Microwave reaction of diazonium salts with nitriles

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A series of aryldiazonium tetrafluorborates dissolved in nitriles have been converted into the corresponding anilides in almost quantitative yield in 1 min by microwave irradiation. When bromoacetonitrile was used, 2,4-bis(bromophenyl)-quinazoline was formed. The reaction of malononitrile with the diazonium salt, in DMF as a solvent, afforded 2-(dimethylaminomethylene) malononitrile and phenylhydrazone propanedinitrile.

Keywords: aryldiazonium tetrafluorborates, anilides, microwaves, 2,4-bis(bromomethyl)-quinazoline

The preparation of anilides by the reaction of an aromatic amine and an acylating reagent is well-known. However, this reaction may become difficult if the aniline has another group which can be acylated, such as an alcohol function. In this case prior protection of this group is required, as well as a final deprotection step to get the desired product. We present a very easy procedure through a simple diazotization followed by a one-minute microwave reaction of the resultant salt with a nitrile. The process is summarised in Scheme 1. Almost quantitative yields of the corresponding anilides **3** were obtained, (Table 1).

An aniline containing another group which can be acylated, such as m-hydroxymethylaniline, has also been studied. Microwave irradiation of the m-hydroxymethyl-benzenediazonium salt led to the corresponding anilide[12] in 71% yield. However, this reaction was highly dependent on the volume of the nitrile employed. The best result (71% yield) was obtained when only 0.3 ml of acetonitrile (vs 1 mmol of the diazonium salt) was used. An increase, for instance to 1 ml/1 mmol of salt (general experimental conditions in all the cases indicated in Table 1) led, surprisingly, to the formation of the doubly acylated product **3'** (as a minor product) in a ratio **3**:**3'** of 60 : 40.

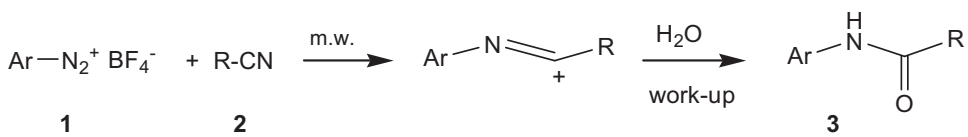
Anilides have important applications in the improvement of perception and memory[13] and as prophylactic and therapeutic treatment of hyperlipidemia and/or arteriosclerosis.[14] When bromoacetonitrile was used, the corresponding acetanilide[15] was obtained, but only in a 5% yield. In this case the main product (73% yield) was the novel 2,4-bis(bromomethyl) quinazoline (**4**). Its formation is indicated in Scheme 2.

The electron-withdrawing effect of the halogen atom, leads to a carbocation which is very reactive towards a bromoacetonitrile. A second carbocation then reacts by an electrophilic substitution on the aromatic ring yielding **4**. Cyclisation reactions from diazonium salts and nitriles affording six- and seven-membered heterocyclic nitrile-adducts have been described previously.[16] Some quinazolines have been employed in flame-resistant thermoplastic moulding composites[17] and as pesticides.[18]

When malononitrile was used, the monoanilide[19] (55%) was the only product, even with an excess of the diazonium salt. However, when a DMF solution (10 ml) of the diazonium salt (2 mmol) with malononitrile (1 mmol) was irradiated for one minute, 2-(dimethylaminomethylene)malononitrile (**5**) (71%) and phenylhydrazone propanedinitrile (**6**) (8%) were obtained. The formation of **5** can be rationalised as indicated in Scheme 3.

In spite of the fact that the equilibrium is shifted to the left, the acidic character of the malononitrile creates traces of the carbanion in solution to allow the reaction to progress.

