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Microwave-assisted synthesis of 4,4′-diaminotriphenylmethanes

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Abstract—A fast, efficient and versatile route of synthesis of 4,4′-diaminotriphenylmethanes under microwave irradiation, suitable for parallel library syntheses were developed.

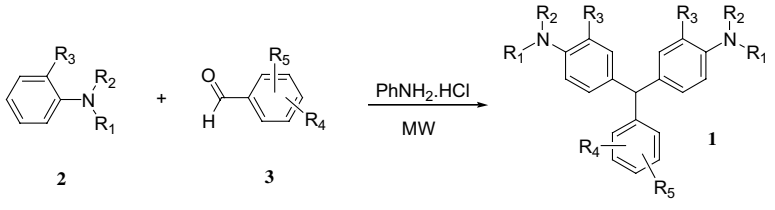
Diaminotriphenylmethanes (DTMs) have received considerable attention because these kind of compounds are widely used as dyes[1] and as antifungal agents in commercial fish hatcheries.[2] These compounds have also been employed as precursors in high performance polymer synthesis,[3] in host–guest chemistry[4] and in materials science.[5] Several DTMs have been evaluated as copper corrosion inhibitors.[6] DTMs present a number of interesting structural properties in solid and solution that have been much studied.[7]

Different methods for the preparation of the aforementioned compounds have been described such as from 4,4′-diaminodiphenylmethanes and amines,[8] by condensation of amines and anilines in acid medium[9] or using zeolites[10] and also by oxidative coupling of anilines with metal catalyst[11] or clay-mediated microwave-assisted chemistry from *N*,*N*-disubstituted anilines, in which DTMs are obtained in low to modest yields.[12] Most of these protocols, however, suffer from drawbacks, namely, long reaction times (1.5–8 h) and the use of corrosive acids or toxic metallic compounds that result in generation of waste streams, complicated workup procedures, byproducts and isomeric mixtures and, consequently, low yields.

Microwave-assisted organic synthesis is a fast growing area of research, due to the generally short reaction times, high purities and yields of the resulting products compared to conventional methods.[13]

Herein, we report a fast, efficient and versatile methodology for synthesizing DTMs focused in microwave (MW), using aniline hydrochloride as catalyst in solvent-free conditions (Scheme 1).

After some experimentation with respect to molar ratio of reagents and catalyst, irradiation time and power level of MW, we have found a set of conditions for the synthesis of DTMs (**1a**–**r**).



Scheme 1. Microwave synthesis of 4,4′-diaminotriphenylmethanes.

Keywords: Diaminotriphenylmethanes; Microwave; Parallel synthesis.
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Table 1. 4,4′-Diaminotriphenylmetanes (**3a**–**q**) synthesized via Scheme 1

Entry	R_1	R_2	R_3	R_4	R_5	Product	Mp (°C)	Reaction time (min)	Yield[a] (%)	Yield[b] (%)
1	H	H	H	H	H	**1a**	130–131	3	91	75
2	H	H	H	4-OH	H	**1b**	202–203	2	90	65
3	H	H	H	4-OMe	H	**1c**	126–127	2	87	62
4	H	H	H	4-OPr	H	**1d**	131–132	2	85	72
5	H	H	H	4-*t*-Bu	H	**1e**	66–67	2	85	66
6	H	H	H	4-F	H	**1f**	139–140	4	89	65
7	H	H	H	4-CF_3	H	**1g**	68–69	4	82	74
8	H	H	H	4-NO_2	H	**1h**	83–84	4	67	28
9	H	H	H	4-NMe_2	H	**1i**	146–147	2	75	78
10	H	H	H	4-Et	H	**1j**	126–127	4	90	60
11	H	H	H	2-OMe	6-OMe	**1k**	174–175	2	80	35
12	H	H	H	3-CF_3	5-CF_3	**1l**	137–138	4	74	74
13	H	H	2-Me	4-OH	H	**1m**	119–120	3	78	66
14	H	H	2-OMe	H	H	**1n**	62–63	2	81	65
15	H	H	2-OMe	4-OH	H	**1o**	111–112	2	83	70
16	Me	H	H	4-F	H	**1p**	163–164	3	81	76
17	Me	H	H	4-OMe	H	**1q**	60–61	2	80	73
18	Me	Me	H	4-NMe_2	H	**1r**	210–211	3	86	84

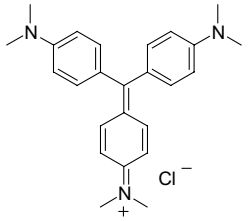
[a] Isolated yields using MW at power 100 W and 90 °C.
[b] Using alternative heating method (oil bath at 150 °C), employing **2** (0.35 mol), **3** (0.1 mol) and aniline hydrochloride (10% w/w respect to **3**) during 2 h under nitrogen atmosphere.

We have found that using microwave-promoted synthesis, the reactions can be carry out in an open vessel and non excess of aniline is required to obtain good yields. Synthesis of these compounds using analogue methodology, employing conventional heating, requires a large excess of highly toxic anilines, which are used as reagent and solvent as well. Additionally traditional syntheses have been carried out in inert atmosphere.[3]

Microwave irradiations were carried out utilizing controlled single-mode MW (MIC-I, max. power 600 W, from SEV, Mexico)[14] using a 50 mL open reaction tubes, with temperature and magnetical stirring controls.

The reactions were monitored by TLC and IR and compared with the compounds prepared by traditional methods. The mass spectrometry molecular weight determination and ^1H and ^{13}C NMR were in agreement with the structures **1a**–**r** in Table 1.

