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General and environmentally friendly synthesis of heterocyclic multidentate molecules based on microwave-assisted heating protocol

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Abstract—An efficient microwave heating methodology for the synthesis of heterocyclic multidentate molecules is reported. Each compound was obtained with high yield and purity in a few minutes from easily available starting materials such as amines, heteroaldehydes and *N*-hydroxymethyl pyrazoles or triazoles. In addition, this approach allows synthesis without any solvent or organic and inorganic by-products.

1. Introduction

A large number of amine and thiophene derivatives have shown real promise for the development of biologically active molecules and also in the area of coordination chemistry. Modular synthetic strategies, allowing structural modifications of a given scaffold, offer the ability to easily generate analogues or diversity.[1] For instance, several analogues of antergan[2] are reported in Figure 1. The substitution of antergan's phenyl rings with thiophenyl or pyridinyl moieties allowed optimization of the target ratio of antihistaminic properties/sedative side effects. In addition to drug discovery, new heterocyclic multidentate molecules are of interest as ligands for coordination chemistry and organometallic catalysis.[3] Thus, methods allowing modulation of electronic strength of donor atoms and steric hindrance of different substituants represent a key tool to prepare a large diversity of multichelating ligands or to elaborate a specific designed molecule.

Herein, we report a general approach for the synthesis of tripodal molecules based on a central nitrogen atom connecting three different functionalized arms (Fig. 2). This method, based on microwave-assisted heating, offers the opportunity (i) to easily change one, two or all building blocks R_3, Z and Y, (ii) to directly prepare these compounds in very high yield and purity and (iii) to perform the

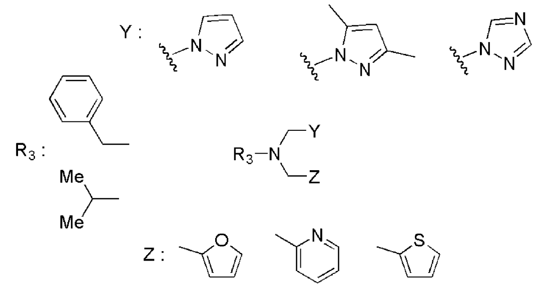

Figure 2. Tripodal molecules with three modular building blocks.

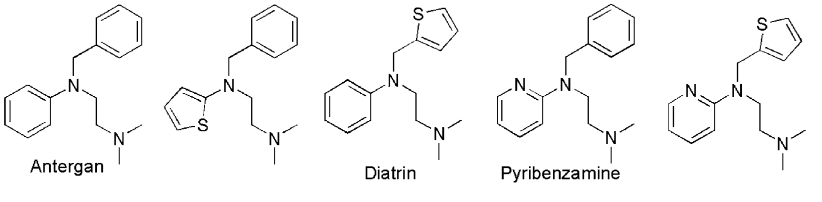

Figure 1. Antergan and analogues.

Keywords: Microwave; Amines; Heterocycles; Pyrazole; Triazole.

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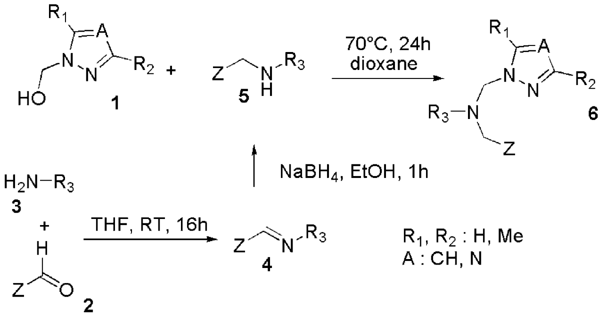
reactions rapidly without solvent and with only water as the by product.

We recently reported solution phase combinatorial access to a set of tripodal compounds.[4] This approach was based on the thermic condensation of 1-hydroxymethyl pyrazoles or 1-hydroxymethyl triazoles **1** with heterocyclic secondary amines **5** (Scheme 1). The later were easily obtained via reductive amination between the corresponding primary amines **3** and aldehydes **2**.



Scheme 1. Initial approach to synthesize tripodal compounds.

Long reaction times were necessary for both imine synthesis and coupling reactions, respectively, 16 and 24 h. This could represent a limitation for thermally sensitive starting reagents or expected products.