The resultant enamine **5** can be used to improve the image contrast in migration imaging members[20] or as phase change inks for ink jet printing.[21]



1 **2** **3**

Scheme 1

Table 1 Yields(%) of anilides (**3**) by microwave radiation; melting points of **3**

Ar: (**1**: Ar-N_2^+ BF_4^-)	R: (**2**: R-CN)	**% 3** Ar-NH-CO-R	M.p./°C of **3**[ref]
a: C_6H_5	Me	97	113–115[1]
b: 4-Et–C_6H_4	Me	98	86–88[2]
c: 3-Me–C_6H_4	Me	97	62–63[3]
d: 2-Me–C_6H_4	Me	96	105–108[4]
e: 4-MeO–C_6H_4	Me	97	129–130[5]
f: 2-MeS–C_6H_4	Me	98	111–113[6]
g: 4-Cl–C_6H_4	Me	96	178[7]
h: 4-Br–C_6H_4	Me	97	167[8]
i: 4-MeCO–C_6H_4	Me	98	168–170[8]
j: 4-MeOCO–C_6H_4	Me	98	127[9]
k: C_6H_5	Et	97	106–108[1]
l: C_6H_5	Pr	95	91–93[1]
m: C_6H_5	C_6H_5	70	161–163[10]
n: C_6H_5	C_6H_5–CH_2	97	116–118[1]
o: C_6H_5	C_6H_5–CH_2–CH_2–	65	98–100[11]

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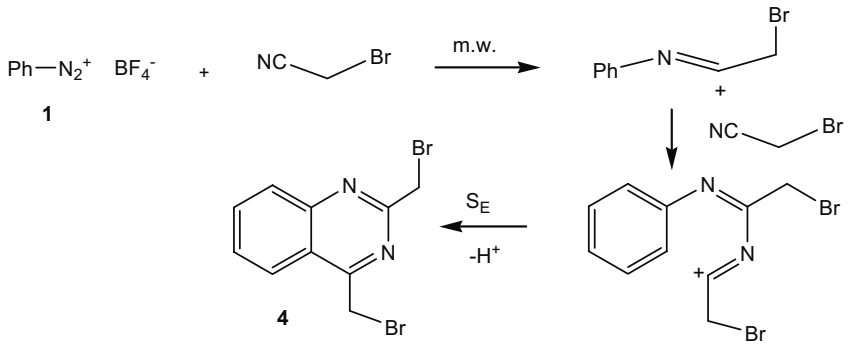
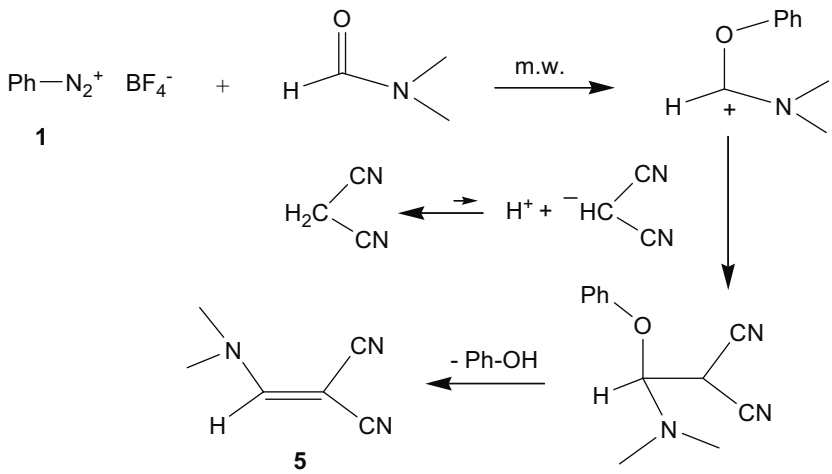


Scheme 2



Scheme 3

However, when a DMF solution (3 ml) of the diazonium salt (2 mmol) with malononitrile (1 mmol) was radiated, the product distribution was changed, affording **5** 21% and **6** 64%, under these more concentrated conditions. The formation of hydrazone **6** can be rationalised as indicated in Scheme 4.

The application of **6** as an insecticide is well known.[22]

In conclusion, we have developed a rapid fairly general protocol for the synthesis of anilides.

