

Hindawi Publishing Corporation
Journal of Chemistry
Volume 2013, Article ID 785930, 7 pages
<http://dx.doi.org/10.1155/2013/785930>



Research Article

Synthesis of Polyfunctionalized 4H-Pyrans

Manisha Bihani, Pranjal P. Bora, and Ghanashyam Bez

Department of Chemistry, North Eastern Hill University, Shillong 793022, India

Correspondence should be addressed to Ghanashyam Bez; ghanashyambez@yahoo.com

Received 29 June 2012; Accepted 5 November 2012

Academic Editor: Joaquin Campos

Copyright © 2013 Manisha Bihani et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Amberlyst A21 catalyzed one-pot three-component coupling of aldehyde and malononitrile with active methylene compounds such as acetylacetone and ethyl acetoacetate for the synthesis of pharmaceutically important polyfunctionalized 4H-pyrans has been reported. Simple experimental procedure, no chromatographic purification, no hazardous organic solvents, easy recovery and reusability of the catalyst, and room temperature reaction conditions are some of the highlights of this protocol for the synthesis of pharmaceutically relevant focused libraries.

1. Introduction

Development of efficient and practical catalyst for organic transformation to synthesize valuable target compounds is one of the most important research areas in academia and industry [1, 2]. Homogeneous catalysts are finding enormous applications in diverse aspects of synthetic chemistry [3] in recent years. However, separation of the catalysts from the products, toxicity associated with such catalysts, and their disposal are limiting their applications in general. Therefore, resin-bound catalysts are getting increasing importance in organic synthesis in recent years, primarily due to their easy removal from reactions by filtration. Additionally, resin-bound catalysts can be used in excess to drive a reaction into completion without introducing any difficulty in purification. Nonetheless, the use of resin-bound catalyst provides some additional advantages such as easy recovery of the catalyst, easy handling, and enhanced safety features for potentially explosive reagents.

Recently, huge environmental awareness has forced the synthetic chemists to design environmentally compatible protocols devoid of hazardous chemical ingredients to eliminate the generation of toxic waste and byproducts. Organic solvents are considered to be the highest contributors toward environmental waste. Therefore, the use of environmentally compatible solvents, such as ethanol or water, is gaining considerable significance. Of late, the emergence of combinatorial synthesis by multicomponent reaction (MCR) has

brought about a paradigm shift in synthetic reaction designs which are made to address the issues of atom economy, economy of steps, and environmental safety. Synthesis of focused libraries for easy access of biologically important scaffolds for their SAR studies has made MCRs very useful tool in synthetic organic chemistry as well as in drug discovery programs. If such MCRs can be performed in environmentally benign solvents in the presence of reusable resin-bound catalyst at room temperature, it is possible to accomplish the synthesis of desired compounds without percolating anything to the environment in the entire reaction process. Therefore, the discovery of novel synthetic methodologies to facilitate the preparation of compound libraries using MCRs without use of hazardous solvent is the focal point in industry and academia [4, 5].

Polyfunctionalized 4H-pyran, a major constituent of many natural products [6–8], is known for its wide array of biological activities such as antitumor, antibacterial, antiviral, spasmolytic, and antianaphylactic [9–12]. Recent findings have suggested that the compounds having 4H-pyran core are useful for the treatment of Alzheimer, Schizophrenia, and Myoclonus diseases [13]. Given the important properties possessed by polyfunctionalized 4H-pyrans, it is natural to have many synthetic endeavors to achieve the target by adopting simple reaction strategies. Commonly used approach for the said synthesis include two-step or three-component synthesis catalyzed by organic bases [14, 15], ionic liquids [16, 17], hexadecyltrimethyl ammonium bromide [18], MgO

[12], Mg/La mixed metal oxides [19], Cu(II) oxymetasilicate [20], rubidium fluoride [21], and Pd/C [6–8]. In spite of being effective, most of these methods suffer from drawbacks such as poor catalyst recovery, high reaction temperature, moderate yields, prolonged reaction time, and the use of hazardous organic solvents in reaction medium and for chromatographic purification. Recently, Zhang et al. [22] have reported a novel MgO–SnO₂ solid superbase as a high-efficiency catalyst for one-pot solvent-free synthesis of polyfunctionalized 4*H*-pyran derivatives at room temperature, but application of this system is limited by the requirement of catalyst synthesis before use. In a bid to use environmentally benign reaction conditions, Pratap et al. [23] reported a biocatalytic approach to achieve polyfunctionalized 4*H*-pyrans to avoid aforesaid drawbacks, but the time taken for completion of the reaction was very high (30 h). Given the said drawbacks, development of an environmentally benign catalytic method at room temperature will definitely add credence to the existing knowledge for the synthesis of 4*H*-pyrans. Here, we report an extremely efficient method for the synthesis of polyfunctionalized 4*H*-pyrans in ethanolic medium at room temperature in the presence of a catalytic amount of highly reusable ion exchange polystyrene resin, Amberlyst A21 (Scheme 1).

