A Cheap Amino Alcohol Catalyzed One-Pot, Tri-Component Synthesis of Tetrahydrochromene Derivatives

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Abstract: An economic, efficient access to 4*H*-chromene derivatives was found. In the presence of *threo*-(1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol, a chiral "waste" in the production of chloromycetin, and one-pot three-component Hantzsch reaction of dimedone, aldehydes and malononitrile at room temperature furnished 4*H*-pyran derivatives in good to excellent yield.

Keywords: 4*H*-chromene, Hantzsch reaction, one-pot synthesis, *threo*-(1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol.

The 4*H*-chromene derivatives possess a variety of biological and pharmacological activities, such as anti-coagulant, anticancer, spasmolytic, anti-anaphylactic, etc [1]. Some 2-amino-4*H*-chromenes can be useful as photoactive materials [2], and pigment [3], whereas polysubstituted 4*H*-chromene constitutes a structural unit of a series of natural products [4]. Considering the importance of the compounds, many methods for the synthesis of 5-oxo-5,6,7,8-tetrahydro-chromene derivatives have been reported successively. The conventional synthesis involves condensation of dimedone with aromatic aldehyde and malononitrile under refluxing in acetic acid [5] or the bicomponent condensation of dimedone with α-cyano- cinnamonitriles in the presence of ethanolic piperidine [6]. Some improved methods are also reported including the use of microwave [7], ultrasonic irradiation [8], and ionic liquid [9]. Recently, some two- and three-component reactions have been catalyzed by utilizing alkylammonium salts [10], (*S*)-proline [11], rare earth perfluorooctanoates [12], base [13], molecular iodine [14], and silica-supported phosphomolybdic acid ($PMA{\cdot}SiO_2$) [15]. Invitingly, Bandgar [16] claimed that his group synthesized high-yieldingly tetrahydrobenzo[*b*]pyran derivatives under reflux through uncatalyzed, three-component, one-pot reactions in aqueous media, though Jin *et al*. [10a] have indicated that the catalyst plays a crucial role for synthesis of tetrahydrobenzo[*b*]pyran derivatives.

Threo-(1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol [ANP], a "chiral waste" in the production of chloromycetin, is one of the cheapest organic basic materials available. Investigation of the reaction and application of **ANP** is significant. For example, alkylation of aldehydes or α-keto esters catalyzed by **ANP** and its derivatives was previously reported [17]. Our group is also interested in **ANP** chemistry, and has revealed some novel chemistry and its derivatives, including selective oxazolidination of **ANP** [18], selective oxidation/formylation of the *N,N*-dimethyl derivative of **ANP** [19], resolution of racemic 1,1'-bi-2-naphthol [20] and ibuprofen [21] using **ANP** derivatives, asymmetric Herny reaction catalyzed by **ANP** derivatives [22] and one-pot, four-component synthesis of 1,4-dihydropyridines catalyzed by **ANP** [23]. In the present letter, we report **ANP**-catalyzed synthesis of 4*H*-chromene derivatives (Scheme **1**).

In the presence of 0.1 equivalent of **ANP**, dimedone was allowed to mix equimolarly with malononitrile and an aldehyde, including aromatic aldehyde, heteroaromatic aldehyde, α,β-unsaturated aldehyde or aliphatic aldehyde, in ethanol at ambient temperature and stirred. A large amount of precipitate isolated out of the reaction system within few minutes (certain reactions were expanded to 20 min), filtered, and the solid was recrystallized in ethanol the desired 4*H*-chromene derivatives were obtained in very high yield for most of the reactions. The **ANP** catalyzed Hantzsch reaction was summarized in Scheme **1**. The results are shown in Table **1**.

Investigation indicated that in the absence of **ANP** or when **ANP** loading was lower than 0.1 equivalent, the Hantzsch reaction merely carried out slowly and furnished the 4*H*-chromene derivatives in low yield, while **ANP** loading was raised to 1 equivalent, the yield of the desired 4*H*-chromene derivatives did not increase obviously. It seems that the selected **ANP** loading is appropriate for efficient occurrence of the Hantzsch reaction.

All the products were characterized by IR, ^{1}H and ^{13}C NMR spectra [25], and **4q** was authorized by the single crystal X ray diffraction analysis [26] (Fig. **1**).

