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Synthesis of several types of 2,8-dioxabicyclo[3.3.1]nonanes using amberlyst-15 as an efficient recyclable heterogeneous catalyst

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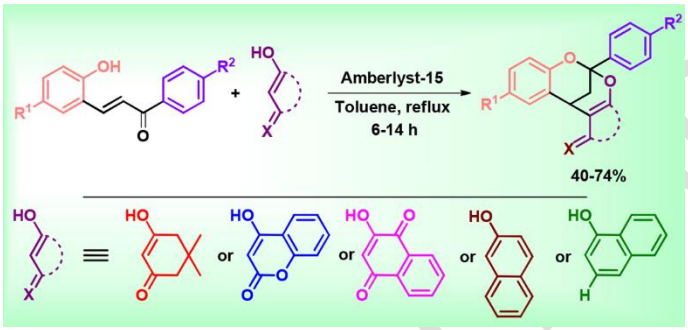
ABSTRACT

A facile synthesis of 2,8-dioxabicyclo[3.3.1]nonane derivatives starting from simple molecules like 2-hydroxychalcones as one component and dimedone, 4-hydroxycoumarin, 2-hydroxynaphthoquinone, 2-naphthol or 1-naphthol, as the other has been achieved by use of amberlyst-15, a sulfonated polystyrene resin, as a recyclable heterogeneous catalyst. The methodology involves a domino sequence of Michael addition and two-stage cyclisation.

GRAPHICAL ABSTRACT



KEYWORDS: 2,8-dioxabicyclo[3.3.1]nonanes, 2-hydroxychalcones, amberlyst-15, recyclable heterogeneous catalyst

Introduction

Compounds containing the bicyclo[3.3.1]nonane framework with one or more heteroatom in their structural motif are very important due to their cleft shaped structure.[1] A good number of 2,8-dioxabicyclo[3.3.1]nonanes are known as natural products and they are reported to show interesting biological activities like anti-inflammatory, antioxidant, COX-2 enzyme inhibitory, antiviral, antitumor and immunomodulatory activities.[2] Several such compounds[3] are shown in **Figure 1**.

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The reported interesting biological activities shown by natural 2,8-dioxabicyclo[3.3.1]nonanes encouraged us to undertake the synthesis different compounds containing this framework, particularly because some of the recently reported methods for synthesis of such compounds[4] suffer from drawbacks like use of expensive catalysts and application of harsh reaction conditions. A common feature of the reported methods for synthesis from 2-hydroxychalcones and cyclic active methylene compounds or phenols is that they involve a domino sequence of Michael addition and ketalization.[4] Amberlyst-15, a sulphonated polystyrene resin, has been known to be effective in Michael addition[5] and ketalization reactions[6] and so we undertook a synthesis of compounds of the type **2-6** by reaction of 2-hydroxychalcones with active methylene compounds and naphthols through use of amberlyst-15 as a heterogeneous catalyst in refluxing toluene. In this endeavor we became successful in developing a simple methodology for synthesis of **2-6**, wherein amberlyst-15 was found to be an efficient recyclable catalyst.

Results and Discussion

The present study started with the reaction of 2-hydroxychalcone (**1a**) and dimedone under amberlyst-15 catalyzed reaction condition. The initial success of the reaction to produce the 2,8-dioxabicyclo[3.3.1]nonane derivative **2a** inspired us to optimize the process by variation of the solvent, amount of catalyst and temperature. The results of the optimization study are given in **Table 1**. Under the optimized reaction conditions four more compounds of the series **2** were synthesized by using the 2-hydroxychalcones **1b**-**e** and with variation of reaction time. This reaction condition was then applied to other combinations of 2-hydroxychalcones (**1**) and cyclic active methylene compounds (4-hydroxycoumarin and 2-hydroxynaphthoquinone) and 2-

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hydroxychalcones (**1**) and naphthols (1-naphthol and 2-naphthol) for synthesis of different 2,8-dioxabicyclo[3.3.1]nonane derivatives. The results are shown in Schemes 1 and 2.

Recyclability of the catalyst

The recyclability of the catalyst amberlyst-15in the above reactions was then investigated by taking the synthesis of one compound in each of the series **2-6**. It was observed that the catalyst could be reused up to the fourth recycle without much decrease of catalytic activity. Thus, the results obtained are presented in **Table 2**.