2. Results and Discussion

Tertiary amine substituted macroreticular ion exchange polystyrene resins such as Amberlyst, Amberlite, and Dowex have found a lot of applications in recent years, because they are widely available at very low cost, carry a variety of functionalities, and have high loading capacities. Among these resins, Amberlyst A21 is known for high catalytic activity [24–27] and selectivity [28, 29], long lifetime, superior resistance to thermal, mechanical and osmotic shock, excellent stability, and low leaching. Moreover, it works with equal efficiency in both aqueous and organic solvents. In order to explore the catalytic activity of Amberlyst A21 for the synthesis of polyfunctionalized 4*H*-pyrans, we stirred a mixture of *m*-nitrobenzaldehyde (1 mmol), malononitrile (1 mmol), and acetylacetone (1 mmol) in ethanol in the presence of a catalytic amount of Amberlyst A21 (50 mg/mmol of aldehyde) and the reaction was found to be complete in 3 h. The reaction mixture was filtered and the solid resin was washed with warm ethanol (60 °C) to elute all the compounds from the resin. Reduction of volume of the combined filtrate, followed by keeping in a refrigerator overnight gave the crystalline products in excellent yield (85%).

Given the fact that the reactivity of polystyrene resin is often dictated by the accessibility of the reactants to the catalytic sites *via* swelling of the resin in solvents, we wanted to explore the solvent effect on catalytic behavior of Amberlyst A21. It was observed that the halogenated solvents such as dichloromethane and chloroform gave very low yield in spite of having very good swelling property, while in acetonitrile and DMF the reaction yields did not increase considerably (Table 1) under similar reaction conditions. In neat and aqueous medium, the reaction did not progress at all.

The optimum catalyst loading was also explored for the said reaction under similar reaction conditions (Table 2). Addition of 10 mg Amberlyst A21 against 1 mmol of *m*-nitrobenzaldehyde led to very slow conversion (45% yield) to the product and the reaction was not complete in 12 h. Increase of catalyst loading to 20 mg/mmol of aldehyde led to complete conversion of the starting material in 12 h to give 80% yield of the desired product. Although the increase of catalyst loading to 30 mg led to sharp decrease in reaction time with better yield (85%), further increase of catalyst loading to 40 mg and 50 mg/mmol of aldehyde hardly had any appreciable effect on the reaction time and the yield.

To study the reusability of the catalyst, we choose *m*-nitrobenzaldehyde as model substrate to react with malononitrile and acetylacetone in the presence of Amberlyst A-21 under similar reaction conditions. The recovered Amberlyst A21 resin, obtained by filtering off the reaction product, was washed successively with THF (5 mL) and EtOH (5 mL) thrice and dried at 100 °C for 2 h. The efficiency of the catalyst on using for five consecutive times in the model reaction is shown in Figure 1. It was observed that the recovered catalyst works with same efficiency up to the fourth run, while in the fifth run it takes almost half an hour to complete the reaction. In the sixth run, the partly broken catalyst beads could not complete the reaction even after 4 h.

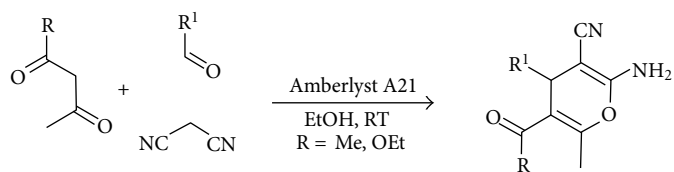
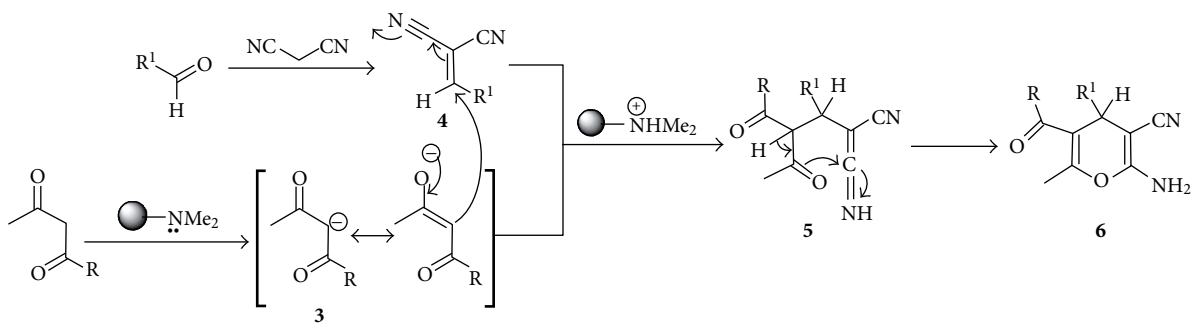
After optimization of solvent and catalyst loading, we applied the optimized protocol for synthesis of different 4*H*-pyrans by varying the aldehyde (Table 3). In general, all the aldehydes gave very good yields under our reaction conditions. Especially, the aromatic aldehydes carrying electron withdrawing group (entries 1–3, Table 3) took much lesser time for complete conversion, while the less electrophilic aromatic aldehydes (entries 4–7, Table 3) took longer time. Highly electrophilic heteroaromatic aldehydes (entries 8–9) were more reactive under our reaction conditions.

