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Microwave assisted Friedländer condensation: A comparative study of conventional *versus* microwave mediated solvent-free methodologies

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4-Arylquinolines have been prepared by Friedländer reaction with acid as a catalyst and without the catalyst under microwave assisted solvent-free conditions and compared with classical heating.

Keywords: 4-Arylquinolines, Microwave synthesis

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The acid catalyzed Friedländer synthesis[1, 2] is one of the most elegant methods for the syntheses of biologically important 4-arylquinolines[3], which involves the condensation between 2-aminobenzophenones and a variety of ketones having α-methyl or α-methylene group. Unlike the classical Friedländer reaction[4], the acid catalyzed condensation improved the yields of 4-arylquinolines and was found to be a convenient method for those ketones, which were otherwise difficult to undergo Friedländer condensation[1].

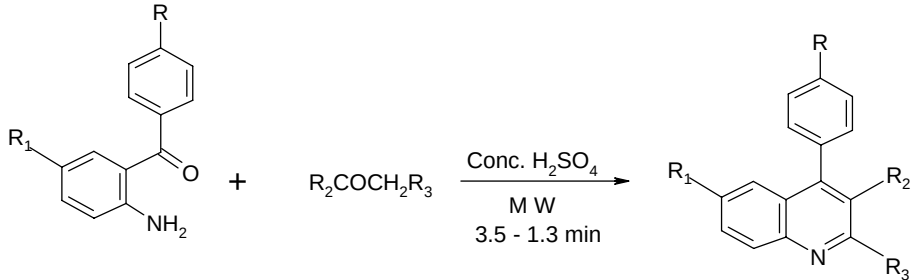
Friedländer reactions are usually carried out in the presence of a base by heating the reactants from 150° to 220°C without solvents and catalysts[1]. The base catalyzed condensation reaction between 2-aminobenzophenones and ethyl acetoacetate could not take place. However, it underwent the thermal cyclization in the absence of a catalyst to give 3-acetyl-4-aryl-2-oxoquinolines[2].

In recent times, microwave assisted chemical reactions[5] have been gaining importance due to its remarkable advantages such as increase in yields, decrease in reaction period, easier work-up and solvent free reaction conditions[6].

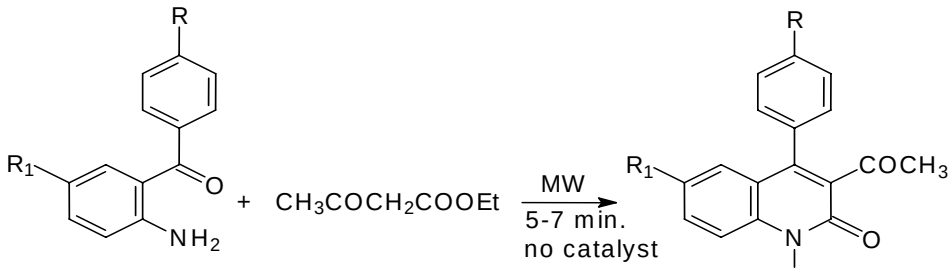
Therefore, in continuation of our interest in microwave-assisted reactions[7-9], we report the Friedländer quinoline synthesis, under solvent-free microwave irradiation using conc. H_2SO_4 as a catalyst and without any catalyst.

When 2-aminobenzophenones **1** were reacted with ketones **2** using conc. H_2SO_4 as a catalyst, 4-arylquinolines **3** were obtained. However, the condensation between 2-aminobenzophenones and ethyl acetoacetate in the absence of a catalyst gave 3-acetyl-4-aryl-2-oxoquinolines **4** under environmentally benign microwave assisted solvent-free conditions.

2-Aminobenzophenones **1**, ketones **2** and 2-3 drops of conc. H_2SO_4 were mixed and irradiated in a domestic microwave oven at an output of 70 W for 3.5 to 13 min to obtain 4-arylquinolines **3** in excellent yields (70-99%). When cyclohexanone and cyclo-



1 **2** **3**



pentanone were used as ketones 1,2,3,4-tetrahydro-9-arylacridines and 2,3-dihydro-9-aryl-1*H*-cyclopenta-[b]quinolines were the main cyclization products, respectively. However, when a mixture of 2-aminobenzophenones **1** and ethyl acetoacetate was irradiated at higher output (700 W) for 5 to 7 min without a catalyst, 3-acetyl-4-aryl-2-oxoquinolines **4** were obtained in excellent yields (80-91%).