The formation of the 2,8-dioxabicyclo[3.3.1]nonane derivatives **2-6** from 2-hydroxychalcones (**1**) and cyclic active methylene compounds (dimedone, 4-hydroxycoumarin or 2-hydroxynaphthoquinone) or naphthols under the amberlyst-15 catalysed condition follow similar pathways and they are analogous to the reported ones.[4b,c,e,h,i] As an example, plausible mechanism for formation of **2** is shown in Scheme 3.

Conclusions

We report simple methods for synthesis of five types of 2,8-dioxabicyclo[3.3.1]nonane derivatives **2-6**in moderate to good yield utilizing the heterogeneous catalyst amberlyst-15, which can be recycled.

Experimental

General

Melting points were recorded on a Köfler block. IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer (Spectrum BX II) in KBr pellets. ^{1}H and ^{13}C NMR spectra were

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recorded in $CDCl_3$ on a Bruker AV-300 (300MHz) or a Bruker AVANCE III HD (400MHz) spectrometer. HRMS data were recorded with a Waters Xevo G2QTof HRMS spectrometer. Analytical samples were routinely dried *in vacuo* at room temperature. Microanalytical data were recorded on two Perkin-Elmer 2400 Series II C, H, N analyzers. TLC was performed with silica gel G made of SRL Pvt. Ltd. Petroleum ether had the boiling range 60-80°C.

General method for synthesis of the 2,8-dioxabicyclo[3.3.1]nonane derivatives 2-6

To a mixture of 2-hydroxychalcone (**1**) (1 mmol) and dimedone / 4-hydroxycoumarin / 2-hydroxynaphthoquinone / 2-naphthol / 1-naphthol (1 mmol) in distilled toluene (10mL) amberlyst-15 (100mg) was added and the mixture was refluxed. The progress of the reaction was monitored with TLC. The reaction mixture was then cooled to room temperature, dichloromethane (DCM, 20mL) was added and the mixture was filtered to separate the catalyst which can be reused after recovery. The filtrate was concentrated and subjected to column chromatography using petroleum ether (PE)–ethyl acetate (EA) mixtures of increasing polarity as eluents. The fractions containing pure compounds were then crystallized from DCM-PE when the members of the series 2-**6** were obtained in pure state. The products were characterized from their physical and spectral data.

Characterization data for selected compounds

The synthesized 2,8-dioxabicyclo[3.3.1]nonane derivatives belonged to five different series (**2-6**), and majority of them are known compounds. The characterization data of one new compound of each series are given below:

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2b: Colorless crystalline solid, mp 115°C, ^{1}H NMR ($CDCl_3$, 300MHz): δ = 0.97 (s, 3H, Aliph. CH_3), 1.12 (s, 3H, Aliph. CH_3), 2.14-2.31(m, 4H), 2.41 (br. s, 2H), 2.43 (s, 3H, Ar-CH_3), 4.24 (br. s, 1H), 6.93 (br. t, 1H, *J* = 7.5Hz), 7.02 (br. d, 1H, *J* = 7.1Hz),7.16 (dt, 1H, *J* = 9.0 and 1.5Hz), 7.28 (d, 2H, *J* = 8.1Hz), 7.40 (dd, 1H, *J* = 7.2 & 1.2Hz) 7.56 (d, 2H, *J* = 8.1Hz), ^{13}C NMR (75MHz , $CDCl_3$): δ = 21.2, 25.2, 27.9, 28.8, 32.4, 33.0, 41.7, 50.4, 99.9, 115.4, 116.0, 121.5, 125.5, 126.6, 127.5, 128.1, 129.1, 137.4, 139.0, 151.5, 167.7, 195.8, HRMS (ESI) *m/z* for $C_{24}H_{25}O_3$ $[M + H]^+$, calcd. 361.1804, found 361.1089, Anal. calcd. for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 79.72; H, 6.53.

3f: Colorless crystalline solid, mp 195°C, ^{1}H NMR (300MHz , $CDCl_3$) δ 2.42 (br. s, 5H), 4.35 (br.s, 1H), 6.97 (d, *J* = 8.5Hz , 1H), 7.13 (dd, *J* = 8.5 and 2.5Hz , 1H), 7.24-7.33 (m, 4H), 7.49-7.54 (m, 2H), 7.62 (d, *J* = 7.9Hz , 2H), 7.86 (d, *J* = 7.8Hz , 1H); ^{13}C NMR (75MHz , $CDCl_3$) δ 21.2, 27.2, 32.6, 100.4, 105.4, 114.9, 116.7, 117.6, 122.8, 124.1, 125.5, 126.7, 126.9, 127.8, 128.3, 129.3, 132.2, 136.4, 139.6, 150.1, 152.5, 158.4, 162.3, Anal. calcd. for $C_{25}H_{17}ClO_4$: C, 72.03; H, 4.11. Found: C, 71.87; H, 4.24.

