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MICROWAVE-PROMOTED SEQUENTIAL THREE-COMPONENT SYNTHESIS OF TETRAHYDROBENZO[*b*]PYRAN IN WATER CATLYZED BY HETEROGENEOUS AMINE GRAFTED ON SILICA

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Abstract – A variety of tetrahydrobenzo[*b*]pyrans have been synthesized by sequential addition of arylaldehydes, cyanoacetate and then dimedone in water under microwave irradiation. A heterogeneous amine, *N,N*-diethylamino-propylated silica, was an effective catalyst for the reaction. The reaction with malononitrile provided the same result. The reaction condition was general to apply to the aldehyde having a Cl, NO_2, OH, OMe, or CO_2H group in satisfactory yield.

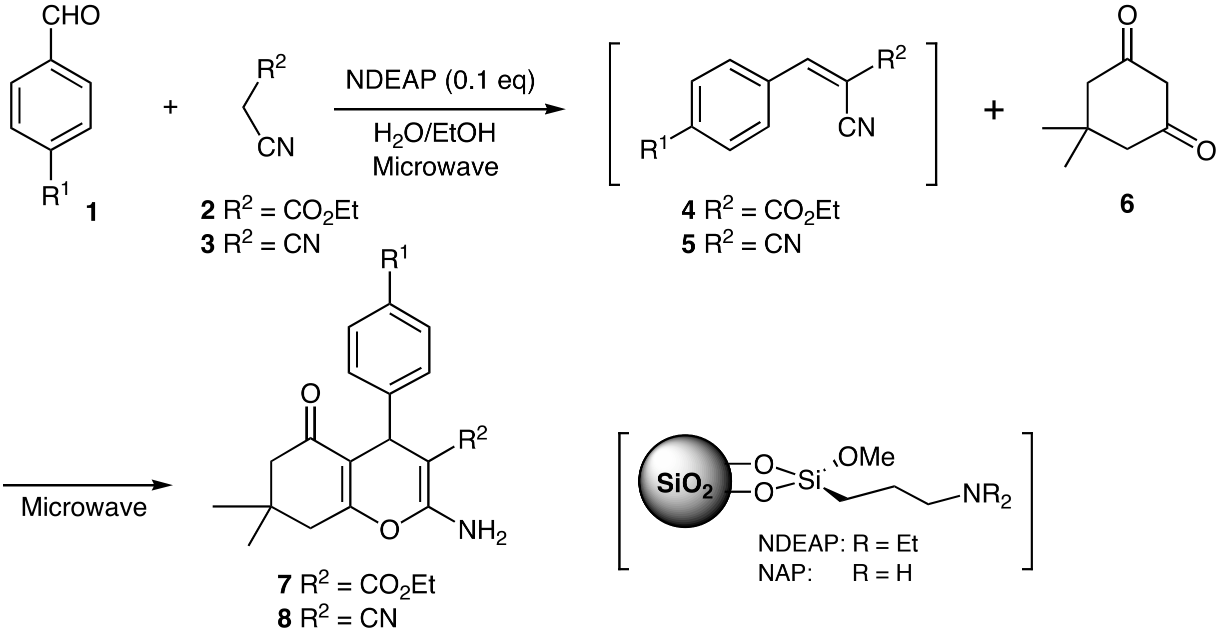
A sustainable and environmentally benign process is required in producing organic compounds. In order to realize such process, a catalytic reaction in environmentally benign reaction media is desired rather than a stoichiometric reaction.[1] A heterogeneous catalyst is preferable to homogeneous catalyst due to its facile recovery, and an organomolecular catalyst is superior to an organometallic catalyst due to its flexible design and safe in disposal.

From such standpoint, we reported nucleophilic reactions in environmentally friendly media such as an ionic liquid, super critical carbon dioxide or water, employing organomolecular catalysts supported on silica gel.[2] The reaction conditions were mild enough to apply to substrates having acid- or base-sensitive substituents. The catalyst could be recycled several times without deterioration.