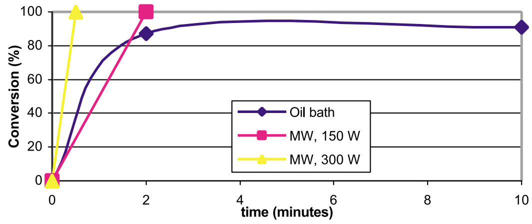
Microwave-assisted chemistry has attracted a considerable attention in recent years and has been applied successfully in various fields of organic chemistry with significant rate enhancement and higher product yields.[5] Therefore, we have investigated a microwave heating methodology in order to generalize the rapid access to tripodal molecules, in very high yield.

Our first study concerned the impact of a microwave-assisted methodology for preparation of imines **4a–f**. We first condensed 2-furaldehyde, 2-pyridylaldehyde or 2-thiophene carboxaldehyde with benzylamine or isopropylamine under microwave irradiation (automatic regulation to 80 °C) for 2 min. In each case, conversion is 100% (determined by ^{1}H NMR spectra). After filtration, the corresponding imines **4a–f** were obtained in high yield (Table 1).

Table 1. Synthesis of imines **4** using microwave heating

Entry	4	R_3	Z	Yield (%)
1	**4a**	Ph–CH_2	2-Furyl	98
2	**4b**	$(CH_3)_2CH$	2-Furyl	97
3	**4c**	Ph–CH_2	2-Pyridyl	98
4	**4d**	$(CH_3)_2CH$	2-Pyridyl	100
5	**4e**	Ph-CH_2	2-Thiophenyl	97
6	**4f**	$(CH_3)_2CH$	2-Thiophenyl	95

We have compared the thermal heating protocol with oil bath and two different power for the microwave irradiation for the amine **4e**, using the same technical conditions (substrates, size of vessels, solvent, temperature set, concentration) (Graph 1).



Graph 1. Synthesis of imine **4e** at 80 °C in *n*-heptane.

We observed that the reaction reached 88% conversion with the oil bath after 2 min and that longer reaction time did not improve this conversion. Purification step was then necessary to obtain pure compound **4e**. By contrast, the same heating time via microwave oven (power 150 W) led to complete conversion, **4e** was obtained in pure form without purification step. More interestingly, using a higher microwave power (300 W) the reaction is complete in 30 s.

We could explain this observation by the fact that this ‘instantenous’ increase of temperature is not possible with oil bath due to slow heat transfer from the wall of the vessel to the solution, even using a pre-heated oil bath.

The second step, that is, reduction of the imine by $NaBH_4$ was performed as already reported[4] and gave amines **5** with moderate to good yields. Hydroxyalkylation of pyrazole,[6] its 3,5-disubstituted derivatives or triazole[7] with formaldehyde afforded the other set of reagents **1**.

The impact of the microwave heating methodology was also applied to the coupling reactions between compounds **5** and **1**. The condensation reaction was performed in *n*-heptane, with $MgSO_4$ as drying agent, under microwave irradiation for 10 min (automatic regulation to 95 °C). A simple filtration and solvent evaporation under reduced pressure provided the tripodal molecules **6** with good yields (Table 2). In addition to several studies,[5] these observations validate the impact of a microwave-assisted reaction conditions. Therefore, we applied this method to the synthesis of new thiophene containing molecules **7a–f** (Fig. 3) with good to excellent yields (Table 2, entries 4–9). All derivatives **7** were obtained in very high purity without need of purification process. It should be noted that this microwave approach was crucial for the synthesis of these new thiophene containing molecules **7** as we observed significant amount of side products when heating in dioxane at 70 °C with oil bath was used.

For comparison, we have used an oil bath at 95 °C: **6a** and **7d** were obtained in quantitative yield after 3 h. After 10 min, the conversion were only 66% (**6a**) and 75% (**7d**) (Graph 2).

We checked that multi-grams synthesis of these new compounds **7a–f** was possible. The synthesis of 1.5 g of each derivative **7** was obtained without affecting yield or purity; the only limitation was the size of microwave vessels.

Interestingly, this microwave method allows also solvent free conditions and no use of drying agents. The new