In an acid catalyzed synthesis, the condensations of aromatic amines occur at the ketone function to produce **3**. The mode of cyclization in an acid catalyzed condensation of 2-aminobenzophenones thus corresponds to that observed in their base catalyzed condensation with 2-aminobenzaldehyde[2]. In an alternative reaction path, the condensation of aromatic amines occur at the ester group of ethyl acetoacetate in the absence of any catalyst to give **4**.

The temperature of the reactants was measured after the completion of the reaction and at that temperature the reactions were carried out in a paraffin bath under solvent-free thermal conditions. The results were similar to those of conventional Friedländer syntheses.

Neither improvement in yields nor reduction in reaction period could be achieved when an oil-bath was used for thermal cyclization. The above facts supported the role of microwave irradiation in rate enhancement of Friedländer condensation.

An attempt to replace conc. H_2SO_4 by an acidic montmorillonite KSF clay was not found beneficial. 2-Aminobenzophenones **1**, ketones **2** and mont-morillonite KSF clay[10] were mixed and stirred with THF thoroughly for 0.5 hr. The THF was distilled off *in vacuo*, and the reactants were irradiated in a microwave oven at higher output (700 W) and longer duration (10-15 min), but the complete conversion could not take place. When ethyl acetoacetate was used, 3-acetyl-4-aryl-2-oxoquinolines **4** was the main cyclization product instead of 4-arylquinolines **3**.

In conclusion, we have developed an environmental friendly Friedländer reaction catalyzed by acid as well as without catalyst under solvent-free microwave irradiation with increase in yields and decrease in the reaction time period.

Experimental Section

Melting points were determined by electrothermal method in an open capillary tube and are uncorrected. The FTIR spectra in cm^{-1} were recorded in KBr pellets on a spectrum one spectrophotometer; and ^1H NMR spectra on a Varian model-400 spectrometer using TMS as the internal reference. The purity of the compounds was routinely checked by TLC using silica gel-G and the spots were exposed in iodine vapour. For the microwave irradiation, a conventional (unmodified) domestic BPL (BMO 700T) microwave oven was used.

General procedure for the synthesis of 4-aryl-quinolines 3. A mixture of 2-aminobenzophenones (**1**, 0.01mole), ketones (**2**, 0.01mole) and conc. H_2SO_4 (2-3 drops, AR grade) was taken in a borosil test tube and irradiated in an unmodified domestic microwave oven at 70 Watts for 3.5 to 13 min (monitored by TLC). The resultant mixture was cooled to room temperature; cold water added, the mixture was neutralized to *p*H 7 by aqueous ammonia solution (10% v/v). 4-Arylquinolines **3** thus separated, was cooled, filtered under suction, washed with cold water, dried and crystallized using ethanol-water (5:5) (see **Table I**).

General procedure for the synthesis of 3-acetyl-4-aryl-2-oxoquinolines 4. A mixture of 2-amino-benzophenones (**1**, 0.01mole) and ethyl acetoacetate (0.01 mole) was subjected to microwave irradiation at an output of 700 Watts for 5 to 7 min (monitored by TLC). The resulting suspension was brought to room temperature, cold water was added and the mixture was neutralized by aqueous ammonia solution (10% v/v), filtered, washed thoroughly with cold water, dried to afford 3-acetyl-4-aryl-2-oxoquinolines **4** which were crystallized from ethyl alcohol (see **Table II**).