Tetrahydrobenzo[*b*]pyrans (**7** and **8**) are useful compounds having various biological activities as antischistosomal agent,[3] immunomodulator, anticoagulant, anticancer and others.[4] Its synthesis has been accomplished by condensation of α,β-unsaturated nitriles (**4** or **5**) with cyclic-1,3-dicarbonyl compounds employing mainly a basic catalyst such as triethylamine,[3] ammonium acetate,[4] potassium fluoride,[5] or hexadecylammonium bromide,[6] while silica gel was an effective catalyst under microwave irradiation without a solvent.[7] In spite of a number of two component-condensation methods cited above, there is only one example of three component condensation mixing aldehyde, cyanoacetate, 1,3-dicarbonyl compound and triethylamine in one pot operation.[8] Another three-component condensation employed a masked aldehyde under acidic reaction conditions.[9]

Our recent results on Knoevenagel reaction in water catalyzed by amine supported on silica gel,[2a] prompted us to investigate a new protocol leading to tetrahydrobenzo[*b*]pyrans (**7** or **8**) under more facile and environmentally benign reaction conditions (Scheme 1).

Based on the results of our Knoevenagel reaction,[2a] we focused again on catalytic activity of the heterogeneous amine supported on silica as a catalyst and on water as reaction medium, which has many advantages from its ability to promote bimolecular reaction due to high cohesive energy density and dielectric constant, safety due to non-flammability, non-toxicity as well as economical standpoint.[10] The previous Knoevenagel reaction was carried out at room temperature for a few hours.[2a] In order to facilitate the initial Knoevenagel reaction and subsequent condensation, internal heating by microwave irradiation was applied,[11] since water has a relatively high loss factor (tan δ) to absorb microwave.[11b]



Scheme 1. One pot sequential three component synthesis of tetrahydrobenzo[*b*]pyrans (**7** and **8**)

The optimum reaction condition was examined employing the reaction of benzaldehyde (**1**) (R^1 = H), ethyl cyanoacetate (**2**) and dimedone (**6**) (Table 1) under microwave heating. Initial attempts to mix all three components (**1**, **2** and **6**) in one portion together with or without catalyst resulted in the exclusive formation of dimeric product (**9**) (Figure 1) by preferential condensation of benzaldehyde (**1**) and dimedone (**6**). This result is not unreasonable due to the higher acidity of dimedone (**9**) (pKa = 11.2) than that of ethyl cyanoacetate (**2**) (pKa = 13.1). Then, sequential addition of dimedone (**6**) was attempted, in which a mixture of benzaldehyde (**1**) and ethyl cyanoacetate (**2**) with catalyst was heated for a certain period of time to complete the initial Knoevenagel reaction followed by addition of dimedone (**6**) and subsequent heating. Though the dimeric product (**9**) was still obtained in 90% yield in the absence of a catalyst under the modified procedure (Table 1, Entry 1), the desired tetrahydrobenzo[*b*]pyran (**7**) was successfully synthesized in the presence of a heterogeneous amine catalyst[2f] (Table 1, Entries 2 and 3). Among the catalysts, NDEAP (3-*N,N*-diethylaminpropylated silica) provided better result than NAP (3-aminpropylated silica). Addition of ethanol, which has higher tan δ to facilitate rapid heating, was effective to improve the yield in 91% (Table 1, Entry 4). The reaction in polyethyleneglycol (PEG) having much higher tan δ than that of ethanol, provided moderate yield of 50 % probably due to overheating (Table 1, Entry 5). Although conventional external heating showed similar result (Table 1, Entry 6), microwave heating was apparently superior in the reaction of a less reactive aldehyde such as anisaldehyde (**1**) (R^1 = OMe) (Table 3, Entry 6). Although present reaction proceeded with 0.1 equiv. of tributylamine in comparable yield (Table 1, Entry 7), heterogeneous amine catalyst has much advantage than homogeneous amine catalyst due to lack of contamination and recyclability (vide infra).

Table 1. Investigation of effective reaction conditions[a] in the synthesis of tetrahydrobenzo[*b*]pyran (**7**)

Entry	Catalyst	Solvent	Yield (%)[b]
1	–	H_2O	0[c]
2	NAP[d]		13
3	NDEAP[e]		17
4		H_2O/EtOH	91
5		PEG	50
6[f]		H_2O/EtOH	87
7[g]	$(n\text{-Bu})_3N$		83

[a] The reaction was carried out with benzaldehyde (**1**) (R^1 = H), ethyl cyanoacetate (**2**) (1.2 equiv) and the catalyst (0.1 equiv) in solvent under microwave (100 W) irradiation for 10 min. After addition of dimedone (**6**) (1.2 equiv), subsequent reaction was carried out under microwave irradiation for 10 min. The temperature ramped from room temperature to 80 °C, which was monitored by radiation thermometer.

