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Microwave enhanced synthesis of 4-aminoquinazolines

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Abstract

Cyanoaromatic compounds react with anthranilonitrile in a domestic microwave oven affording good yields of the corresponding 4-aminoquinazolines in a very short irradiation time.

Keywords: quinazolines; amino nitriles; microwave heating.

Quinazolines are a wide family of compounds with well-known pharmacological properties:[1–5] analgesic, narcotic, anti-malarial, sedative or hypoglycaemic. Among the different substitution patterns that are known, 4-aminoquinazolines are useful as fungicides[6,7] and as anti-inflammatory,[8,9] anti-cancer,[10] anti-microbial and anti-hypertensive agents.[11,12]

Quinazolines have not been the object of new synthetic developments in the last few years and recent reports on their preparation use only classical methods.[13] This fact joined to the circumstance that the main part of the literature on 4-aminoquinazolines is covered by patents, led us to carry out studies to improve the synthesis of these compounds bearing in mind new synthetic methodologies. In later years, microwaves have become popular among synthetic organic chemists both to improve classical organic reactions[14–20] shortening reaction times and/or improving yields, as well as to promote new reactions.

Our previous experience in the use of microwaves,[21,22] led us to check if there was any possibility for improvement in methods used for the synthesis of 4-aminoquinazolines. Most of them start from cyanophenyltriazenes,[23] *o*-azidobenzonitriles and nitriles,[24] *o*-aminonitriles and nitriles.[25] These procedures employ high temperatures and various solvents. Often when carrying out a reaction in a microwave oven, the use of a solvent can be avoided which is important in order to make the synthesis more environmentally friendly (‘green chemistry’).

We performed our first experiment by heating anthranilonitrile (**1a**) in the presence of *t*-BuOK and after 1 min we obtained 4-amino-2-(2-aminophenyl)quinazoline **2a** (Scheme 1). We assayed different ratios of alkoxide, obtaining our best yield (82%) using 10% of *t*-BuOK; other bases such as: NaH, MeONa and lithium bis(trimethylsilyl)amide were unsuitable for our experiments.

Once we realised the viability of the use of a microwave oven for this reaction, we studied the possibility of mixed couplings. Anthranilonitrile was reacted with several aromatic nitriles (Table 1, entries

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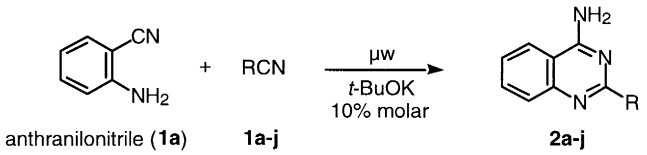

anthranilonitrile (**1a**) **1a-j** **2a-j**

a R= 2-aminophenyl, **b** R= phenyl, **c** R= 4-methoxyphenyl, **d** R= 3-cyanophenyl, **e** R= 2-thiophenyl, **f** R= 2-furanyl, **g** R= 4-pyridyl, **h** R= 3-pyridyl, **i** R= 2-pyridyl, **j** R= benzyl

Scheme 1. Synthesis of 4-aminoquinazolines

2–10). Benzonitrile (**1b**) gave **2b** in a very good yield (93%) using a ratio of anthranilonitrile:benzonitrile 1:1, without any self condensation product **2a**. A synthesis of **2b** has been described[25] in 39% yield, by heating anthranilonitrile with a slight molar excess of benzonitrile in methanolic ammonia in a sealed tube (20 h at 200°C); no reaction occurred in refluxing methanol in the presence of sodium methoxide. These authors also reported the absence of a reaction between anthranilonitrile and nitrile **1c**. Meanwhile, we obtained quinazoline **2c** (76% yield) from 4-methoxybenzonitrile (**1c**) under microwave irradiation for 1 min.