It can be seen in Table **1** that under catalysis of 0.1 equivalent of **ANP**, most of the reactions of aromatic aldehydes afforded the desired product in more than 90% yield, and the composition of aromatic aldehydes and electronic property of the substituent in benzene ring did not influence considerably on the selectivity of the reaction. However, the lower aliphatic aldehyde (Entries 18 and 19) and the α,β-unsaturated aldehyde (Entry 16) furnished the desired products in lower yield as compared with the aromatic or heteroaromatic aldehydes due to better solubility

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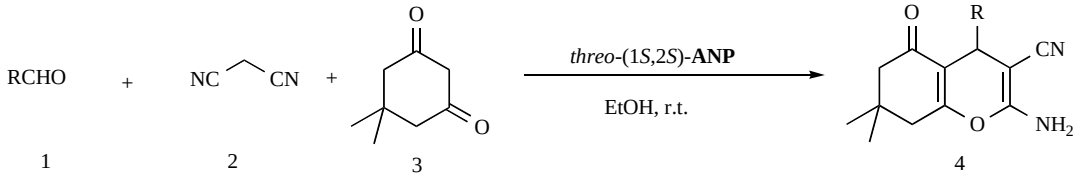


Scheme 1. ANP-catalyzed Hantzsch reaction of dimedone, malononitrile and aldehyde.

Table 1. ANP-Catalyzed Synthesis of 4*H*-Chromene Derivatives[a]

Entry	R of aldehyde	Time (min)	Product	Yield (%)[b]	Mp(°C)	
					Observed	Reported
1	C_6H_5	5	4a	90	228-230	228-230[11]
2	2-ClC_6H_4	5	4b	99	129-131	129-131[9a]
3	4-ClC_6H_4	5	4c	92	208-209	209-210[11]
4	2,4-Cl_2C_6H	5	4d	95	192-194	192-194[11]
5	2,6-$Cl_2C_6H_3$	5	4e	86	236-238	236-238[7c]
6	2-BrC_6H_4	5	4f	95	150-152	150-152[7d]
7	3-BrC_6H_4	5	4g	98	192-194	188-190[9c]
8	4-BrC_6H_4	5	4h	94	203-204	203-205[11]
9	3-$NO_2C_6H_4$	5	4i	97	214-216	212-214[11]
10	4-$NO_2C_6H_4$	5	4j	97	177-178	179-180[11]
11	4-$CH_3C_6H_4$	5	4k	94	213-215	210-212[9a]
12	4-OHC_6H_4	20	4l	89	208-210	206-208[8]
13	2-$CH_3OC_6H_4$	5	4m	83	200-202	201[24]
14	4-$CH_3OC_6H_4$	5	4n	99	199-201	198-200[14]
15	4-$(CH_3)_2NC_6H_4$	5	4o	93	210-212	208-210[8]
16	C_6H_5CH=CH	20	4p	81	182-184	182-184[12]
17	Fur-2-yl	5	4q	98	216-217	218-220[14]
18	$CH_3CH_2CH_2$	20	4r	76	169-171	172-174[12]
19	CH_3CH_2	20	4s	51	174-176	172-174[9c]

[a]All the reactions were carried out in ethanol in the presence of 0.1 equivalent of **ANP**.
[b]isolated yield after recrystallization in ethanol.

