A facile synthesis of 2-aminobenzene-1,3-dicarbonitrile

Mazaahir Kidwai*, Shilpi Saxena & Shweta Rastogi
Department of Chemistry, University of Delhi, Delhi 110 007, India
E-mail: mkidwai@mantraonline.com

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An efficient facile synthesis of 2-aminobenzene-1,3-dicarbonitrile using inorganic solid support under microwave activation is described. It is a non conventional synthetic approach wherein inorganic solid support is used as energy transfer medium under microwave that devoids hazards of solution phase reactions. The reaction time has been brought down from hours to minutes with improved yield as compared to conventional heating.

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Substituted or unsubstituted chalcones and their derivatives are important intermediates in organic synthesis. They serve as starting materials for the synthesis of heterocyclic compounds which are of physiological importance. The presence of enone functionality in chalcone moiety confers biological activity upon it, viz. antibacterial, anticonvulsant, antimicrobial and cytotoxic. m-Terphenyls are useful intermediates and act as building blocks for cyclophanes to create a large molecular cavity and host-guest complexes.

In recent years, organic reactions on solid supports and those assisted by microwaves have attracted attention as they offer potential advantages of enhanced selectivity, milder reaction conditions and associated ease of manipulation. During the course of investigation of organic reactions under microwave irradiation we have observed that such procedures lead to faster reactions with improved yield. Further the reactions in dry media conditions are especially appealing as they provide an opportunity to work with open vessels, thus avoiding the risk of high pressure development and offer the possibility of carrying out reactions that can be scaled up by the industries.

Though various methods for the synthesis of m-terphenyls are reported, the majority of them are multistep with poor yield. In continuation to our ongoing endeavour on the application of microwave irradiation for the synthesis of bioactive compounds using dry conditions, we herein describe a convenient one pot microwave accelerated solid state approach for the synthesis of 2-aminobenzene-1,3-dicarbonitrile derivatives. In the present work, we have made an attempt to provide an environmentally benign synthesis of m-terphenyls that have interesting and useful properties and also the differential activity of solid supports under microwave irradiation is studied.

Results and Discussion

Synthesis of 2-aminobenzene-1,3-dicarbonitrile benzene is generally achieved by refluxing chalcone, malononitrile and a secondary amine (morpholine/piperidine/pyrrolidine) in ethanol for 8-10 hr and the product is isolated in low yield by concentrating the reaction mixture. This methodology is time consuming. Further, in a process of investigating a rapid and expeditious methodology for the synthesis of m-terphenyls, we decided to explore the effect of different inorganic supports under MWI. Chalcone, malononitrile and base adsorbed over neutral alumina/basic alumina in 1:2 mole ratio afforded the desired products 3a-f (Scheme I). Better results in terms of yield and reaction time were observed with basic alumina. In 3-5 min of MWI, 75-85% of the products 3a-f were obtained over basic alumina in comparison to neutral alumina in which 60-65% yield of the product was obtained in 6-8 minutes of irradiation. An attempted reaction of 1 and 2 in 1:2 mole ratio with only a few drops of base adsorbed over basic alumina under MWI was comparatively faster with approximately same yield. The enhancement in reaction rate is attributed to the fact that basic alumina acts both as catalyst as well as base. The results (Table I) demonstrate the versatility...
of solid support coupled with microwave as considerable reaction rate enhancement has been observed by bringing down the reaction time from hours to minutes with improved yield as compared to conventional heating. The structures of all the synthesized compounds were established on the basis of their spectroscopic data (Table II). In the IR spectra, the appearance of band at 2210-2240 and 3450-3470 cm\(^{-1}\) due to C=N and NH\(_2\), respectively and the disappearance of band at 1685-1710 cm\(^{-1}\) due to C=O group of chalcone confirmed the formation of product. The appearance of broad singlet at \(\delta\) 5.4 due to NH; and singlet at 6.8 due to H-5 in \(^1\)H NMR spectra further confirmed the formation of product.

### Experimental Section

Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. IR (KBr) spectra (\(v_{\text{max}}\) in cm\(^{-1}\)) were obtained on a Perkin-Elmer FTIR-1710 spectrophotometer. \(^1\)H NMR spectra were recorded in CDCl\(_3\) and DMSO-\(d_6\) on FTNMR Hitachi R-600 spectrometer operating at 60 MHz using TMS as internal standard (chemical shifts in \(\delta\), ppm). Elemental analyses were performed on a Heraeus CHN Rapid Analyser. A Kenstar (Model No. OM-9925E) household microwave oven (2450 MHz, 800 W) was used for all experiments. The purity of compounds was checked on silica gel coated aluminium plates (Merck).