When the same reaction protocol was applied to the reaction of ethyl acetoacetate with aldehyde and malononitrile, excellent formation of ethyl 6-amino-5-cyano-2-methyl-4-alkyl/aryl-4*H*-pyran-3-carboxylates was observed (Table 4), but the reaction was found to be faster with ethyl acetoacetate than acetylacetone. Most of the aromatic aldehydes took almost similar reaction time irrespective of electron accepting/donating nature of substituents on the phenyl ring and gave very good yields. True to the less reactive nature of aliphatic aldehydes, heptanal (entry 8, Table 4) took almost double the time to its aromatic counterparts.

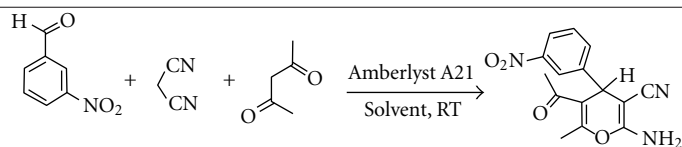
As for the mechanism, the active methylene compounds generated the carbanions **3** which might reacted with the product **4**, formed by base catalyzed Knoevenngel reaction, *via* a Michael type addition reaction. The intermediate **5**, so generated, undergoes intramolecular cyclization to give the 4*H*-pyran **6** (Scheme 2).

3. Conclusions

In summary, we report a completely green method for the synthesis of a diverse range of polyfunctionalized 4*H*-pyran using Amberlyst A21 as a reusable catalyst. No chromatography, no hazardous organic solvents, no elevated temperature,

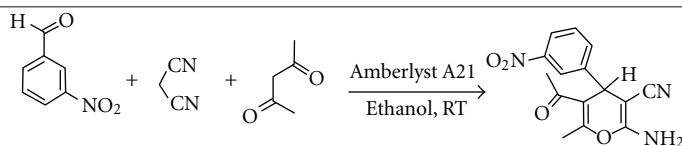
SCHEME 1: Synthesis of polysubstituted 4*H*-pyran.

SCHEME 2: Plausible mechanism.

TABLE 1: Screening of solvents.^a

Entry	Solvent	Isolated Yield (%)
1	No solvent	0
2	Dichloromethane	15
3	Chloroform	12
4	Acetonitrile	33
5	DMF	40
6	Ethanol	85
7	Water	0

^a Reaction conditions: stoichiometric ratio of all the reactants with base (30 mg/mmol) in ethanol at RT for 5 h.

TABLE 2: Optimization of catalyst loading.^a

Entry	Catalyst (mg)	Time (h)	Yield (%)
1	10	12	45 ^b
2	20	12	80
3	30	3	85
4	40	3	87
5	50	3	85

^a Reaction conditions: stoichiometric ratio of all the reactants with base in ethanol at RT; ^b incomplete conversion.

TABLE 3: Synthesis of substituted pyrans from acetylacetone *via* Scheme 1.^{a,b}

Entry	R	Product	Time (h)	% Yield ^c	m.p. (°C)
1	3-NO ₂ C ₆ H ₄	1a	3	85	161-162 [17]
2	4-NO ₂ C ₆ H ₄	1b	3.0	82	168-169
3	4-ClC ₆ H ₄	1c	3.5	88	130-131
4	Ph	1d	5	72	293-195 [17]
5	3-OHC ₆ H ₄	1e	3	82	158-159
6	4-MeOC ₆ H ₄	1f	6	78	210-213 [17]
7	4-CH ₃ C ₆ H ₄	1g	6	81	274-276 [17]
8	3-Pyridyl	1h	3	87	163-164
9	2-Furfuryl	1i	3.5	90	166-167

^aAll reactions were carried out at room temperature; ^bequimolar ratio of all the reactants with 30 mg Amberlyst A21/mmol of aldehyde; ^cisolated yields.

TABLE 4: Synthesis of substituted pyrans from ethyl acetoacetate *via* Scheme 1.^{a,b}

Entry	R	Product	Time (h)	% Yield ^c	m.p. (°C)
1	3-NO ₂ C ₆ H ₄	2a	2.5	91	182-184 [12]
2	4-NO ₂ C ₆ H ₄	2b	2.5	88	180-181 [12]
3	4-ClC ₆ H ₄	2c	3.0	83	173-174 [12]
4	Ph	2d	3.0	75	194-196 [12]
5	4-MeOC ₆ H ₄	2e	4.0	77	135-136 [12]
6	3,4,5-(OMe) ₃ C ₆ H ₂	2f	5.0	81	165-166
7	3-OHC ₆ H ₄	2g	3.5	86	161-162 [12]
8	<i>n</i> -C ₆ H ₁₃	2h	6	82	163-165

^aAll reactions were carried out at room temperature; ^bequimolar ratio of all the reactants with 30 mg Amberlyst A21/mmol of aldehyde; ^cisolated yields.

