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Note

Convenient synthesis of 5-oxo-5,6,7,8-tetrahydro-4*H*-1-benzopyrans using LiCl /Al_2O_3 under microwave irradiation

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2-Amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-1-benzopyran-3-carbonitriles **3** have been synthesized conveniently by treating dimedone (5,5-dimethyl-1,3-cyclohexanedione) **1** with arylidenemalononitriles **2** in the presence of lithium chloride in dry media using basic alumina as solid support under microwave irradiation with very good yields.

Keywords: Dimedone (5,5-dimethyl-1,3-cyclohexanedione), arylidenemalononitriles, benzopyran, lithium chloride, basic alumina, solid support, microwave irradiation

In recent years, the synthesis of benzopyran derivatives has attracted great interest. Since the discovery of cromakalim as a typical ATP-sensitive potassium channel opener (PCO), a large number of benzopyran derivatives have been synthesized and demonstrated to possess potent relaxant activity on blood vessels, cardiac muscle and other smooth muscles[1]. These agents may find use in the treatment of a variety of diseases such as hypertension, asthma, ischemia and urinary incontinence. The pyran pharmacophore is an important core structure of many natural products showing antibacterial, antitumor, antiallergic, antibiotic, hypolipidemic and immuno-odulating activities[2,3]. When the hydrogen atom of pyran ring is substituted by amino or cyano, they become synthons[4,5] of some natural products.

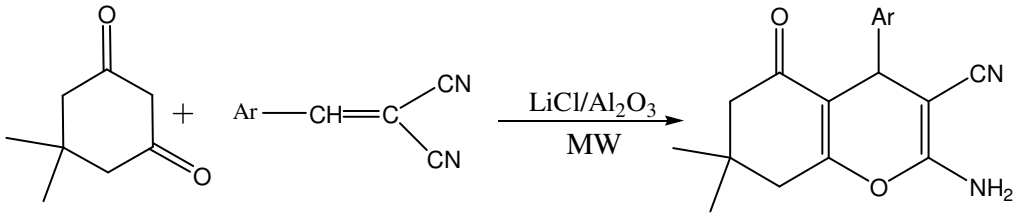
Microwave assisted organic reactions have attracted considerable attention in organic synthesis because of their simplicity, greater selectivity, and rapidity in operation, for the synthesis of a variety of organic compounds[6-8]. Recently, more interest has been focused on "dry media" synthesis using inorganic solid supports. The coupling of microwave heating mode with the use of mineral solid support[9-11] such as alumina, silica and clays have been allowed the synthesis of several organic compounds with higher selectivity, yield and purity compared to traditional methods.

The utility of chloride salts as potential base in variety of synthetic reactions has been recognized in recent years[12]. However, low solubility of chloride salts in ordinary solvents hamper their wide applications in organic synthesis. In our previous papers, we have reported that LiCl is a versatile catalyst for Claisen Schmidt condensation[13], Knoevenagel condensation[14], Doebner modification of the Knoevenagel condensation[15] and Friedlander condensation[16]. LiCl is readily available at low cost and requires no special handling. In this paper, we report LiCl catalyzed synthesis of 2-amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-1-benzopyran-3-carbonitriles under microwave irradiation using basic alumina as solid support.

Treatment of dimedone **1** with arylidenemalono-itriles **2** in the presence of lithium chloride under microwave irradiation using basic alumina as solid support furnished the desired 2-amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-1-benzopyran-3-carbonitriles **3** (**Scheme I**). The reaction proceeds efficiently to completion giving very good yields at ambient pressure within a few minutes. The products were obtained with high degree of purity by this procedure and no further purification was required. It is interesting to note that this reaction did not proceed at all when performed without LiCl. The process is environmentally benign. The experimental procedure is very simple.

In a typical case, an equimolar mixture of dimedone **1**, benzylidenemalanonitrile **2a** and LiCl, deposited on basic alumina, was exposed to microwave irradiation at 800 W for 4.5 min. The reaction was allowed to attain RT and extracted with methanol. After usual work up 2-amino-4-phenyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-1-benzopyran-3-carbonitrile **3a** (Ar = C_6H_5) was obtained in 85% yield. The reaction is of general applicability and the different benzopyrans **3** synthesized are given in **Table I**.

The reaction proceeds to only 5-8% in 4.0-5.0 min, when conducted under conventional conditions in an oil-bath preheated to 120ºC (measured at the end of exposure during microwave experiment), thus



1 **2** **3**

Ar	**Ar**
a : C_6H_5	**g** : 4-NO_2 C_6H_4
b : 4 – $CH_3C_6H_4$	**h** : 4-HOC_6H_4
c : 4 – $CH_3OC_6H_4$	**I** : 4-HO-3-$CH_3OC_6H_3$
d : 2 - Cl C_6H_4	**j** : 3,4-$(CH_3O)_2C_6H_3$
e : 4 -Cl C_6H_4	**k**: 3,4-$(OCH_2O)C_6H_3$
f : 3-NO_2 C_6H_4	

Scheme I

Table I — 2-Amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-1-benzopyran-3- carbonitriles **3**.