### General procedure for the synthesis of 2-aminobenzene-1,3-dicarbonitriles 3a-f

#### Solution Phase Conventional (Method A)

A mixture of chalcone 1 (9.6 mmoles), malononitrile 2 (19.24 mmoles) and heterocyclic secondary amine (9.6 mmoles) in 20 mL ethanol was refluxed for 8-10 hr in a 100 mL round bottom flask. On completion of reaction (monitored by TLC), the reaction mixture was concentrated. The solid obtained was filtered, washed with methanol and recrystallised from the appropriate solvent.

#### Solid Support Microwave (Method B)

A mixture of chalcone 1 (9.6 mmoles), malononitrile 2 (19.24 mmoles) and heterocyclic secondary amine (9.6 mmoles) dissolved in ethanol (15 mL) was taken in a beaker and adsorbed over basic/neutral alumina (20 g). The reaction mixture was air dried, kept in an alumina-bath and irradiated in microwave oven for specified time (Table I). On completion of reaction (monitored by TLC) at an interval of every 30 seconds, the product was extracted into ethanol (3 x 15 mL). Recovering the solvent under reduced pressure yielded the product which was purified by recrystallization from the chloroform-pet. ether mixture.

#### Solid Support Microwave (Method C)

A mixture of chalcone 1 (9.6 mmoles), malononitrile 2 (19.24 mmoles) and heterocyclic secondary
amine (2-3 drops) dissolved in ethanol (15 mL) was taken in a beaker and adsorbed over basic alumina (15 g). Further, the reaction was carried out as described in Method B.

Conclusion

An ecofriendly approach for the synthesis of 2-aminobenzene-1,3-dicarbonitrile has been developed. The procedure clearly highlights the versatility of inorganic solid supports under microwave irradiation for the preparation of bioactive compounds.

Acknowledgement

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References


Table II—Physical and spectral data of compounds 3a-f

<table>
<thead>
<tr>
<th>Compd</th>
<th>Mol. formula</th>
<th>Mol. Wt</th>
<th>Found/% (Calcd)</th>
<th>m.p. °C</th>
<th>1H NMR (DMSO-d6 + CDCl3, δ ppm)</th>
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<tbody>
<tr>
<td>3a</td>
<td>C20H13N3</td>
<td>295</td>
<td>81.37 4.42 14.21</td>
<td>216-18</td>
<td>5.4 (brs, 2H, D2O), 6.8 (s, 1H, H-5), 7.4-7.6 (m, 10H, Ar-H)</td>
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<tr>
<td>3b</td>
<td>C20H12ClN3</td>
<td>329.5</td>
<td>72.82 3.66 12.77</td>
<td>249-50</td>
<td>5.4 (brs, 2H, D2O), 6.8 (s, 1H, H-5), 7.4 (d, 2H), 7.6 (d, 2H), 7.7-7.9 (m, 5H, Ar-H)</td>
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<tr>
<td>3c</td>
<td>C20H13N3O</td>
<td>325</td>
<td>77.57 4.64 12.90</td>
<td>177-78</td>
<td>3.8 (s, 3H), 5.3 (brs, 2H, D2O), 6.7 (s, 1H, H-5), 7.0 (d, 2H), 7.4-7.6 (m, 7H)</td>
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<tr>
<td>3d</td>
<td>C20H12BrN3O2</td>
<td>418</td>
<td>60.30 2.85 10.01</td>
<td>251-52</td>
<td>5.4 (brs, 2H, D2O), 5.9 (s, 2H, OCH3), 6.5-8.2 (m, 8H, Ar-H), piperonal + H-5)</td>
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<tr>
<td>3e</td>
<td>C20H13N3O</td>
<td>223</td>
<td>69.97 4.01 18.81</td>
<td>&gt;300</td>
<td>2.3 (s, 3H, CH3), 5.3 (brs, 2H, D2O), 6.7 (s, 1H, H-5), 6.9-7.3 (m, 3H, furan)</td>
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<tr>
<td>3f</td>
<td>C20H12BrN4</td>
<td>413</td>
<td>63.94 3.11 13.57</td>
<td>159-61</td>
<td>5.4 (brs, 2H, D2O), 6.6-7.9 (m, 11H, indole + H-5)</td>
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