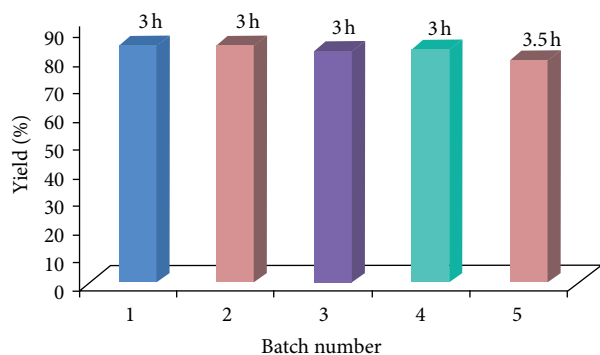


FIGURE 1: Study of catalyst reusability.

and very good to excellent yield of the products are some of the major achievements of this reaction protocol that

has potential to be extremely useful for the synthetic and medicinal chemists.

4. Experimental Section

IR spectra were recorded on a Perkin-Elmer Spectrum One FTIR spectrometer. ¹H and ¹³C NMR spectra were recorded on a Bruker (400 MHz) spectrometer using TMS as internal reference. Chemical shifts for ¹H NMR spectra are reported with (CD₃)₂SO as solvents. ¹³C NMR spectra were recorded at 100 MHz. Chemical shifts for ¹³C NMR spectra are reported with (CD₃)₂SO as solvents. Mass spectra were obtained from Waters ZQ 4000 mass spectrometer by the ESI method, while the elemental analyses of the complexes were performed on a Perkin-Elmer-2400 CHN/S analyzer. TLC plates were visualized by UV or by immersion in anisaldehyde

stain (by volume: 95% ethanol, 3.5% sulfuric acid, 1% acetic acid, and 2.5% anisaldehyde) followed by heating.

4.1. Typical Procedure. To a solution of *m*-nitrobenzaldehyde (0.151 g, 1 mmol), malononitrile (0.066 g, 1 mmol) in ethanol (10 mL), were added acetylacetone (0.1 g, 1 mmol) and Amberlyst A21 (0.030 g). As the reaction progressed, precipitation of the product was observed. Upon stirring at room temperature for 3 h, the reaction was found to be completed as indicated by TLC. Warm ethanol (60 °C) was added to dissolve the solid product and filtered. The residue of Amberlyst A21 was washed thoroughly with warm ethanol until no compound was detected in the residue. The combined ethanolic solution was concentrated and allowed to stand in a refrigerator to get pure crystalline product. Yield 85%, Yellow crystal, 0.254 g; IR (KBr, ν_{\max} , cm^{-1}): 1527 (NO_2), 1679 ($\text{C}=\text{O}$), 2190 ($\text{C}\equiv\text{N}$), 3396 (NH_2). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} 1.89 (3H, s, $-\text{CH}_3$), 2.06 (3H, m, $-\text{CO}-\text{CH}_3$, acetyl), 4.47 (1H, s, $-\text{CH}$), 6.83 (2H, s, NH_2), 7.42–7.45 (2H_{arom} , m), 7.87–7.90 (2H_{arom} , m). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ_{C} 18.7 ($-\text{CH}_3$), 30.1 ($-\text{CH}_3-\text{CO}-$), 38.2 ($-\text{CH}-$), 56.7 ($=\text{C}-\text{CN}$), 114.5 ($-\text{C}-\text{CO}-$), 119.4 ($\text{C}\equiv\text{N}$), 121.4, 122, 130.4, 133.9, 146.9, 147.9 (6C_{arom}) 156 ($=\text{C}(\text{O})-\text{CH}_3$), 158.5 ($=\text{C}(\text{O})-\text{NH}_2$), 197.8 ($-\text{C}=\text{O}$, acetyl). MS (ES^+) m/z 300 ($\text{M} + \text{H}$) $^+$. Elemental analysis for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_4$: calculated C 60.20, H 4.38, N 14.04%. Found C 60.15, H 4.40, N 14.01%.

4.2. Spectral Data for New Compounds

4.2.1. 5-Acetyl-2-amino-6-methyl-4-(4-nitrophenyl)-4H-pyran-3-carbonitrile (1b). Yellow crystal, yield 89%, 0.266 g; IR (KBr, ν_{\max} , cm^{-1}): 1520 (NO_2), 1679 ($\text{C}=\text{O}$), 2190 ($\text{C}\equiv\text{N}$), 3356 (NH_2). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} 1.89 (3H, s, $-\text{CH}_3$), 2.08 (3H, s, $-\text{CO}-\text{CH}_3$, acetyl), 4.43 (1H, s, $-\text{CH}$), 6.84 (2H, s, NH_2), 7.24 (2H_{arom} , d, $^2J_{\text{H,H}} = 8.2$ Hz), 7.99 (2H_{arom} , $^2J_{\text{H,H}} = 8$ Hz). ^{13}C NMR (75 MHz, $\text{CDCl}_3 + \text{DMSO}-d_6$): δ_{C} 18.6 ($-\text{CH}_3$), 29.7 ($-\text{CH}_3-\text{CO}-$), 38.7 ($-\text{CH}-$), 57.8 ($=\text{C}-\text{CN}$), 113.9 ($-\text{C}-\text{CO}-$), 118.7 ($\text{C}\equiv\text{N}$), 123.6, 127.7, 146.3, 150.5 (6C_{arom}) 156 ($=\text{C}(\text{O})-\text{CH}_3$), 157 ($=\text{C}(\text{O})-\text{NH}_2$), 197 ($-\text{C}=\text{O}$, acetyl). MS (ES^+) m/z 300 ($\text{M} + \text{H}$) $^+$, 322 ($\text{M} + \text{Na}$) $^+$. Elemental analysis for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_4$: calculated C 60.20, H 4.38, N 14.04%. Found C 60.12, H 4.34, N 14.12%.

