Journal of the Korean Chemical Society
2011, *Vol. 55, No. 4*
Printed in the Republic of Korea
DOI 10.5012/jkcs.2011.55.4.662

Silica Gel을 이용한 효율적인 3,4-dihydropyrano[*c*]chromenes의 합성

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(접수 2011. 2. 1; 수정 2011. 3. 4, 게재확정 2011. 3. 17)

Silica Gel Promoted Mild, Efficient and Inexpensive Protocol for the Preparation of 3,4-dihydropyrano[*c*]chromenes

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(Received February 1, 2011; Revised March 4, 2011; Accepted March 17, 2011)

요 약. 실온에서 방향족 알데히드, 말론니트릴과4-히드록시쿠마린을neat 실리카젤 속에서 one-pot반응시켜서 3,4-dihydropyrano[*c*]chromenes을 좋은 수율로 합성하였다.
주제어: 실리카젤, one pot three-component 축합반응, 방향족 알데히드, 말론니트릴, 4-히드록시쿠마린

ABSTRACT. Highly efficient, three-component condensation of aromatic aldehyde, malononitrile and 4-hydroxycoumarin promoted by neat silica gel at room temperature is described. The method offers an excellent alternative to the synthesis of 3,4-dihydropyrano[*c*]chromenes. The reactions are fast and clean, and the products are obtained with good yield and purity.
Keywords: Silica gel, one pot three-component condensation, aromatic aldehyde, malononitrile, 4-hydroxycoumarin.

INTRODUCTION

Multicomponent reactions (MCRs) allow assembly of several flexible, readily available building blocks in a single operation to give highly functionalized organic molecules.[1,2] MCRs, by virtue of their convergence, productivity, facile execution and generally high yields of products have attracted considerable attention from the point of view of combinatorial chemistry.[3] This synthetic strategy has occupied a unique place in synthetic organic chemistry and in the past decade there has been tremendous development in three- and four- component reactions and great efforts are on to find and develop new MCRs.[4] 3,4-Dihydropyrano[*c*]chromenes (*Fig.* 1) and its derivatives are very useful compounds in various fields of chemistry, biology and pharmacology. Some of these compounds exhibit spasmolytic, diuretic, anticoagulant, anti-cancer, and anti-anaphylactic activity.[6] In addition, they can be used as cognitive enhancers for the treatment of neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, AIDS associated dementia and Down's syndrome for the treatment of schizophrenia and myoclonus.[6] Previously synthesis of 2-amino-4-aryl-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile (*Fig.* 1) from aromatic aldehyde, malononitrile and 4-hydroxycoumarin has been achieved in the presence of a variety of catalysts such as diammonium hydrogen phosphate,[7] $H_6P_2W_{18}O_{62}18H_2O$,[8] TBABr,[9] K_2CO_3 under microwave irradiation.[10] Various organic bases like piperidine, pyridine in organic solvents like ethanol and pyridine,[11] and (*S*)-proline[7] are some of the other catalysts used for the synthesis of this molecule. However, many of these reported methods suffer from drawbacks such as harsh reaction conditions, unsatisfactory yields, prolonged reaction times, cumbersome product isolation procedures and difficulty in recovery and reusability of the catalysts. The development of new methods with the objective of improved yields and green chemistry for the synthesis of above said molecules is a welcome goal because of the wide spectrum of biological activities these molecules possess. Silica gel due to its unique properties like high thermal stability, easy availability, nontoxicity, lowcost and reusability has served as a catalyst in several reactions.[12] Several potential catalyst

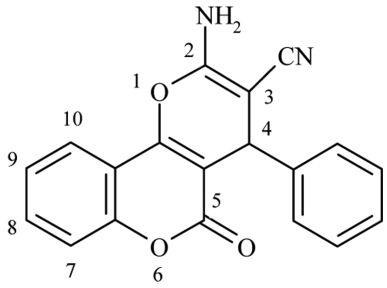


***Fig.* 1.** 2-Amino-4-aryl-5-oxo-4*H*, 5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile.

reuses and waste production minimization are the advantages of using silica gel as a heterogeneous catalyst. Enhanced reaction rates and improved selectivity are obtained in the presence of this catalyst.