The NMR spectrum of **1k** shown that this compound exists as a mixture of rotomers in dynamic equilibrium at room temperature, while for **1r** (crystal violet) the signal for the methyne proton is not present in ^1H NMR and signals suggest that for this compound an ionic structure is favourable, as is well known for 4,4′,4″-*N*,*N*′,*N*″-disubstituted analogues.[7d]



1r

Good isolated yields were obtained with all aryl aldehydes tested, demonstrating that electro-withdrawing (entries 7, 8, 12 and 16) and electro-donating groups (entries 2–5, 9–11, 15, 17 and 18), in addition to *ortho* (entry 11) and *meta* substituents (entry 12), are well tolerated. The reaction was also well performed with *ortho* substituted anilines such as toluidine and anisidine (entries 13–15) and with *N*-substituted amines, such as *N*-methyl aniline (entries 16 and 17) and *N*,*N*′-dimethylaniline (entry 18).

These reactions shown high regioselectivity, the regioisomer 4,4′-diamino was almost exclusively detected in the reaction mixture (>94% in all cases).

The fact that readily available aryl aldehydes and amines are used along with the versatility of this synthetic method and short reaction time required, makes this approach a feasible protocol for generation of a large library of DTM immediately available for screening, considering that compounds are obtained with purities higher than 85% before the purification process.[15] In all cases the main byproducts were 4,2′- and 2,4′-diaminotriphenylmethanes.

All compounds can be recrystallized from benzene or toluene, but this operation is complicated because the crude mixtures and some pure products are so strongly colored in solution that is very difficult to see when the solid dissolves and when crystals form.

A comparison between thermal heating (TH), using a thermostated oil bath preheated at 90 °C and MW procedure for entry 1 (Table 1), with similar profile of raises in temperature and reaction time is shown in Figure 1.

When the catalyst is used in less rate than 10% w/w respect to the aldehyde or non catalyst is used the imine formation (Schiff base) is the favourable or almost the

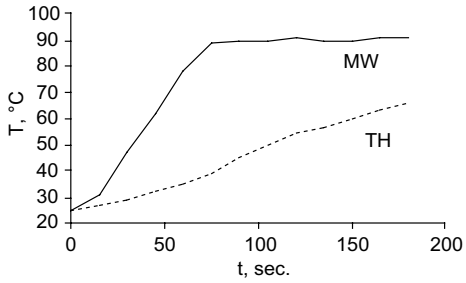


Figure 1. Temperature profile for the synthesis of **1a** under TH and MW.

unique product, respectively, so this procedure can be used for a fast imine synthesis.[16,17]

In conclusion, a solvent-free MW-assisted protocol for the synthesis of DTM, suitable for combinatorial synthesis, is developed.

All reagents were purchase from Aldrich and used as received, except aniline, which was distilled under vacuo prior to be used. IR spectra were recorded on a Nicolet FT-IR 5DX FT spectrometer using KBr as solid support. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) were determined on a Varian-Mercury 200 spectrometer using property solvent and TMS as internal reference. MS spectra were obtained in a HP 6890 Plus spectrometer (70 eV). Microwave irradiations were performed in a monomode MIC-I from SEV, Mexico.[14]

Typical reaction conditions and representative spectroscopic data. Freshly distilled aniline (0.2 mol), 4-ethylbenzaldehyde (0.1 mol) and aniline hydrochloride (10% w/w of aldehyde) were mixed thoroughly in a 50 mL open Pyrex tube containing a Teflon-coated stirring bar. The mixture was irradiated during 4 min in a MIC-I MW oven at power 100 W at 90 °C. The reaction mixture was purified by recrystallization from toluene or by silica gel flash chromatography column (hexane/ethyl acetate gradient) to afford 90% of **1j** as a white solid, mp: 126–127 °C; IR (KBr) 3427, 3352, 3016, 2962, 2927, 2870, 1716, 1620, 1512, 1263, 1178, 1018, 819 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18 (t, $J = 7.2$ Hz, 3H), 2.57 (q, $J = 7.2$ Hz, 2H), 3.4 (br s, 4H), 5.26 (s, 1H), 6.48, 6.83 (AB system, 8H), 7.01 (AB system, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.9, 28.6, 54.9, 114.5, 127.0, 128.6, 129.4, 134.1, 140.9, 141.6, 143.7; MS (70 eV) 302 (M^+, 40), 210 (42), 197 (58), 180 (60), 117 (39), 93 (100), 65 (72), 43 (85).

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Supplementary data

Supplementary data associated with this article can be found, in the online version at, doi:10.1016/j.tetlet.2004.12.091. A supplementary data is provided, which includes spectroscopic data (IR, NMR and MS) of **1a**–**r**. The supplementary data is available online with the paper in Science Direct.

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16. As example, when the reaction for obtaining **1i** was carried out using aniline (0.2 mol), *p*-dimethylaminobenzaldehyde (0.1 mol) and aniline hydrochloride (3% w/w respect to the aldehyde), the imine [4-(*N*,*N*′-dimethyl)-benzylidene]phenylamine (**4i**) was obtained in 63% yield after purification by sublimation to give an orange solid, mp: 229–230 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.99 (s, 6H), 6.76, 7.62 (AB system, 4H), 7.31–7.49 (m, 3H), 8.04 (d, J = 9.2 Hz, 2H), 8.66 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 31.3, 104.6, 105.8, 111.0, 119.8, 121.7, 128.1, 130.0, 148.8, 149.5; MS (70 eV) 224 (100), 223 (82), 207 (12), 77 (11).
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