4.2.2. 5-Acetyl-2-amino-6-methyl-4-(4-chlorophenyl)-4H-pyran-3-carbonitrile (1d). Yellow crystal, yield 88%, 0.253 g; IR (KBr, ν_{\max} , cm^{-1}): 1666 ($\text{C}=\text{O}$), 2190 ($\text{C}\equiv\text{N}$), 3330 (NH_2). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} 1.82 (3H, s, $-\text{CH}_3$), 2.00 (3H, s, $-\text{CO}-\text{CH}_3$, acetyl), 4.26 (1H, s, $-\text{CH}$), 6.70 (2H, s, NH_2), 6.96 (2H_{arom} , d, $^2J_{\text{H,H}} = 8$ Hz), 7.15 (2H_{arom} , d, $^2J_{\text{H,H}} = 8$ Hz). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ_{C} 18.5 ($-\text{CH}_3$), 29.8 ($-\text{CH}_3-\text{CO}-$), 38.0 ($-\text{CH}-$), 57.2 ($=\text{C}-\text{CN}$), 114.7 ($-\text{C}-\text{CO}-$), 119.6 ($\text{C}\equiv\text{N}$), 128.6, 129, 129, 129.9, 131.5, 143.5 (6C_{arom}) 155 ($=\text{C}(\text{O})-\text{CH}_3$), 158.2 ($=\text{C}(\text{O})-\text{NH}_2$), 198.1 ($-\text{C}=\text{O}$, acetyl). MS (ES^+) m/z 289 ($\text{M} + \text{H}$) $^+$. Elemental analysis for $\text{C}_{15}\text{H}_{13}\text{ClN}_2\text{O}_2$: calculated C 62.40, H 4.54, N 9.70%. Found C 62.35, H 4.49, N 9.78%.

4.2.3. 5-Acetyl-2-amino-6-methyl-4-(3-hydroxyphenyl)-4H-pyran-3-carbonitrile (1e). Light yellow crystal, yield 82%, 0.221 g; IR (KBr, ν_{\max} , cm^{-1}): 1666 ($\text{C}=\text{O}$), 2196 ($\text{C}\equiv\text{N}$), 3337 (NH_2). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} 1.82 (3H, s, $-\text{CH}_3$), 1.98 (3H, m, $-\text{CO}-\text{CH}_3$, acetyl), 4.12 (1H, s, $-\text{CH}$), 6.31–6.39 (3H_{arom} , m), 6.62 (2H, s, NH_2) 6.87 (1H_{arom} , t, $^3J_{\text{H,H}} = 8$ Hz), 9.21 (1H, s, phenolic $-\text{OH}$). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ_{C} 18.3 ($-\text{CH}_3$), 29.7 ($-\text{CH}_3-\text{CO}-$), 38.6 ($-\text{CH}-$), 57.7 ($=\text{C}-\text{CN}$), 113.8, 114, 114.9 (3C_{arom}), 117.7 ($-\text{C}-\text{CO}-$), 119.8 ($\text{C}\equiv\text{N}$), 129, 145.9, 154.5 (3C_{arom}) 157.6 ($=\text{C}(\text{O})-\text{CH}_3$), 158.2 ($=\text{C}(\text{O})-\text{NH}_2$), 198.4 ($-\text{C}=\text{O}$, acetyl). MS (ES^+) m/z 271 ($\text{M} + \text{H}$) $^+$, 293 ($\text{M} + \text{Na}$) $^+$. Elemental analysis for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3$: calculated C 66.66, H 5.22, N 10.36%. Found C 66.59, H 5.19, N 10.41%.

4.2.4. 5-Acetyl-2-amino-6-methyl-4-(pyridin-3-yl)-4H-pyran-3-carbonitrile (1h). Brown crystal, yield 87%, 0.221 g; IR (KBr, ν_{\max} , cm^{-1}): 1686 ($\text{C}=\text{O}$), 2190 ($\text{C}\equiv\text{N}$), 3356 (NH_2). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} 1.93 (3H, s, $-\text{CH}_3$), 2.10 (3H, s, $-\text{CO}-\text{CH}_3$), 4.36 (1H, s, $-\text{CH}(\text{C}_6\text{H}_4\text{N})-$), 6.38 (2H, $-\text{NH}_2$), 7.18–7.21 (1H_{arom} , m), 7.39 (d, $^2J_{\text{H,H}} = 8$ Hz, 1H), 8.25–8.28 (2H_{arom} , m). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ_{C} 18.7 (CH_3), 30 ($\text{CH}_3-\text{CO}-$), 36.2 ($-\text{CH}$), 56.8 ($\text{C}-\text{CN}$), 114.4, 119.6, 123.9 (3C , pyridyl), 134.8 ($=\text{C}-$), 140 ($\text{C}\equiv\text{N}$), 148.1 ($-\text{C}-\text{N}$, pyridyl), 148.3 ($-\text{C}=\text{N}$, pyridyl), 155.8 ($=\text{C}(\text{O})-\text{CH}_3$), 158.4 ($=\text{C}(\text{O})-\text{NH}_2$), 197.9 ($-\text{C}=\text{O}$, acetyl). MS (ES^+) m/z 256 ($\text{M} + \text{H}$) $^+$, 278 ($\text{M} + \text{Na}$) $^+$. Elemental analysis for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2$: calculated C 65.87, H 5.13, N 16.46%. Found C 65.78, H 5.15, N 16.12%.