EXPERIMENTAL

All the chemicals used are of commercial grade and were used without further purification. The known compounds were characterized by comparison of their physical data, IR, ^{1}H NMR, and LC-mass spectra with those reported in the literature and the novel compounds with their spectral analysis.

General procedure for the synthesis of 2-amino-4-aryl-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitriles

A mixture of aldehyde (**1**,1 mmol), malononitrile (**2**, 1.2 mmol), 4-hydroxycoumarin (**3**,1 mmol) and silica gel (300 wt%) in absolute ethanol (20 vol) was stirred at room temperature for 4h. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the reaction mass was filtered, silica gel washed with THF, filtrate containing the product was reduced to one fourth the volume and the pure product precipitated was filtered, washed with cold ethanol and dried to afford title compound in good to excellent yield.

Products (**4a-4g**) are known compounds and their physical data, IR, and ^{1}H NMR spectra were essentially identical with those of authentic samples. Other products (**4h-4l**), which are new, were characterized by IR, ^{1}H NMR and LCMS analysis.

Novel compound data

Compound 4h: Brown solid, IR (KBr): υ max = 3386, 3132, 1728, 1685, 1645, 1586, 1438, 1246, 817 cm^{-1}; ^{1}H NMR: (400 MHz, DMSO-d$_6$) δ 4.96 (s, 1H), 7.22-7.23 (d, 1H, *J*=4.4 Hz), 7.48-7.52 (t, 2H, *J*=8.0 Hz), 7.72-7.77 (m, 3H), 7.87-7.89 (d, 1H), 8.018.02 (d, 1H, *J*=6.44 Hz); ^{13}C NMR (400 MHz, DMSO-d$_6$) 58.93, 104.87, 113.79, 117.61, 120.52, 123.44, 122.34, 125.24, 127.17, 128.01, 129.97, 133.87, 144.72, 153.60, 154.52, 158.47, 160.14 ppm; MS: *m/z* = 368 (M$^+$).

Compound 4i: Creamish solid, IR (KBr): υ max = 3402, 3224, 1665, 1519, 1434, 1338, 1234, 1068, 813 cm^{-1}; ^{1}H NMR: (400 MHz, DMSO-d$_6$) δ 4.52 (s, 1H), 7.31-7.33 (t, 2H, *J*=1.6 Hz), 7.48-7.54 (m, 4H), 7.72-7.77 (m, 1H), 7.90-7.92 (m, 1H), 8.518.52 (m, 2H); ^{13}C NMR (400 MHz, DMSO-d$_6$) 58.83, 104.87, 113.89, 117.41, 120.12, 123.24, 122.94, 125.54, 127.97, 128.51, 129.37, 133.77, 144.22, 153.00, 154.22, 158.87, 160.44 ppm; MS: *m/z* = 368 (M$^+$).

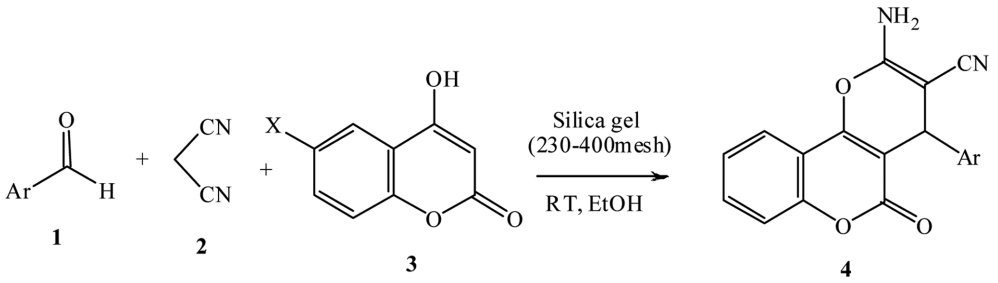
Compound 4j: White solid, IR (KBr): υ max = 3479, 3321, 3197, 2923, 2198, 1704, 1665, 1585, 1377, 1257, 821 cm^{-1}; ^{1}H NMR: (400 MHz, DMSO-d$_6$) δ 2.43 (s, 3H), 3.72 (s, 3H), 4.41(s, 1H), 6.78-6.83 (m, 3H), 7.21-7.25 (t, 1H, *J*=8.0 Hz) 7.35-7.38 (d, 3H, *J*=8.8 Hz), 7.52-7.55 (m, 1H), 7.71 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d$_6$) 57.89, 104.83, 113.81, 117.44, 120.17, 123.29, 122.91, 125.56, 127.98, 128.50, 129.31, 133.72, 144.23, 153.04, 154.25, 158.86, 160.47 ppm; MS: *m/z* = 361 (M$^+$).