[b] Yields are for isolated pure product based on benzaldehyde (**1**).

[c] A dimeric product of dimedone (**9**) was obtained in 90% yield.

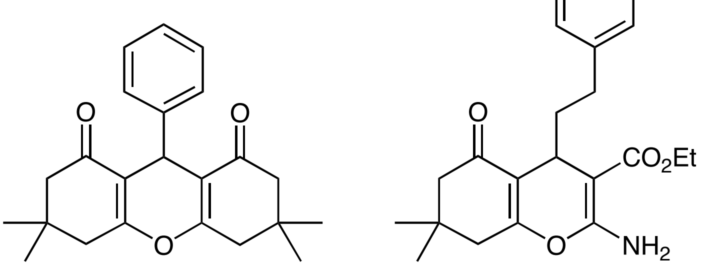
[d] 3-Aminpropylated silica.

[e] 3-*N,N*-Diethylaminpropylated silica.

[f] External heating at 80 °C for 20 min in an oil bath.

[g] Anisaldehyde (**1**) (R^1 = OMe) was employed.

Figure 1. Other products



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Employing the optimized reaction condition[12] (Table 1, Entry 4), the catalyst, NDEAP, could be recycled at least three times as shown in Table 2, though a certain amount of decrease of the catalytic activity could not be denied as shown in yields and reaction time. The end-capped NDEAP as trimethylsiloxide showed similar reactivity and recyclability as non-capped NDEAP.

Table 2. Recycle use of NDEAP in the synthesis of tetrahydrobenzo[*b*]pyran (**7**)[a]

Entry	Total irradiation time (min)	Yield (%)[b]
1	19	91
2	30	75
3	45	69
4	57	72

[a] See Ref. 12.
[b] Yields are for isolated pure product based on benzaldehyde (**1**).

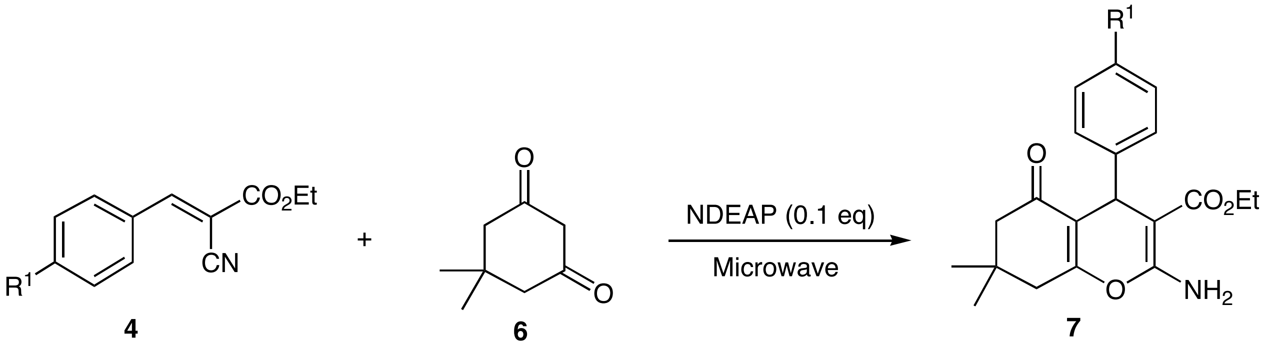
The present reaction condition (Table 1, Entry 4) was applied to a variety of aldehydes and the results are compiled in Table 3. Arylaldehydes (**1**) having not only electron-withdrawing (Table 3, Entries 2 and 3) but also electron-donating groups (Table 3, Entries 4 and 5) provided the desired products (**7**). It is worthy of note that the reaction proceeded without the protection of acidic substituents (Table 3, Entries 7 and 8).

Table 3. Synthesis of tetrahydrobenzo[*b*]pyran (**7**) from various aldehydes (**1**)[a]

Entry	Aldehyde (**1**) (R^1 =)	Time[b] (min)	Yield (%)[c]
1	H	6	91
2	NO_2	5	93
3	Cl	12	92
4	Me	24	86
5	OMe	21	79
6[d]		20	12
7	OH	15	65
8	CO_2H	23	84
9	OAc	30	66
10	OTHP	33	29
11	Hydrocinnamaldehyde	37	35

[a] See Ref. 12.
[b] Total irradiation time
[c] Yields are for isolated pure product based on aldehyde (**1**).
[d] External heating at 80 °C in an oil bath.