4.2.5. 5-acetyl-2-amino-4-(furan-2-yl)-6-methyl-4H-pyran-3-carbonitrile (1i). Light brownish crystal, yield 90%, 0.219 g; IR (KBr, ν_{\max} , cm^{-1}): 1666 ($\text{C}=\text{O}$), 2203 ($\text{C}\equiv\text{N}$), 3403 (NH_2). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ_{H} 2.18 (3H, s, $-\text{CH}_3$), 2.19 (3H, s, $-\text{CO}-\text{CH}_3$, acetyl), 4.61 (1H, s, $-\text{CH}$), 6.13 (1H, d, $^2J_{\text{H,H}} = 3.2$ Hz, CH_{arom}), 6.35–6.36 (1H, m, CH_{arom}), 7.01 (2H, s, NH_2), 7.54 (1H, d, $^2J_{\text{H,H}} = 2$ Hz, CH_{arom}). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ_{C} 18.5 ($-\text{CH}_3$), 29.5 ($-\text{CH}_3-\text{CO}-$), 38.4 ($-\text{CH}-$), 54.3 ($=\text{C}-\text{CN}$), 105.6, 110.5 (2C , furyl) 112.9 ($-\text{C}-\text{CO}-$), 119.7 ($\text{C}\equiv\text{N}$), 142.4, 155.7 (2C , furyl) 155.8 ($=\text{C}(\text{O})-\text{CH}_3$), 159.4 ($=\text{C}(\text{O})-\text{NH}_2$), 197.8 ($-\text{C}=\text{O}$, acetyl). MS (ES^+) m/z 345 ($\text{M} + \text{H}$) $^+$. Elemental analysis for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_3$: calculated C, 63.93; H, 4.95; N, 11.47%. Found C 63.91, H 4.89, N 11.31%.

4.2.6. Ethyl 6-amino-5-cyano-2-methyl-4-(3,4,5-trimethoxyphenyl)-4H-pyran-3-carboxylate (2f). Yellow crystal, yield 81%, 0.302 g; IR (KBr, ν_{\max} , cm^{-1}): 1261 (OCH_3), 1692 (COOEt), 2196 ($\text{C}\equiv\text{N}$), 3489 (NH_2). ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ_{H} 1.06 (3H, t, $^3J_{\text{H,H}} = 6.9$ Hz, OCH_2CH_3), 2.28 (3H, s, $-\text{CO}-\text{CH}_3$), 3.36 (9H, s, 3OCH_3), 3.97–4.02 (2H, m, CH_2), 4.26 (1H, s, CH), 6.38 (2H, s, NH_2), 6.93 (2H_{arom} , s, 2CH, phenyl). ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ_{C} 14.3 (CH_3 , OEt), 18.6 (CH_3), 56.2 ($-\text{CH}-$), 57.3 ($\text{C}-\text{CN}$), 60.4 (3OCH_3), 60.7 (CH_2), 104.7, 107.6 (2C_{arom}), 120.4 ($=\text{C}-$), 136.8 ($\text{C}\equiv\text{N}$), 141.0 (2C_{arom}), 153.2 ($3\text{C}_{\text{arom}}-\text{OCH}_3$), 156.7

(=C(O)-CH₃), 159 (=C(O)-NH₂), 166 (COOEt). MS (ES⁺) *m/z* 375 (M + H)⁺, 397 (M + Na)⁺. Elemental analysis for C₁₉H₂₂N₂O₆: calculated C 60.95, H 5.92, N 7.48%; observed C 60.89, H 5.91, N 7.31%.

4.2.7. *Ethyl 6-amino-5-cyano-2-methyl-4-pentyl-4H-pyran-3-carboxylate (2h)*. White crystal, yield 82%, 0.227 g; IR (KBr, ν_{\max} , cm⁻¹): 1699 (COOEt), 2190 (C≡N), 3403(NH₂). ¹H NMR (400 MHz, DMSO-d₆): δ_{H} 0.83 (3H, t, ³J_{H,H} = 6.4 Hz, CH₃), 1.04–1.37 (11H, m, 4CH₂ + CH₃), 2.19 (3H, s, CH₃), 3.19 (1H, t, ³J_{H,H} = 4.4 Hz, CH), 4.06–4.20 (2H, m, CH₂), 6.81 (2H, s, NH₂). ¹³C NMR (75 MHz, DMSO-d₆): δ_{C} 14.4 (CH₃), 14.4 (CH₃), 18.5 (CH₃), 22.4, 24.6, 28.9, 31.6, 32.8 (5CH₂), 36.5 (CH), 54.8 (C-CN), 60.7 (-OCH₂), 108.2 (=C-), 120.8 (C≡N), 157.6 (=C(O)-CH₃), 160.5 (=C(O)-NH₂), 166.3 (COOEt). MS (ES⁺) *m/z* 279 (M + H)⁺, 301 (M + Na)⁺. Elemental analysis for C₁₅H₂₂N₂O₃: calculated C 64.73, H 7.97, N 10.06%. Found C 64.69, H 7.91, N 10.1%. See Supplementary Material available online at doi:<http://dx.doi.org/10.1155/2013/785930>.