Compound 4k: Cream solid, IR (KBr): υ max = 3460, 3325, 3213, 2927, 2194, 1697, 1670, 1380, 1130, 779 cm^{-1}. ^{1}H NMR: (400 MHz, DMSO-d$_6$) δ 2.43 (s, 3H), 3.69 (s, 3H) 3.73 (s, 3H), 4.58(s, 1H), 6.42-6.45 (m, 1H), 6.52-6.53 (d, 1H, *J*=2.4 Hz), 6.97-6.99 (d, 1H, *J*=8.0 Hz), 7.17 (s, 2H) 7.34-7.36 (d, 1H, *J*=8.4 Hz), 7.50-7.53 (m, 1H), 7.71 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d$_6$) 58.89, 103.88, 113.87, 117.46, 121.15, 123.24, 121.93, 125.52, 127.91, 128.59, 129.37, 134.74, 144.26, 153.07, 155.28, 158.89, 160.40 ppm; MS: *m/z* = 390 (M$^+$).

Compound 4l: Yellow solid, IR (KBr): υ max = 3477, 3336, 2198, 1758, 1685, 1586, 1410, 1190, 1185, 1058, 817 cm^{-1} ; ^{1}H NMR: (400 MHz, DMSO-d$_6$) δ 2.43 (s, 3H), 4.66 (s, 1H), 7.36-7.38 (d, 1H, *J*=8.4 Hz) 7.53-7.59 (m, 4H), 7.72 (s, 1H), 8.17-8.19 (d, 2H, *J*=8.8 Hz); ^{13}C NMR (400 MHz, DMSO-d$_6$) 58.13, 104.27, 113.39, 117.41, 120.52, 123.24, 122.94, 125.34, 127.47, 128.51, 129.57, 132.67, 145.22, 152.00, 154.92, 157.77, 160.54 ppm; MS: *m/z* = 375 (M$^+$).

RESULTS AND DISCUSSION

We wish to report a simple, convenient and efficient method for the preparation of 2-amino-4-aryl-5-oxo-4*H*, 5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile using neat silica gel (230-400 mesh) (*Scheme* 1).



***Scheme* 1.**

Reaction of benzaldehyde **1**, malononitrile **2**, and 4-hydroxycoumarin **3** was selected as model reaction and carried out several set of reactions to optimize the conditions. Initially 300 wt% of silicagel was used and the reaction mixture stirred at room temperature in ethanol and the course of the reaction was monitored by TLC analysis. Interestingly the reaction went into completion in 4 hrs and the required product formed as indicated by LCMS. Isolation of the product was done as follows. The reaction mixture was filtered, the silica gel was washed with tetrahydrofuran, the filtrate was evaporated to one fourth the volume and the precipitated compound was filtered, washed with cold ethanol and dried. Meanwhile citric acid, copper iodide, DOWEX and amberlyst were also screened. We found that most of them catalyzed this reaction efficiently in ethanol but the maximum yield obtained was less than the yield with silica gel (300 wt%).

Our next attempt was to reduce the silica gel quantity to see whether we can get the same conversion. But the yields gradually reduced with reduction in the quantity of silica gel (*Table* 1, entries 5,6). One reaction was done without silica gel to see whether silica gel really plays the role. No product formation was observed even after prolonged stirring at room temperature (*Table* 1, entry 8). Since we observed that best conversion of 95% was achieved in ethanol we did not attempt experiments related to change of solvent. From the above observations the optimum condition for the synthesis of 2-amino-4-aryl-5-oxo-4H,5H-pyrano[3,2-c]chromene-3-carbonitriles came out to be the one with ethanol as solvent and 300 wt% of silica gel at room temperature.