Experimental

MS spectra (EI, ionising voltage 70ev) were determined with a Hewlett–Packard Model 5988A mass-selective detector equipped with a Hewlett–Packard MS Chem Station. IR spectra were obtained, as dispersions in KBr, on a Perkin–Elmer FT-IR spectrometer Model Spectrum 2000. ^{1}H NMR and ^{13}C NMR (300 MHz & 75.4 MHz respectively) spectra were recorded on a Varian Unity 300 with deuteriochloroform as an internal standard. The chemical shifts are given in ppm. Microwave reaction was performed in a Moulinex domestic oven, model Quickchef 600.

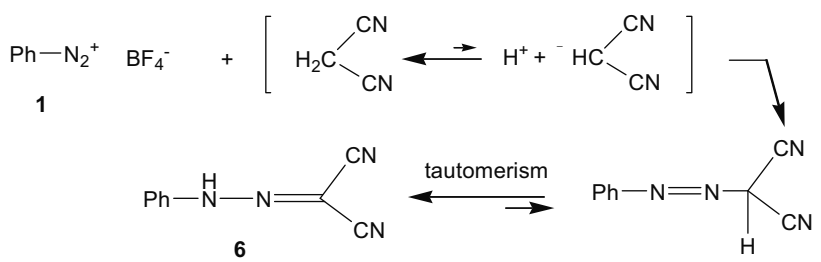
Melting points were determined on a Reichert Thermovar microhot stage apparatus, and are uncorrected. Elemental analyses were performed on a Perkin–Elmer Model 240-B analyser. The products were purified by silica gel 60 (35–70 mesh).

The tetrafluorborates of aryl diazonium (**1**) were prepared according to conventional methods.[23] The microwave apparatus was calibrated at 70watts.

General procedure

A solution of **1** (192 mg, 1 mmol) in dry nitrile (**2**) 1 ml was exposed to the microwave radiation for one minute. The remaining nitrile was then removed under reduced pressure. The residue was extracted with diethyl ether (3 × 50 ml)/water and the organic phase dried over Na_2SO_4 and concentrated by evaporation. The resulting solid, was chromatographed on silica gel (16 × 2.5 cm) column, using CH_2Cl_2/EtOH (25 : 1) as eluent. The physical and spectroscopic properties of the resultant anilides (**3**) were coincident with those described in the literature.

When the reaction is carried out with malononitrile, under the same experimental conditions, but in the presence of DMF as solvent (10 ml or 3 ml), compounds **5** or **6** were respectively obtained.



Scheme 4

2,4-Bis(bromomethyl)quinazoline (**4**): (232 mg, 73% yield). m.p. 155–157 °C (from EtOH). IR (KBr) ν/cm^{-1} = 3018, 2965, 1612, 1558, 1202, 1124, 776. ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 4.74 (s, 2H), 4.9 (s, 2H), 7.70 (t, 1H, *J* = 8.5 Hz), 7.90 (t, 1H, *J* = 8.5 Hz), 8.11 (d, 1H, *J* = 8.5 Hz), 8.22 (d, 1H, *J* = 8.5 Hz).^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 29.0, 34.3, 121.0, 124.8, 128.7, 129.4, 134.8, 151.3, 161.9, 166.3. MS *m/z* (relative intensity) EI: 318(M^+ + 4, 21), 316 (M^+ + 2, 45), 314(M^+, 23), 237(96), 235(100), 156(59), 155(62), 129(45), 128(46), 116(80), 89(49), 63(44). Anal. Calc. for $C_{10}H_8N_2Br_2$: C, 37.97; H, 2.53; N, 8.86. Found: C, 38.14; H, 2.38; N, 8.77%.

2-(Dimethylaminomethylene)malononitrile (**5**): (86 mg, 71% yield). m.p. = 82–83 °C.[24] IR(KBr) ν/cm^{-1} 2988, 2217, 2199, 1371. ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 3.21 (s, 3H), 3.36 (s, 3H), 6.99 (s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 38.2, 48.0, 66.1, 115.2, 117.3, 158.0. MS *m/z* (relative intensity) EI: 121(M^+, 100), 120(M^+-1, 48), 106(48), 93(26) 77(56).