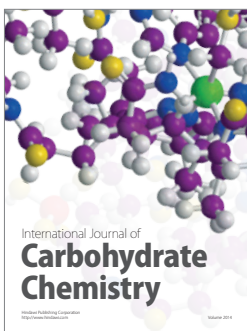
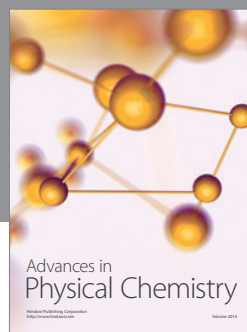
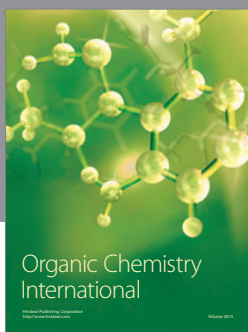
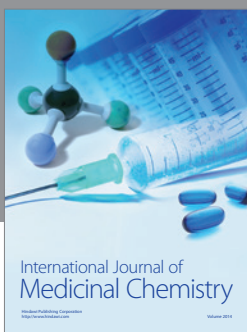
Acknowledgments

The authors thank University Grants Commission-Special Assistance Programme (UGC-SAP), North Eastern Hill University (NEHU), Shillong, for partial financial assistance. Analytical service for Sophisticated Analytical Instrumentation Facility, NEHU is gratefully acknowledged.