***Table* 1.** Synthesis of **4a** using different catalysts at room temperature

Entry	Catalyst	Quantity	Time (hrs)	Yields (%)[b]
1	Citric acid	10 (mole%)	4	68
2	Copper iodide	10 (mole%)	4	70
3	Amberyst	100 (wt%)	4	83
4	DOWEX	100 (wt%)	4	80
5	SiO_2	100 (wt%)	4	82
6	SiO_2	200 (wt%)	4	88
7	SiO_2	300 (wt%)	4	95
8	No catalyst	-	4	100

[a]Reagents: **1a** (1 mmol), **2** (1.2 mmol), **3** (1 mmol), EtOH (20 volume). [b]Isolated yield.

***Table* 2.** Efficiency of the recovered catalyst in the model reaction (in 4 hrs)

Entry	No. of cycles	Yield (%)[a]
1	First	95
2	Cycle I	92
3	Cycle II	89
4	Cycle III	84
5	Cycle IV	80

[a]Isolated yield.

Finally catalyst reusability was checked to see whether the catalyst is more ecofriendly and efficient. After the reaction was over the reaction mixture was filtered and the silica gel bed was washed with enough amount of THF to take out the product. Silica gel that was filtered was dried at 100 °C under reduced pressure for 2 h and the same experiment was done with 300 wt% of the catalyst. Surprisingly the same conversion was observed within 4 hrs. It was reused four times after the same treatment with the catalytic activity reducing only by 15% at the end of the fourth cycle (*Table* 2).

To explore the application of this method, the scope of the substrates was evaluated with a variety of aromatic aldehydes (*Table* 3). It appeared that the electronic nature of the substituent groups in the aromatic ring had no influence on the yield. Both electron donating and electron withdrawing substituents reacted very well to give the products in excellent yields. It is noteworthy that no remarkable steric hindrance on the reaction was observed, for example, the desired products were obtained in good yields when the ortho substituted benzaldehydes were used (*Table* 3, entries 6,7,11).

***Table* 3.** Synthesis of 2-amino-4-aryl-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromenes in the presences of silica gel

Entry	Ar	X	Product	Time (hrs)	Yield (%)	Mp (°C)/(lit.)
1	C_6H_5	H	4a	4	95	257-258 (256-258)[7]
2	4-$CH_3OC_6H_4$	H	4b	4	90	243-244 (240-242)[7]
3	4-$O_2NC_6H_4$	H	4c	4	92	259-261 (258-260)[7]
4	3-$O_2NC_6H_4$	H	4d	4	93	260-261 (262-264)[7]
5	4-ClC_6H_4	H	4e	4	92	265-267 (263-265)[7]
6	2,4-ClC_6H_3	H	4f	4	94	257-258 (257-259)[7]
7	2,3-ClC_6H_3	H	4g	4	91	283-284 (280-282)[8]
8	2-C5H5N	H	4h	4	92	182-184*
9	8-C9H6N	H	4i	4	91	218-220*
10	3-$CH_3OC_6H_4$	CH_3	4j	4	93	266-268*
11	2,4-$(CH_3O)_2C_6H_3$	CH_3	4k	4	92	225-227*
12	4-$O_2NC_6H_4$	CH3	4l	4	94	152-153*

[a]Yields are related to isolated pure products
*Novel compounds

CONCLUSION

In conclusion a new green methodology for the preparation of dihydropyrano[*c*]chromenes through the three-component reaction of aromatic aldehydes, malononitrile (2), and 4-hydroxycoumarin (3) using silica gel in ethanol is described. This procedure offers several advantages including mild reaction conditions, cleaner reaction and satisfactory yields of products as well as simple experimental and isolating procedure which make it an useful and attractive protocol for the synthesis of these compounds.

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