Compd	Ar	Reaction Time (min)	Yield (%)	m.p.(°C) Found	m.p.(°C) Reported[17-19]
3a	C_6H_5	4.5	85	226-28	226-28
3b	4 – $CH_3C_6H_4$	4.0	92	208-09	208-10
3c	4 – $CH_3OC_6H_4$	4.5	90	198-200	198-200
3d	2 - Cl C_6H_4	4.0	87	201-03	200-02
3e	4 -Cl C_6H_4	4.5	95	207-09	207-09
3f	3-NO_2 C_6H_4	4.5	86	213-14	213-14
3g	4-NO_2 C_6H_4	5.0	84	176-77	176-78
3h	4-HO-C_6H_5	4.0	85	211-12	211-12
3i	4-HO-3-$CH_3OC_6H_3$	4.5	85	239-40	239
3j	3,4-$(CH_3O)_2C_6H_3$	4.5	87	181-83	181-83
3k	3,4-$(OCH_2O)C_6H_3$	4.0	88	211-13	212-14

demonstrating the advantage of the microwave heating method.

To the best of our knowledge this is the first report on rapid synthesis of benzopyrans using LiCl as catalyst under microwave irradiation.

In conclusion, we have developed a facile and effective procedure for carrying out the synthesis of 2-amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-1-benzopyran-3-carbonitriles **3** in the presence of LiCl under microwave irradiation. Compared to the previous methods, this new protocol has the advantages of very good yields, low cost, short reaction time, simple operation and environmental friendliness.

Experimental Section

All the melting points were measured on a Cintex melting point apparatus and are uncorrected. The homogeneity of the compounds was checked using precoated TLC plates (Merck, 60F-254). IR spectra (KBr) were recorded on a Perking-Elmer spectrum BX series FT-IR spectrophotometer and ^{1}H NMR spectra on a Varian Gemini 200 MHz spectrometer (chemical shifts in δ, ppm). Microwave irradiation was carried out in a domestic microwave oven (LGMG 556P, 2450 MHz).

General procedure for the preparation of 2-amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahyro-4*H*-1-benzopyran-3-carbonitriles, 3. Alumina (3 g) was added to the mixture of dimedone 1 (0.01 mol), appropriate arylidenemalononitrile 2 (0.01 mol) and lithium chloride (0.01 mol) at RT. The reaction mixture was thoroughly mixed and the powder was then subjected to microwave irradiation at 800 W intermittently at 30 sec intervals for the specified time (**Table I**). After completion of the reaction as indicated by TLC, the reaction mixture was cooled to RT and treated with methanol (25 mL). The methanol solution was poured into ice cold water, the precipitated solid was filtered, washed with water and purified by recrystallization from ethanol to afford **3** (**Table I**). The products were identified by comparison with authentic samples[17-19] as well as spectroscopic techniques.

Spectral data for selected compounds

3a: R (KBr): 3397, 3325, 2961, 2200, 1661, 1604 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.03 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.20 (d, 1H, C_8-H), 2.89 (d, 1H, C_8-H), 2.47-2.58 (m, 2H, C_6-H_2), 4.33 (s, 1H, C_4-H), 5.76 (s, 2H, NH_2), 7.16-7.51 (m, 5H, Ar-H).

3b: IR (KBr): 3395, 3333, 2958, 2196, 1667, 1602 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 1.03 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.20 (d, 1H, C_8-H), 2.61 (d, 1H, C_8-H), 2.28 (s, 3H, CH_3), 2.45-2.58 (m, 2H, C_6-H_2), 4.32 (s, 1H, C_4-H), 5.39 (s, 2H, NH_2), 7.04-7.40 (m, 4H, Ar-H).

3c: IR (KBr): 3337, 3325, 2963, 2199, 1684, 1608 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 1.02 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.19 (d, 1H, C_8-H), 2.89 (d, 1H, C_8-H), 2.46-2.58 (m, 2H, C_6-H_2), 3.76 (s, 3H, OCH_3), 4.29 (s, 1H, C_4-H), 5.74 (s, 2H, NH_2), 7.12-7.43 (m, 4H, Ar-H).

3d: IR (KBr): 3338, 3330, 2961, 2194, 1665, 1600 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 1.05 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.18 (d, 1H, C_8-H), 2.57 (d, 1H, C_8-H), 2.47-2.57 (m, 2H, C_6-H_2), 4.84 (s, 1H, C_4-H), 5.75 (s, 2H, NH_2), 7.10-7.48 (m, 4H, Ar-H).

3e: IR (KBr): 3392, 3360, 2963, 2192, 1655, 1605 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 1.02 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.19 (d, 1H, C_8-H), 2.58 (d, 1H, C_8-H), 2.20-2.45 (m, 2H, C_6-H_2), 4.36 (s, 1H, C_4-H), 5.62 (s, 2H, NH_2), 7.15-7.33 (m, 4H, Ar-H).

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