References

- [1] B. Cornils, W. A. Herrmann, M. Muhler, and C. H. Wong, *Catalysis from A to Z: A Concise Encyclopedia*, Wiley-VCH, Weinheim, Germany, 2007.
- [2] R. Sheldon, I. Arends, and U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim, Germany, 2007.
- [3] P. W. N. M. van Leeuwen, *Homogeneous Catalysis-Understanding the Art*, Kluwer Academic, Dordrecht, The Netherlands, 2004.
- [4] L. A. Thompson, "Recent applications of polymer-supported reagents and scavengers in combinatorial, parallel, or multistep synthesis," *Current Opinion in Chemical Biology*, vol. 4, no. 3, pp. 324–337, 2000.
- [5] A. Nefzi, J. M. Ostresh, and R. A. Houghten, "The current status of heterocyclic combinatorial libraries," *Chemical Reviews*, vol. 97, no. 2, pp. 449–472, 1997.
- [6] S. Hatakeyama, N. Ochi, H. Numata, and S. Takano, "A new route to substituted 3-methoxycarbonyldihydropyrans; enantioselective synthesis of (-)-methyl elenolate," *Journal of the Chemical Society, Chemical Communications*, no. 17, pp. 1202–1204, 1988.
- [7] K. Singh, J. Singh, and H. Singh, "A synthetic entry into fused pyran derivatives through carbon transfer reactions of 1,3-oxazinanes and oxazolidines with carbon nucleophiles," *Tetrahedron*, vol. 52, no. 45, pp. 14273–14280, 1996.
- [8] N. Martin, A. Martinez-Grau, C. Seoane, J. L. Marco, A. Albert, and F. H. Cano, "Michael addition of malononitrile to α -acetylcinnamamides," *Liebigs Annalen der Chemie*, vol. 7, pp. 801–804, 1993.
- [9] J. L. Wang, D. Liu, Z. J. Zhang et al., "Structure-based discovery of an organic compound that binds Bcl-2 protein and induces apoptosis of tumor cells," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 13, pp. 7124–7129, 2000.
- [10] A. Martinez-Grau and J. L. Marco, "Friedlander reaction on 2-amino-3-cyano-4H-pyrans: synthesis of derivatives of 4H-pyran[2,3-b]quinoline, new tacrine analogs," *Bioorganic & Medicinal Chemistry Letters*, vol. 7, no. 24, pp. 3165–3170, 1997.
- [11] L. Bonsignore, G. Loy, D. Secci, and A. Calignano, "Synthesis and pharmacological activity of 2-oxo-(2H) 1-benzopyran-3-carboxamide derivatives," *European Journal of Medicinal Chemistry*, vol. 28, no. 6, pp. 517–520, 1993.
- [12] D. Kumar, V. B. Reddy, S. Sharad, U. Dube, and S. Kapur, "A facile one-pot green synthesis and antibacterial activity of 2-amino-4H-pyrans and 2-amino-5-oxo-5,6,7,8-tetrahydro-4H-chromenes," *European Journal of Medicinal Chemistry*, vol. 44, no. 9, pp. 3805–3809, 2009.
- [13] C. S. Konkoy, D. B. Fick, S. X. Cai, N. C. Lan, and J. F. W. Keana, "Substituted 5-oxo-5,6,7,8-tetrahydro-4H-1-benzopyrans and benzothiopyrans and the use thereof as potentiators of AMPA," *Chemical Abstracts*, vol. 134, Article ID 29313a, 2001, International Application WO 00/75123 A1, 2000.
- [14] N. Martin, C. Seoane, and J. L. Soto, "A convenient, one step synthesis of pyrano[2,3-b]pyridines," *Tetrahedron*, vol. 44, no. 18, pp. 5861–5868, 1988.
- [15] D. Heber and E. V. Stoyanov, "Synthesis of functionalized 4H-pyran and cyclohexanone derivatives via three-component reactions of dimethyl acetonedicarboxylate, aromatic aldehydes, and malononitrile," *Synthesis*, no. 2, pp. 227–232, 2003.
- [16] Y. Peng and G. Song, "Amino-functionalized ionic liquid as catalytically active solvent for microwave-assisted synthesis of 4H-pyrans," *Catalysis Communications*, vol. 8, no. 2, pp. 111–114, 2007.
- [17] Y. Peng, G. Song, and F. Huang, "Tetramethylguanidine-[bmim][BF₄]. An efficient and recyclable catalytic system for one-pot synthesis of 4H-pyrans," *Monatshfte fur Chemie*, vol. 136, no. 5, pp. 727–731, 2005.
- [18] T. S. Jin, L. B. Liu, Y. Zhao, and T. S. Li, "Clean, one-pot synthesis of 4H-pyran derivatives catalyzed by hexadecyltrimethyl ammonium bromide in aqueous media," *Synthetic Communications*, vol. 35, no. 14, pp. 1859–1863, 2005.
- [19] N. S. Babu, N. Pasha, K. T. V. Rao, P. S. S. Prasad, and N. Lingaiah, "A heterogeneous strong basic Mg/La mixed oxide catalyst for efficient synthesis of polyfunctionalized pyrans," *Tetrahedron Letters*, vol. 49, no. 17, pp. 2730–2733, 2008.
- [20] M. M. Heravi, Y. S. Beheshtiha, Z. Pirnia, S. Sadjadi, and M. Adibi, "One-pot, three-component synthesis of 4H-pyrans using Cu(II) oxymetasilicate," *Synthetic Communications*, vol. 39, no. 20, pp. 3663–3667, 2009.
- [21] B. P. V. Lingaiah, G. V. Reddy, T. Yakaiah et al., "Efficient and convenient method for the synthesis of poly functionalised 4H-pyrans," *Synthetic Communications*, vol. 34, no. 23, pp. 4431–4437, 2004.
- [22] S. G. Zhang, S. F. Yin, Y. D. Wei, S. L. Luo, and C. T. Au, "Novel MgO-SnO₂ solid superbase as a high-efficiency catalyst for one-pot solvent-free synthesis of polyfunctionalized 4H-pyran derivatives," *Catalysis Letters*, vol. 142, no. 5, pp. 608–614, 2012.
- [23] U. R. Pratap, D. V. Jawale, P. D. Netankar, and R. A. Mane, "Baker's yeast catalyzed one-pot three-component synthesis of

- polyfunctionalized 4*H*-pyrans,” *Tetrahedron Letters*, vol. 52, no. 44, pp. 5817–5819, 2011.
- [24] N. Srinivasan, A. Yurek-George, and A. Ganesan, “Rapid deprotection of *N*-Boc amines by TFA combined with freebase generation using basic ion-exchange resins,” *Molecular Diversity*, vol. 9, no. 4, pp. 291–293, 2005.
- [25] R. Ballini, L. Barboni, and P. Filippone, “Amberlyst A-21 an excellent heterogeneous catalyst for the conversion of carbonyl compounds to oximes,” *Chemistry Letters*, no. 5, pp. 475–476, 1997.
- [26] R. Ballini, G. Bosica, and P. Forconi, “Nitroaldol (Henry) reaction catalyzed by Amberlyst A-21 as a far superior heterogeneous catalyst,” *Tetrahedron*, vol. 52, no. 5, pp. 1677–1684, 1996.
- [27] F. Bonfils, I. Cazaux, P. Hodge, and C. Caze, “Michael reactions carried out using a bench-top flow system,” *Organic and Biomolecular Chemistry*, vol. 4, no. 3, pp. 493–497, 2006.
- [28] S. M. Dhuri and V. V. Mahajani, “Studies in transesterification of ethylene carbonate to dimethyl carbonate over Amberlyst A-21 catalyst,” *Journal of Chemical Technology and Biotechnology*, vol. 81, no. 1, pp. 62–69, 2006.
- [29] S. Mustafa, M. Khalid, A. Naeem, N. Rehana, and S. Murtaza, “Selective removal of chromates by macroporous exchanger Amberlyst A-21,” *Environmental Technology*, vol. 23, no. 5, pp. 583–590, 2002.



Hindawi

Submit your manuscripts at
<http://www.hindawi.com>