In spite of the successful result of 4-acetoxybenzaldehyde (**1**) (Table 3, Entry 9), the reaction of arylaldehyde (**1**) having an OTHP substituent did not give satisfactory results (Table 3, Entry 10) due to recovery of the starting aldehyde (**1**). This issue was solved by two- component synthesis starting from α-cyanocinnamate (**4**) prepared independently by NAP-catalyzed Knoevenagel condensation in good yields[2a] (Scheme 2 and Table 4).



Scheme 2. Synthesis of tetrahydrobenzo[*b*]pyran (**7**) from cyanocinnamate (**4**)

Table 4. Synthesis of tetrahydrobenzo[*b*]pyran (**7**) from cyanocinnamate (**4**)[a]

Entry	cinnamate (**4**) (R^1 =)	Time[b] (min)	Solvent	Yield (%)[c]
1[d]	H	10	H_2O	0
2	H	10		14
3	H	10	PEG	64
4	H	10	H_2O/ EtOH	81
5	OAc	18		74[e]
6	OTHP	25		56[f]

[a] The reaction was carried out with cyanocinnamate (**4**), dimedone (**6**) (1.2 equiv) and NDEAP (0.1 equiv) in water and ethanol (1 : 1) under microwave heating (100 W).
[b] Total irradiation time
[c] Yields are for isolated pure product based on cinnamate (**4**).
[d] NDEAP was not added.
[e] Yield based on recovered cinnamate (**4**) was 99%.
[f] Yield based on recovered cinnamate (**4**) was 74%.

The reaction with malononitrile also proceeded in satisfactory yields as shown in Table 5. Different from sequential addition employing ethyl cyanoacetate (**2**) described above, all three components were added all at once in the present reaction.

Table 5. Synthesis of tetrahydrobenzo[*b*]pyran (**8**) with malononitrile (**3**)[a]

Entry	Aldehyde (**1**) (R^1 =)	Time (min)[b]	Yield (%)[c]
1[c]	H	10	99
2	OMe	24	94
3	Cl	12	96
4	OH	23	77
6	OTHP	19	86

[a] The reaction was carried out with arylaldehye (**1**), malononitrile (**3**), dimedone (**6**) (1.2 equiv) and NDEAP (0.1 equiv) in water and ethanol (1 : 1) under microwave heating (100 W).
[b] Total irradiation time
[c] Yields are for isolated pure product based on aldehyde (**1**).

In summary, we have developed a new protocol for synthesis of tetrahydrobenzo[*b*]pyrans (**7** and **8**) catalyzed by heterogeneous amine grafted on silica gel (NDEAP) in water under microwave heating. The catalyst was effectively recycled. The present reaction is mild, practical, environmentally benign, and sustainable than the methods developed so far, which would be useful for large-scale preparation.

ACKNOWLEDGEMENTS

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12. Typical experimental procedure: Microwave (100 W) was irradiated in a domestic microwave oven to a mixture of benzaldehyde (**1**) (50 μL, 0.5 mmol), ethyl cyanoacetate (**2**) (65 μL, 0.6 mmol) and NDEAP powder (amine loading: 1.1 mmol/g by combustion analysis, 47 mg, 0.05 mmol) in water (0.5 mL) and ethanol (0.5 mL) for 9 min. The temperature was ramped from room temperature to 80 °C, which was monitored by radiation thermometer. After addition of dimedone (**4**) (71 mg, 0.51 mmol), microwave was irradiated for 10 min. Product was dissolved into ethyl acetate by gentle warming by heat gun. The aqueous layer was extracted with ethyl acetate twice. The combined organic layer was passed through short silica gel column to remove excess dimedone (**4**) and evaporated to dryness. Recrystallization of the residue and subsequent medium-pressure LC purification (eluent: ethyl acetate : hexane = 1 : 1) of the mother liquor provided hydropyran (**5**) (155 mg, 91%).

13. All new compounds have satisfactory analytical data including ^{1}H-NMR, IR and exact MS.