Phenylhydrazone propanedinitrile (**6**): (110 mg, 64% yield). m.p. = 145–147 °C (decompn.).[22] IR(KBr) ν/cm^{-1} 3194, 3059, 2233, 2211, 1603, 1547, 1474, 756, 696. ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm): 7.15–7.24 (m, 3H), 7.36 (d, 2H, *J* = 7.6 Hz), 9.57 (bs, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 86.5, 108.2, 112.3, 116.3, 127.1, 130.2, 140.0. MS *m/z* (relative intensity) EI: 170(M^+, 28), 92(19), 91(17), 77(100), 65(41), 51(22).

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References

1 X. Li and Y.-M. Zhang, *J.Chinese Chem. Soc.* (Tapei; Taiwan), 2005, **52**, 1219.
2 R. Bacaloglu, A. Moraru, M. Nutiu, S. Iluc, C. Csunderlik and E. Lungu, *Revue Romaine de Chimie,* 1980, **25**, 921.
3 Y. Tamura, Y. Yoshimoto, K. Sakai and Y. Kita, *Synthesis,* 1980, 483.
4 I. Cepanec, M. Litvic, J. Udikovic, I. Pogorelic and M. Lovric, *Tetrahedron*,2007, **63**, 5614.
5 Ch. Ramalingan and Y.-T. Park, *J. Org. Chem*., 2007, **72**, 4536.
6 K. Pilgram and R.D. Skiles, *J. Org. Chem*., 1974, **39**, 3277.
7 N.N. Karade, G.B. Tiwari, D.B. Huple and T.A.J. Siddiqui, *J. Chem. Res.,* 2006, 366.
8 N. P. Peet, S. Sunder, R.J. Barbuch, M.R. Whalon, E.W. Huber and J.C. Huffman, *J. Het. Chem.,* 1989, **26**, 1611.
9 S. R. Varma, *J. Indian Soc.,* 1978, **55**, 1052.
10 X. Li and Y.-M. Zhang, *J. Chin. Chem. Soc.,* (Tapei; Taiwan) 2006, **53**, 375.
11 L.R. Lampariello, D. Peruzzi, A. Sega and M. Taddei, *Lett. Org. Chem.,* 2005, **2**, 265.
12 H. Plieninger and A.-G. Knoll. *Chem. Ber.,* 1954, **87**, 228.
13 J. Luithle, F.-G. Boess, Ch. Erb, T. Flessner, M. Hendrix, M. Van Kampen and Ch. Methfessel. DE Patent 10, 162, 442, 2003.
14 S. Yokomoto, Y. Hirao, K.Tamura, K. Inokuma and H. Akamatsu, JP Patent 212179, 2002.
15 E. Briard and V.W. Pike, *J. Labell. Comds & Radiopharmaceut.,* 2004, **47**, 217.
16 R.R. Schmidt, W. Schneider, J. Karg and U. Burkert. *Chem. Ber.,* 1972, **105**, 1634.
17 H. Hagen, H. Naarmann and K. Penzien, DE Patent 2, 734, 926, 1979.
18 K. Findeisen, H. Holtschmidt and K.Wagner, DE Patent 2, 125, 229, 1972.
19 N.Y. Gorobets, B.H. Yousefi, F. Belaj and C.O. Kappe, *Tetrahedron,* 2004, **60**, 8633.
20 W.W. Limburg, J. Mammino, G. Liebermann, C.H. Griffiths, M.M. Shahin, S.L. Malhotra, L. Chen and M.-Eve Perron, US Patent 5, 514, 505, 1996.
21 S.L. Malhotra, W.R. Wong and M.P. Breton, US Patent 6, 336, 963, 2002.
22 R.W. Addor Jr. and D.P. Wright Jr., (American Cyanamid Co.) US Patent 3 157 569, 1964.
23 R.E. Krieger, *Organic reactions*, (ed), Huntington N.Y., 1977. vol. 5, pp.198.
24 W. Kantlehner, J.J. Kapassakalidis and T. Maier, *Liebigs Annal. Chem.,* 1980, 1448.