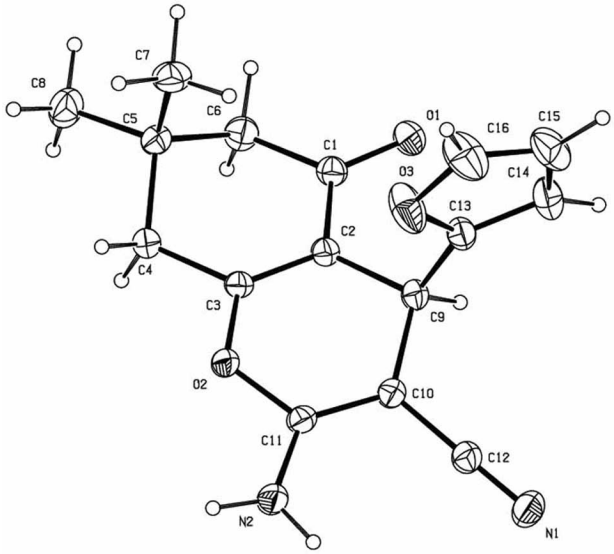
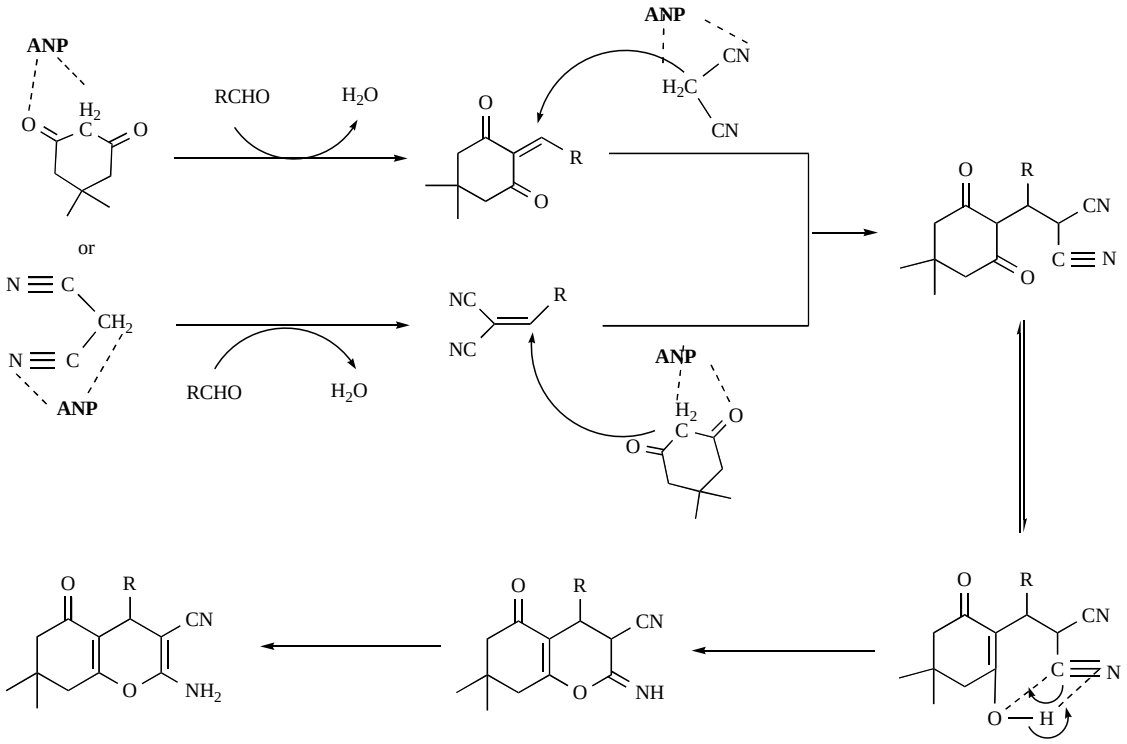


Fig. (1). ORTEP of 4*H*-Chromene **4q** with numbering scheme.



Scheme 2. A possible mechanism of **ANP**-catalyzed Hantzsch reaction.

of the 4*H*-chromene derivatives generated from these aldehydes in ethanol.

In general, in the reaction mediated by methylene compounds bearing α-electron-withdrawing group, the frequently addition of a base can improve reaction efficiency. **ANP** is a 2-amino-1,3-propane- diol derivative. As a base, it can simultaneously activate the C-H bonds of malononitrile and dimedone in the reaction system, thereby promotes the formation of a carbon anion. Furthermore, the H bonding interaction between the hydroxyl group of **ANP** with the cyano group of malononitrile or the carbonyl group of dimedone may stabilize the conformation of the reaction intermediates. Thus, it is favorable for the reaction of the methylene compounds with aldehyde and sequential formation reaction of the desired 4*H*-chromene products. Without doubt, it is because of the characteristics of **ANP** in composition that results in the high efficiency of the Hantzsch reaction. A possible catalytic mechanism of **ANP** towards the one- pot, tri-component reaction was outlined in Scheme **2**.