4b: Yellow crystalline solid, mp 230-231°C, ^{1}H NMR (300MHz , $CDCl_3$) δ 2.30 (dd, *J* = 13.5 and 2.9Hz , 1H), 2.43 (s, 3H), 2.47 (dd, *J* = 13.5 and 2.7Hz , 1H), 4.57 (t, *J* = 2.7Hz , 1H), 6.98 (t, *J* = 7.5Hz , 1H), 7.06 (d, *J* = 8.1Hz , 1H), 7.20 (br. t, *J* = 7.8Hz , 1H), 7.30 (d, *J* = 8.2Hz , 2H), 7.49 (br. d, *J* = 7.5Hz , 1H), 7.66 (d, *J* = 8.1Hz , 2H), 7.65-7.76 (m, 2H), 8.10-8.12 (m, 2H), ^{13}C NMR (75MHz , $CDCl_3$) δ 21.2, 26.2, 32.1, 100.2, 116.6, 121.9, 124.2, 124.7, 125.7, 126.2, 126.5, 128.4, 128.5, 129.2, 131.0, 131.8, 133.4, 134.0, 136.5, 139.2, 151.9, 153.3, 178.8, 182.8, Anal. calcd. for $C_{26}H_{18}O_4$: C, 79.17; H, 4.60. Found: C, 79.29; H, 4.39.

5b: Light yellow crystalline solid, mp 230-232°C, ^{1}H NMR (300MHz , $CDCl_3$) δ 2.45 (s, 3H), 2.43-2.55 (m, 2H), 4.88 (s, 1H), 6.90 (t, *J* = 7.2Hz ,1H), 7.06-7.15(m, 3H), 7.30-7.33 (m,

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2H), 7.41 (t, *J* = 7.2Hz ,1H), 7.55 (d, *J* = 7.2Hz ,1H), 7.61-7.74 (m, 4H), 7.82 (d, *J* = 7.8Hz , 1H), 8.37 (d, 1H, *J* = 7.8Hz); ^{13}C NMR (75MHz , $CDCl_3$) δ 21.2, 28.8, 33.3, 98.4, 116.7, 118.2, 118.6, 121.1, 121.8, 123.7, 125.7, 126.1, 126.8, 127.2, 127.8, 128.3, 128.9, 129.1, 129.7, 130.9, 138.5, 138.7, 149.8, 152.6; HRMS (ESI) *m/z* for $C_{26}H_{20}NaO_2$ $[M + Na]^+$, calcd. 387.1361, found 387.1313, Anal. calcd. for $C_{26}H_{20}O_2$: C, 85.69; H, 5.53. Found: C, 85.82; H, 5.63.

6e: Light yellow crystalline solid, mp 178°C, ^{1}H NMR (300MHz , $CDCl_3$) δ 2.44 (br. s, 2H), 4.15 (br. s, 1H), 6.97 (d, *J* = 8.6Hz , 1H), 7.09 (dd, *J* = 8.7 and 2.2Hz , 1H), 7.31-7.37 (m, 2H), 7.45-7.55 (m, 6H), 7.79 (br. d, *J* = 8.4Hz , 1H), 7.86 (d, *J* = 6.7Hz , 2H), 8.35 (br. d, *J* = 8.4Hz , 1H); ^{13}C NMR (75MHz , $CDCl_3$) δ 33.1, 34.2, 99.1, 118.1, 119.5, 121.4, 121.8, 124.6, 125.2, 125.9, 126.0, 126.3, 126.7, 127.6, 127.9, 128.2, 128.5, 129.0, 133.7, 141.2, 147.0, 150.8, 162.3, Anal. calcd. for $C_{25}H_{17}ClO_2$: C, 78.02; H, 4.45. Found: C, 77.82; H, 4.71.

Recovery of the catalyst

The catalyst was separated from the reaction mixture by filtration and washed thoroughly with ethyl acetate-acetone (1:1) till the washings became colorless. It was then dried in a hot air oven at 100°C for 8h . The recovered catalyst (weight 85-90% of the amount taken for the reaction) was then used in the next cycle by taking proportionate amount of the starting materials.

