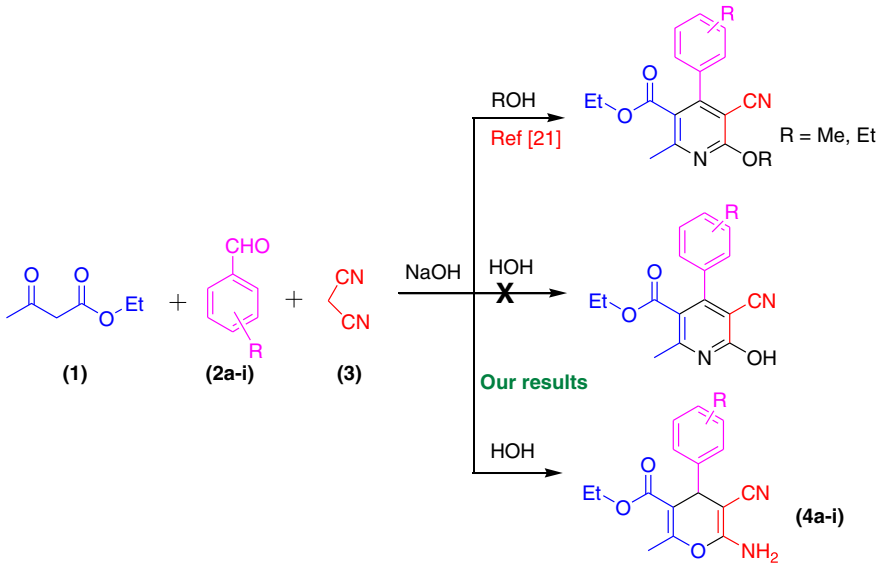


Table 2

Multicomponent reaction for the synthesis of tetra- substituted 4*H*-pyrans (**4a–i**).

Entry	Product no.	R_1	Time (h)	Yield [a] (%)	MP (°C)/(lit)
1	4a	H	4.0	99.0	186–188 (192) [15]
2	4b	4-OCH_3	4.0	95.0	130–132 (136) [15]
3	4c	4-Br	3.5	98.0	172–173 (172–174) [22]
4	4d	4-Cl	4.0	97.0	166–168 (170) [15]
5	4e	4-NO_2	4.0	96.0	178–180 (182) [15]
6	4f	4-OH	4.0	99.0	179–181 (175–177) [23]
7	4g	4-$N(CH_3)_2$	4.0	98.0	163–165
8	4h	2-Cl	3.5	98.0	168–170
9	4i	2-Br	3.5	96.0	176–178

[a]Isolated yields.

mmol) and ethylacetoacetate (1.0 mmol). After 5 min of stirring 15 ml of NaOH (4.0 equiv.) solution was added, stirring at RT. The reaction mixture was stirred at RT for 4 h. After, the starting material was consumed (monitored by TLC [EtOAc/hexane = 4:6)] and then poured saturated aqueous NaCl (15 mL) solution into the reaction mixture. The reaction mixture was stirred for 30 min and set on one side to separate solid. Solid deposit was collected by the filtration and was washed with water to give a pure product **4a** (99% yield) as a white solid.

The spectral (IR, 1H-NMR, and MS) data of the unknown products are given.

6-Amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylic acid ethyl ester (4a). White solid; ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 1.05(3H, t, *J* = 7.0 Hz), 2.33 (3H, s), 3.97–4.00 (2H, m), 4.31 (1H, s), 6.92 (2H, s), 7.15–7.35 (5H, m); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 13.6, 18.0, 57.1, 60.1, 107.1, 119.6, 126.7, 127.1, 128.3, 144.8, 156.5, 158.4, 165.4; IR (KBr, cm^{-1}) 3395, 3327, 2189, 1682; HRMS of [$C_{16}H_{16}N_2O_3$ + Na] (*m/z*): 307.1066 (100%); calcd mass: 307.1059; Anal. calcd: C 67.59, H 5.67, N 9.85%. Found: C 67.57, H 5.68, N 9.88%.