Table 1
Synthesis of 4-aminoquinazolines

Entry	Nitrile	4-Aminoquinazoline	t/min	Yield[a,b] (%)	mp (ref.)/°C
1	**1a**	**2a**	1	82	Hydrochloride 287-288 (288-290[26])
2	**1b**	**2b**	2	93	143-145 (145-146[25])
3	**1c**	**2c**	1	76	Hydrochloride 257-260 (256-259[27])
4	**1d**	**2d**	2	85	226-227
5	**1e**	**2e**	1.5	90	188-190
6	**1f**	**2f**	1.5	84	216-218 (219-221[11])
7	**1g**	**2g**	2	91	Hydrochloride 280-281 (280[11])
8	**1h**	**2h**	0.5	79	Hydrochloride 232-233 (232-235[11])
9	**1i**	**2i**	1.5	85	Hydrochloride 235-237 (235[11])
10	**1j**	**2j**	3	73	218 (221[24])

[a] All yields are from the products purified by crystallization.

[b] All products gave satisfactory combustion analyses.

In these reactions we had to define the amount of base and, after several experiments, we fixed the ratio of *t*-BuOK as 10% with respect to the molar amount of **1a**.

When 1,3-dicyanobenzene (**1d**) was treated with anthranilonitrile in a ratio of 1:1, it gave an 85% yield of 4-amino-2-(3-cyanophenyl)quinazoline (**2d**).† The yields were also very good with 2-thiophenenitrile (**1e**) and with 2-furanonitrile (**1f**) yielding **2e**‡ and **2f**, respectively. In the series of 2-pyridinoquinazolines,

† 4-Amino-2-(3-cyanophenyl)-quinazoline (**2d**). ^{1}H NMR (Cl_3CD, 300 MHz): δ 8.84 (s, 1H), 8.78 (d, 1H), 7.95 (d, 1H), 7.82–7.72 (m, 3H), 7.61–7.52 (m, 2H), 5.81 (br s, 2H). ^{13}C NMR (Cl_3CD, 75 MHz): δ (selected C=N signals) 161.5, 150.8. MS: *m/z* 246 (M^+, 24%).

‡ General procedure. A mixture of anthranilic acid (**1**) (100 mg, 0.846 mmol), 2-thiophenenitrile (**1e**) (92 mg, 0.843 mmol) and potassium *tert*-butoxide (10 mg, 0.089 mmol) in a test tube was heated in a domestic microwave oven (1000 W, 70% of total power) until no starting materials were observed by TLC (1.5 min). The crude reaction was purified by crystallization from methanol to afford 4-amino-2-(2-thiophenyl)-quinazoline (**2e**) (173 mg, 90%). ^{1}H NMR (CD_3OD, 300 MHz): δ 8.19 (d, 1H), 8.14 (d, 1H), 7.89 (s, 2H), 7.68 (d, 1H), 7.55 (m, 1H), 7.28 (t, 1H). ^{13}C NMR (CD_3OD, 75 MHz): δ (selected C=N signals) 164.8, 160.0. MS: *m/z* 227 (M^+, 100%).

we prepared 4-amino-2-(4-pyridyl)quinazoline (**2g**), 4-amino-2-(3-pyridyl)quinazoline (**2h**) and 4-amino-2-(2-pyridyl)quinazoline (**2i**) in good yields.

We also prepared 4-amino-2-benzylquinazoline (**2j**) using an equimolar ratio of **1a** and benzyl cyanide. We wanted to check the performance of the classical methods for the preparation of this quinazoline. Thus we refluxed **1a** with an excessive amount of **1j** (400% molar) and *t*-BuOK (100% molar) in isopropanol; after 48 h we isolated only a 40% yield[§] of quinazoline **2j**.

We have established the advantages of using a domestic microwave oven as a heating device in the synthesis of 4-aminoquinazolines as: the absence of solvent, a radical decrease in reaction time, the use of a catalytic amount of base, and an improvement over precedent synthesis using conventional heating.

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[§] If the reaction is carried out using equimolar amounts of **1a** and **1j**, no formation of the 4-aminoquinazoline **2j** is observed.