In conclusion, we have successfully developed a convenient, efficient and versatile method for the synthesis of 4*H*-chromene derivatives *via* one-pot, three-component reaction of dimedone, aldehydes and malononitrile in the presence of **ANP**. Using more inexpensive catalyst, rapid reaction at room temperature, lower energy-consuming, the simple experimental procedure and high yield are the major advantages of this method.

A TYPICAL EXPERIMENTAL PROCEDURE

To a stirred mixture of dimedone (2 mmol), malononitrile (2 mmol) and **ANP** (0.2 mmol) in ethanol (4 mL), aldehyde (2 mmol) was added at room temperature. The reaction was completed within 5 min (in the cases of Entries 12, 16, 18 and 20, the reaction time was extended to 20 min), the resulting precipitate was filtered and recrystallized from ethanol to afford the 4*H*-chromene derivatives in good to excellent yield.

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[25] Spectral data for the selected compounds:
2-amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrochromene-3-carbonitrile (4c) ^{1}H NMR (300 MHz, d_6-DMSO): δ 7.26 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 4.57 (s, 2H), 4.39 (s, 1H), 2.45 (s, 2H), 2.22 (m, 2H), 1.11 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 200.5 161.9, 158.3, 142.6, 131.8, 128.7, 128.0, 119.2, 112.9, 59.1, 50.2, 35.0, 31.7, 28.5, 27.1; IR (KBr): 3381, 2188, 1685, 1674, 1365, 1216 cm^{-1}.
2-amino-4-(3-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrochromene-3-carbonitrile (4g) ^{1}H NMR (300 MHz, d_6-DMSO): δ 7.36 (d, *J* = 7.8 Hz, 1H), 7.27 (s, 1H), 7.22 (d, *J* = 5.7 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.06 (s, 2H), 4.17 (s, 1H), 2.49 (s, 2H), 2.06-2.25 (m, 2H), 1.10 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 200.9, 168.0, 163.7, 152.6, 135.8, 135.1, 134.7, 131.5, 126.7, 124.7, 117.2, 62.8, 55.1, 40.5, 37.0, 33.5, 31.9; IR (KBr): 3345, 2192, 1684, 1669, 1372, 1216 cm^{-1}.
2-amino-4-(4-dimethylaminophenyl)-7,7-dimethyl-5-oxo-5,6,7, 8-tetrahydrochromene-3-carbonitrile (4o) ^{1}H NMR (300 MHz, d_6-DMSO): δ 6.95 (d, *J* = 7.5 Hz, 2H), 6.87 (2H, s), 6.63 (d, *J* = 7.5 Hz, 2H), 4.05 (s, 1H), 2.84 (s, 6H), 2.48 (d, *J* = 5.1 Hz, 2H), 2.10-2.21 (m, 2H), 1.03 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 200.9, 167.1, 163.6, 154.5, 137.8, 133.0, 125.2, 118.5, 117.6, 64.2, 55.3, 39.8, 37.0, 33.7, 32.0; IR (KBr): 3383, 3321, 2191, 1681, 1666, 1368, 1213 cm^{-1}.

[26] Crystallographic data for **4q**: empirical formula, $C_{16}H_{16}N_2O_3$; formula weight, 284.31; calculated density, 1.271 g/cm^3; volume (V), 1485.6(3) Å^3; crystal system, Monoclinic; space group, P2(1)/c; Z = 4; unit cell dimensions, *a* =10.8394 (12) Å, *b* = 9.2687(10) Å, *c* = 14.9186(16) Å, *β* = 97.615(2)°, absorption

coefficient (μ),0.089 mm^{-1}; index ranges: -11≦h≦13, -11≦k≦11, -18≦l≦18; F(000), 600; GOF, 0.974. *T* =273 (2) K, μ(Mo Kα) = 0.71073 mm,$^{-1}$ Of the 8680 measured reflections, 3071 were independent (*R*(int) =0.0189). The final refinements converged at R1 = 0.0396 for $I > 2\acute{o}(I)$ and wR2 = 0.0919 for all data. The structural parameters exhibited are in good agreement with the standard values.

Final atomic coordinates of the crystal, along with lists of anisotropic thermal parameters, hydrogen coordinates, bond lengths, and bond angles, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 695748. Data can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.cn; web: http//www.ccdc.cam.ac.uk).