6-Amino-5-cyano-2-methyl-4-(4-(dimethylamino)phenyl)-4H-pyran-3-carboxylic acid ethyl ester (4g). Off-white solid; ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 0.94 (3H, t, *J* = 7.0 Hz), 2.37 (3H, s), 3.0 (6H, s), 3.9 (2H, q, *J* = 4.5 Hz), 4.84 (1H, s), 6.83 (2H, d, *J* = 9.1 Hz), 6.91 (2H, s), 7.81 (2H, d, *J* = 9.1 Hz); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 13.5, 18.0, 35.1, 56.2, 60.0, 68.5, 105.4, 119.1, 126.6, 127.8, 128.9, 144.4, 157.6, 158.8, 165.6; IR (KBr, cm^{-1}) 3402, 3328, 2197, 1679; LCMS of [$C_{18}H_{21}N_3O_3 + H^+$] (*m/z*): 328 (100%); Anal. calcd: C 66.04, H 6.47, N 12.84%. Found: C 66.08, H 6.45, N 12.87%.

6-Amino-5-cyano-2-methyl-4-(2-chlorophenyl)-4H-pyran-3-carboxylic acid ethyl ester (4h). Off-white solid; ^{1}H-NMR (400 MHz, DMSO-d_6) δ = 0.93 (3H, t, *J* = 7.0 Hz), 2.33 (3H, s), 3.89 (2H, q, *J* = 4.5 Hz), 4.87 (1H, s), 6.92 (2H, s), 7.17–7.28 (4H, m); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 13.5, 18.0, 35.2, 56.0, 60.0, 105.9, 119.1, 127.7, 128.3, 129.2, 129.7, 131.9, 142.0, 157.7, 158.4, 165.1; IR (KBr, cm^{-1}) 3425, 3330, 2194, 1684; LCMS of [$C_{16}H_{15}ClN_2O_3 + H^+$] (*m/z*): 319 (100%); Anal. calcd: C 60.29, H 4.74, N 8.79%. Found: C 60.35, H 4.72, N 8.84%.

6-Amino-5-cyano-2-methyl-4-(2-bromophenyl)-4H-pyran-3-carboxylic acid ethyl ester (4i). Off-white solid; ^{1}H-NMR

(400 MHz, DMSO-d_6) $\delta = 0.94$ (3H, t, $J = 7.0$ Hz), 2.33 (3H, s), 3.89 (2H, q, $J = 4.0$ Hz), 4.87 (1H, s), 6.91 (2H, s), 7.12–7.55 (4H, m); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 13.5, 18.0, 35.1, 56.2, 60.0, 106.1, 119.0, 122.6, 128.3, 128.6, 129.7, 132.4, 143.8, 157.7, 158.3, 165.1; IR (KBr, cm^{-1}) 3429, 3334, 2190, 1685; LCMS of $[C_{16}H_{15}BrN_2O_3 + H^+]$ (*m/z*): 364 (100%); Anal. calcd: C 52.91, H 4.16, N 7.71%. Found: C 52.87, H 4.21, N 7.78%.

Acknowledgments. We gratefully acknowledge the School of Chemistry and Physics for the facilities and the University of KwaZulu-Natal, Durban for funding.

REFERENCES AND NOTES

[1] (a) Lu, P.; Wang, Y. G. Synlett 2010, 165; (b) Ganem, B. Acc Chem Res 2009, 42, 463; (c) Dömling, A. Chem Rev 2006, 106, 17; (d) Ramon, D. J.; Yus, M. Angew Chem Int Ed 2005, 44, 1602; (e) Orru, R. V. A.; de Greef, M. Synthesis 2003, 1471; (f) Ugi, I.; Heck, S. Comb Chem 2001, 4, 1; (g) Weber, L.; Illgen, K.; Almstetter, M. Synlett 1999, 366.