Table I — Microwave assisted synthesis of compounds **3a-p**

Compd	R	R_1	R_2	R_3	Time observed (reported)	Yield (%) observed (reported)	m.p. °C observed (reported)
3a	H	H	CH_3	COOEt	3.5 min (2 hr[1])	91 (85[1])	99-100 (99-100[1])
3b	H	H	CH_3	$COCH_3$	8 min (2 hr[2,13])	91 (84[2,11])	114-15 (113-14[11])
3c	H	H	$CH_2CH_2CH_2CH_2$		7 min (4 hr[1])	86 (83[1])	143-44 (142-43[1])
3d	H	H	$CH_2CH_2CH_2$		7 min (6 hr[1])	88 (87[1])	133-34 (134-35[1])
3e	CH_3	H	CH_3	COOEt	5 min —	93 —	123-24 —
3f	CH_3	H	CH_3	$COCH_3$	4 min —	93 —	130-31 —
3g	CH_3	H	$CH_2CH_2CH_2CH_2$		5 min —	82 —	145-46 —
3h	CH_3	H	$CH_2CH_2CH_2$		8 min —	93 —	143-44 —
3i	**F**	H	CH_3	COOEt	5 min (10 hr[3])	92 —	119-20 (121-22[3])
3j	F	H	CH_3	$COCH_3$	13 min —	97 —	137-40 —
3k	F	H	$CH_2CH_2CH_2CH_2$		6 min —	70 —	170-71 —
3l	F	H	$CH_2CH_2CH_2$		9 min —	90 —	146-47 —
3m	H	Cl	CH_3	COOEt	5 min (10-11 hr[14])	95 (60-96[12])	100-101 (101-02[12])
3n	H	Cl	CH_3	$COCH_3$	5 min (10-11 hr[14])	94 (60-96[12])	152-53) (153-55[12])
3o	H	Cl	$CH_2CH_2CH_2CH_2$		4 min (3.5 hr[15])	85 (52[13])	158-60 (160-61[13])
3p	H	Cl	$CH_2CH_2CH_2$		7 min —	99 —	99-100 —

Table II — Microwave assisted synthesis of compounds **4a-d**

Compd	R	R_1	Time observed (reported)	Yield (%) observed (reported)	m .p. °C observed (reported)
4a	H	H	7 min (1.5 hr[14])	80 (60[14])	247-48 (251-52[14])
4b	CH_3	H	6 min —	87 —	252-53 —
4c	F	H	5 min —	80 —	248-50 —
4d	H	Cl	5 min (3 hr[15])	91 (81[15])	273-74 (274-75[15])

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References

1 Fehnel E A, *J Org Chem*, 31, **1966**, 2899.
2 Fehnel E A, *J Heterocycl Chem*, 4, **1967**, 565.
3 Yoshihiro F, Mitio S, Hiroshi I, Mitsuaki S & Masaki K, *Eur Par Appl EP* 304, 063 (Cl C07 D 215/14), 22 Feb **1989**, *JP Appl* 87/207, 224, 20 Aug **1987**, 46pp.
4 Friedländer P, *Ber dt chem Ges*, *15*, **1882,** 2572.

5 (a) Abramovich R A, *Org Prep Proceed Int*, 23, **1991,** 683.
(b) Laurent R, Laporterie A, Berlan J D J, Lefeuvre S & Audhuy M, *J Org Chem*, 57, **1992**, 7099.
(c) Bose A, Manhas M, Shah M, Raju V, Bari S, Newz S, Banik B, Chaudary A & Barakat K, *J Org Chem*, 58, **1991**, 6968.
(d) Caddick S, *Tetrahedron*, 51, **1995**, 10403.
6 (a) Varma R S, Dahiya R & Saini R K, *Tetrahedron Lett*, 38, **1997**, 8819.
(b) Varma R S, Dahiya R & Saini R K, *Tetrahedron Lett*, 38, **1997**, 7029.
7 Dave C G & Shah R D, *Heterocycl*, 51, **1999**, 1819.
8 Dave C G & Augustine C, *Indian J Chem*, 40B, **2001**, 403.
9 Dave C G & Joshipura H M, *Indian J Chem*, 41B, **2002**, 650.
10 Sabitha G, Satheeshbabu R, Subbareddy B V & Yadav J S, *Synth Commun*, 29, **1999**, 4403.
11 Fehnel E A & Cohn D E, *J Org Chem* 31, **1966**, 3852.
12 Yasuo T, Kakuzo I & Yasaburo F, *Chem Abstr*, 70, **1969**, 106347d.
13 Mack H M, Davis E A, Kadkhodayan B, Taylor R A, Duncan D C & Bean C F J, *Heterocycl Chem*, 24, **1987**, 1733.
14 Borsche W & Sinn F, *Ann Chem*, 538, **1939**, 283.
15 Szmuszkovicz J, Baczynskyj L, Chidester C C & Duchamp D, *J Org Chem*, 41, **1976**, 1743.