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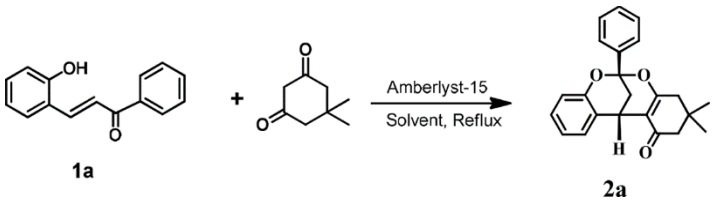
Table 1. Optimization of reaction condition for synthesis of 2a[a]



1a 2a

Entry	Solvent	Amount of Catalyst (mg)	Time (h)	Yield (%)b
1	Ethanol	100	9	–
2	Isopropanol	100	9	24
3	THF	100	9	12
4	Acetonitrile	100	9	45
5	Dioxane	100	9	44
6	o-Xylene	100	4	46
7	DMF	100	9	56
9	o-Xylene	100	9	64
10	Toluene	50	9	36
11	Toluene	80	9	56
12	Toluene	100	5	45
13	Toluene	100	7	52

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14	Toluene	100	8	61
15	Toluene	100	9	66
16	Toluene	100	10	66
17	Toluene	120	10	64

[a]The reaction were carried out with 1 mmol of each of the reactants under refluxing condition.

[b]Isolated yield for this table.

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Table 2. Results of recyclability study of amberlyst-15 in the synthesis of **2a**, **3a**, **4a**, **5a** and **6a**

Synthesis of 2,8-dioxabicyclo-[3.3.1]nonane	Reaction time (h)	Yield of product (%)				
		Fresh catalyst	First recycle	Second recycle	Third recycle	Fourth recycle
2a	9	66	65	63	63	61
3a	6	65	62	62	60	59
4a	6	67	63	61	61	58
5a	10	74	72	71	69	69
6a	14	40	37	37	35	34

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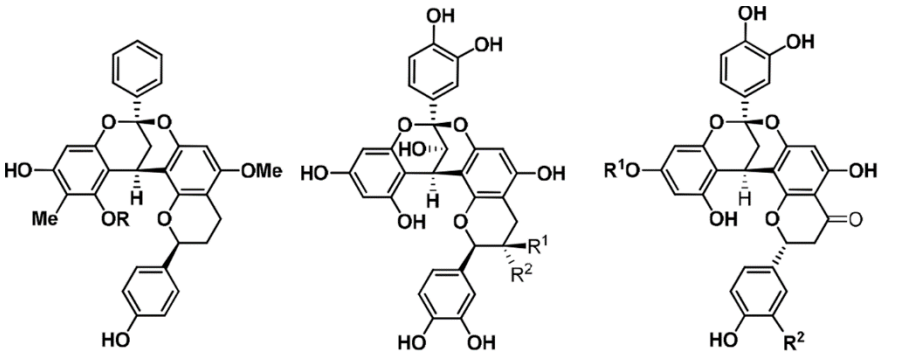
Figure 1. Some biologically active natural 2,8-dioxabicyclo[3.3.1]nonanes[3]



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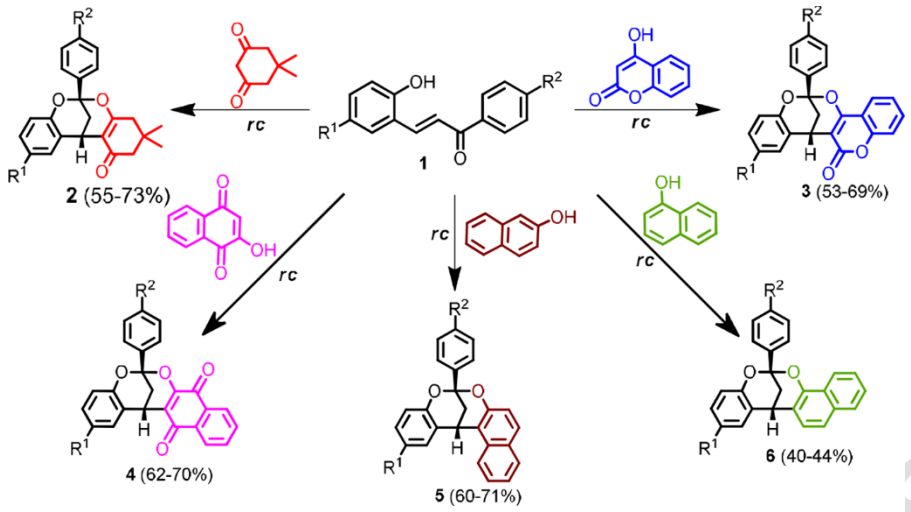
Scheme 1. Synthesis of five types of 2,8-dioxabicyclo[3.3.1]nonanes from 2-hydroxychalcones