[2] (a) Maddila, S.; Jonnalagadda, S. B. Bull Chem Soc Ethiopia 2012, 26, 121; (b) Jonnalagadda, S. B. Pullabhotla, V. S. R. Maddila, S.; Estelle, C. C. Int J Chem 2012, 1, 119; (c) Ramakanth, P.; Jyotsna, S. M.; Himani, N. C.; Venkateshwarlu, J.; Uppalaiah, K.; Udayini, V. Med Chem 2012, 7, 325; (d) Ramakanth, P.; Jyotsna, S. M.; Himani, N. C.; Nagender Reddy, P. J Heterocycl Chem 2010, 47, 350; (e) Ramakanth, P.; Parvez, A.; Jyotsna, S. M. J Coord Chem 2009, 62, 4009.

[3] (a) Li, C. J Chem Rev 1993, 93, 2023; (b) Ulf, M. L. Chem Rev 2002, 102, 2751.

[4] (a) Seddon, K. R. J Chem Technol Biotechnol 1997, 68, 351; (b) Welton, T. Chem Rev 1999, 99, 2071; (c) Davis, J. H.; Fox, P. A. Chem Commun 2003, 1209.

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

[6] Gonzalez, R.; Martin, N.; Seoane, C.; Marco, J. L.; Albert, A.; Cano, F. H. Tetrahedron Lett 1992, 33, 3809.

[7] Zhang, S.; Fernandez, F.; Hazeldine, S.; Deschamps, J.; Zhen, J.; Reith, M. E. A.; Dutta, A. K. J Med Chem 2006, 49, 4239.

[8] Xu, Z. Q.; Pupek, K.; Suling, W. J.; Enache, L.; Flavin, M. T. Bioorg Med Chem 2006, 14, 4610.

[9] Souza, L. C.; Santos, A. F.; Goulart Sant' Ana, A. E.; Oliveira Imbroisi, D. Bioorg Med Chem 2004, 12, 865.

[10] Ndi, C. P.; Semple, S. J.; Griesser, H. J.; Pyke, S. M.; Barton, M. D. Phytochemistry 2007, 68, 2684.

[11] Perez-Sacau, E.; Diaz-penate, R. G.; Estevez-Braun, A.; Ravelo, A. G.; Garcia-Castellano, J. M.; Pardo, L.; Campillo, M. J Med Chem 2007, 50, 696.

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

[13] Schiller, R.; Tichotova, L.; Pavlik, J.; Buchta, V.; Melichar, B.; Votruba, I.; Kunes, J.; Spulak, M.; Pour, M. Bioorg Med Chem Lett 2010, 20, 7358.

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

[15] Bhattacharyya, P.; Pradhan, K.; Sanjay, P.; Das, A. R. Tetrahedron Lett 2012, 53, 4687.

[16] Babu, N. S.; Pasha, N.; Rao, K. T. V.; Prasad, P. S. S.; Lingaiah, N. Tetrahedron Lett 2008, 49, 2730.

[17] Heravi, M. M.; Beheshtiha, Y. S.; Pirnia, Z.; Sadjadi, S.; Adibi, M. Syn Commun 2009, 39, 3663.

[18] (a) Martin, N.; Seoane, C.; Soto, J. L. Tetrahedron 1988, 44, 5861; (b) Heber, D.; Edmont, V.; Stoyanov, Synthesis 2003, 227; (c) Jin, T. S.; Xiao, J. C.; Wang, S. J.; Li, T. S.; Song, X. R. Synlett 2003, 2001; (d) Balalaie, S.; Bararjanian, M.; Amani, A. M.; Movassagh, B. Synlett 2006, 263; (e) Jin, T. S.; Wang, A. Q.; Wang, X.; Zhang, J. S.; Li, T. S. Synlett 2004, 871.

[19] Pratap, U. R.; Jawale, D. V., Netankar, P. D.; Mane, R. A. Tetrahedron Lett 2011, 52, 5817.

[20] Peng, Y.; Song, G. Catal Commun 2007, 8, 111.

[21] Xin, X.; Wang, Y.; Kumar, S.; Liu, X.; Lin, Y.; Dewen D. Org Biomol Chem 2010, 8, 3078.

[22] Guo-Ping L.; Chun C. J Heterocycl Chem 2011, 48, 124.

[23] Jitender M. K.; Ankita C. Green Chem Lett Rev 2012, 5, 633.