a: $R^1 = R^2 = H$; **b**: $R^1 = H$, $R^2 = Me$; **c**: $R^1 = H$, $R^2 = OMe$
d: $R^1 = H$, $R^2 = Cl$; **e**: $R^1 = Cl$, $R^2 = H$; **f**: $R^1 = Cl$, $R^2 = Me$
rc (reaction conditions): Amberlyst-15, toluene, reflux

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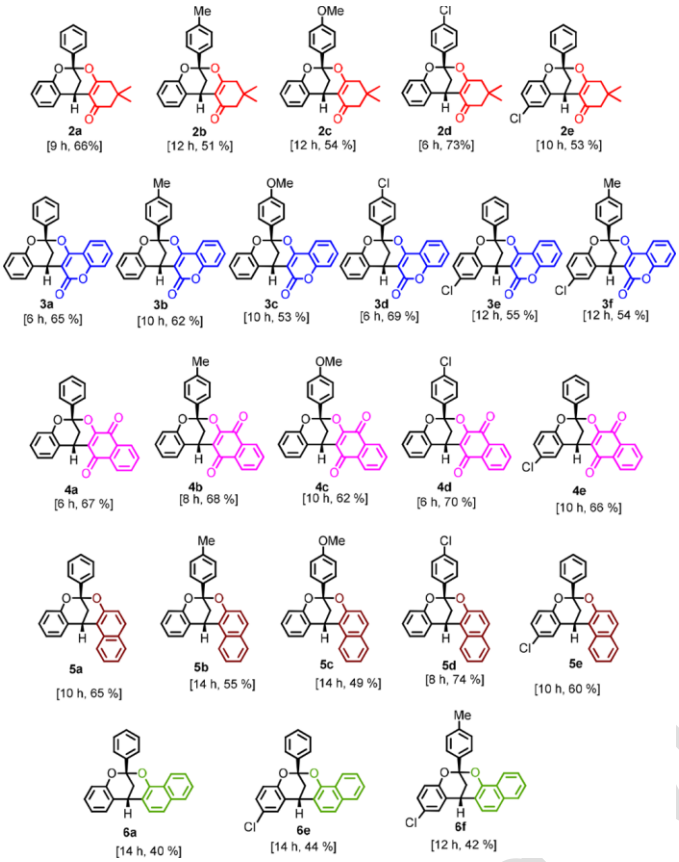
Scheme 2. 2,8-Dioxabicyclo[3.3.1]nonane derivatives synthesized [reaction time, yield]



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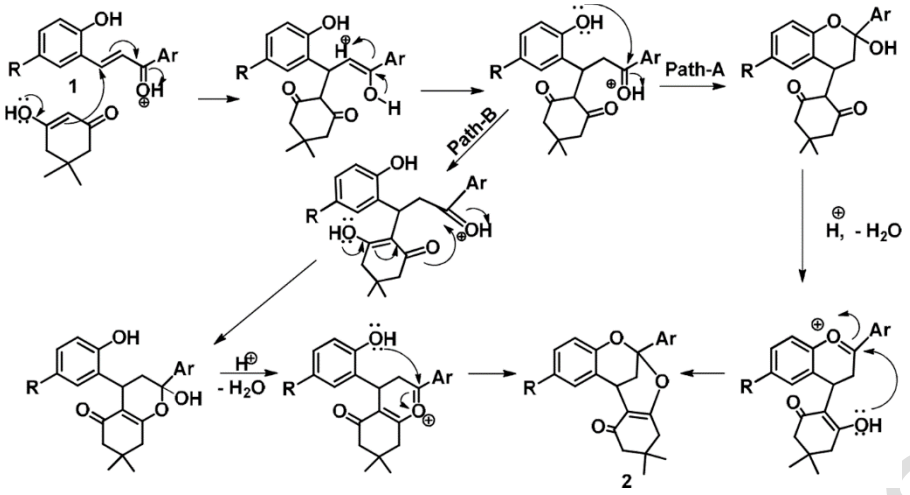
Scheme 3. Plausible mechanism of formation of 2,8-dioxabicyclo[3.3.1]nonane derivatives



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