Pergamon

Tetrahedron Letters 41 (2000) 5031–5034

TETRAHEDRON LETTERS

Microwave-assisted synthesis of substituted imidazoles on a solid support under solvent-free conditions

Alexander Ya. Usyatinsky and Yuri L. Khmelnitsky*

EnzyMed Division, Albany Molecular Research Inc., 2501 Crosspark Rd., Iowa City, IA 52242, USA

Received 3 April 2000; revised 8 May 2000; accepted 9 May 2000

Abstract

The solvent-free microwave-assisted synthesis of 2,4,5-substituted and 1,2,4,5-substituted imidazoles is reported. Imidazoles are obtained as a result of the condensation of a 1,2-dicarbonyl compound with an aldehyde and an amine using acidic alumina impregnated with ammonium acetate as the solid support.

Keywords: microwave chemistry; solvent-free synthesis; substituted imidazoles; combinatorial synthesis.

Microwave-assisted organic synthesis (MAOS) is a new and quickly growing area in synthetic organic chemistry.[1] This synthetic technique is based on the empirical observation that some organic reactions proceed much faster and with higher yields under microwave irradiation compared to conventional heating. In many cases reactions that normally require many hours at reflux temperature under classical conditions can be completed within several minutes or even seconds in a microwave oven, even at comparable reaction temperatures. Recently, we developed a new highly efficient MICROCOS technology (microwave-assisted combinatorial synthesis) for generating combinatorial libraries.[2] The technology was applied to the high throughput, automated, one-step, parallel synthesis of diverse substituted pyridines using the Hantzsch synthesis.[2] In the present work we further expand the scope of reactions applicable to MICROCOS technology by introducing the microwave-assisted synthesis of diverse substituted imidazoles.

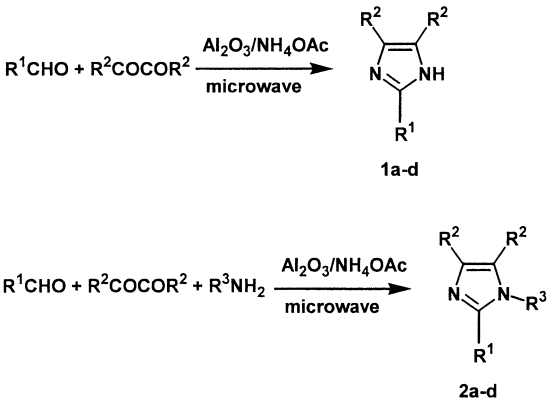
The synthetic strategy is based on the condensation of 1,2-diarylethandienones with aldehydes or aldehydes and amines resulting in 2,4,5-substituted or 1,2,4,5-substituted imidazoles, respectively, using ammonium acetate as the ammonia source.[3] A solid-phase version of this method was used to generate libraries of substituted imidazoles.[4] The multicomponent nature of the synthesis of 1,2,4,5-substituted imidazoles together with the existence of a wide variety of commercially available aldehydes and amines makes this reaction an ideal candidate for the MICROCOS technology. To the best of our knowledge, the microwave-assisted version of this reaction has

* Corresponding author. Tel: (319)-621-5410; fax: (319)-612-5400; e-mail: ykhmelnitsky@enzymed.com

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00771-1

not been reported, although several papers describing other microwave-assisted syntheses of benzimidazoles and *N*-substituted imidazoles have been published.[5]

Generally, the synthetic procedure involved impregnating the mixture of solid support and ammonium acetate (ammonia source) with ether solution of starting reagents, evaporating the solvent, and heating the solid residue in a microwave oven (Scheme 1). Preliminary optimization of reaction conditions was done using the pair benzyl/benzaldehyde ($R^1 = R^2 =$ phenyl). Among different supports tested the expected product **1a** was formed on acidic, basic and neutral alumina, bentonite, montmorillonite K10, montmorillonite KSF, silica gel, and florisil. It was found that the addition of a small amount (several drops) of acetic acid was required for the reaction to occur on neutral and basic supports, such as basic and neutral alumina, silica gel, or florisil.[6] On the other hand, when acidic supports were used (bentonite, montmorillonite K10, montmorillonite KSF, or acidic alumina) the reaction was successful without additional acid. Comparison of different supports showed that acidic alumina was the most suitable support for the synthesis of **1a**, and therefore it was used in all subsequent experiments. Optimal conditions for the synthesis were found to be 20 min reaction time with a microwave irradiation power of 130 W. No reaction was observed without heating or when the support was omitted from the reaction mixture.



Scheme 1. Microwave-assisted synthesis of substituted imidazoles

The optimal conditions were then applied for the preparation of the series of 2,4,5-substituted imidazoles **1a**–**d** and 1,2,4,5-substituted imidazoles **2a**–**d**. In a typical reaction, a mixture of acidic alumina (9.3 g) and ammonium acetate (4.4 g) was ground in a mortar until a homogeneous powder was formed. A solution of 0.5 mmol of 1,2-dicarbonyl compound and 0.5 mmol of aldehyde in 2 ml of diethyl ether or methylene chloride (synthesis of **1a**–**c**), or a solution of 0.5 mmol of 1,2-dicarbonyl compound, 0.5 mmol of aldehyde and 0.5 mmol of amine in 2 ml of ethyl ether or methylene chloride (synthesis of **2a**–**c**) was added to 2.5 g of the alumina/ammonium acetate mixture in a 20 ml glass vial. The solvent was allowed to evaporate and the dry residue was irradiated in a domestic Kenmore microwave oven at 130 W (10% power) for 20 min in the open vial. The mixture was then allowed to cool to room temperature and washed with a mixture of acetone/triethylamine (7:3 v:v), 3×10 ml to extract the product. The combined washes were filtered and the solvent was evaporated under reduced pressure. The resulting solid residue was purified by flash chromatography using a FlashElute™ system from Elution Solutions on a 90 g silica cartridge. A mixture of hexane:ethyl acetate (4:1 v:v) was used as eluent for the purification

of **1a**–**d**, **2a**, and the solvent system hexane:ethyl acetate (7:1 v:v) was used for the isolation of **2b**–**d**. The identity of imidazoles **1a**,**c**,**d** was confirmed by analytical comparison (HPLC and mass spectrometry) with authentic standards either obtained from commercial source (Aldrich, for **1a**,**c**), or prepared according to the established procedure[3] (for **1d**). The structures of **1b** and **2a**–**d** were confirmed by NMR and mass spectral analysis.[7]

The structures of products and product yields are shown in Fig. 1. The results show that the microwave-assisted synthesis provides an efficient way to access diverse, highly functionalized imidazoles under solvent-free conditions. In contrast to the traditional solid-phase synthesis,[4] the microwave technology does not require the development of solid phase linking and cleaving chemistries. Similar to solution-phase combinatorial synthesis, the MICROCOS procedure produces compounds in a soluble form immediately available for biological testing. Indeed, even without any additional purification the HPLC purity of substituted imidazoles prepared by microwave-assisted method is typically 75 to 85%, which is usually sufficient for primary biological screening. Furthermore, the MICROCOS technique eliminates the necessity to reflux the reaction mixture in the aggressive solvent (acetic acid) which is required under the standard procedure,[4] and the reaction time is reduced from approximately 4 h[4] to several minutes. The MICROCOS procedure is expected to be applicable to a wide range of different building blocks (R^1, R^2 and R^3 in Scheme 1) to provide access to structurally diverse libraries of imidazole derivatives.

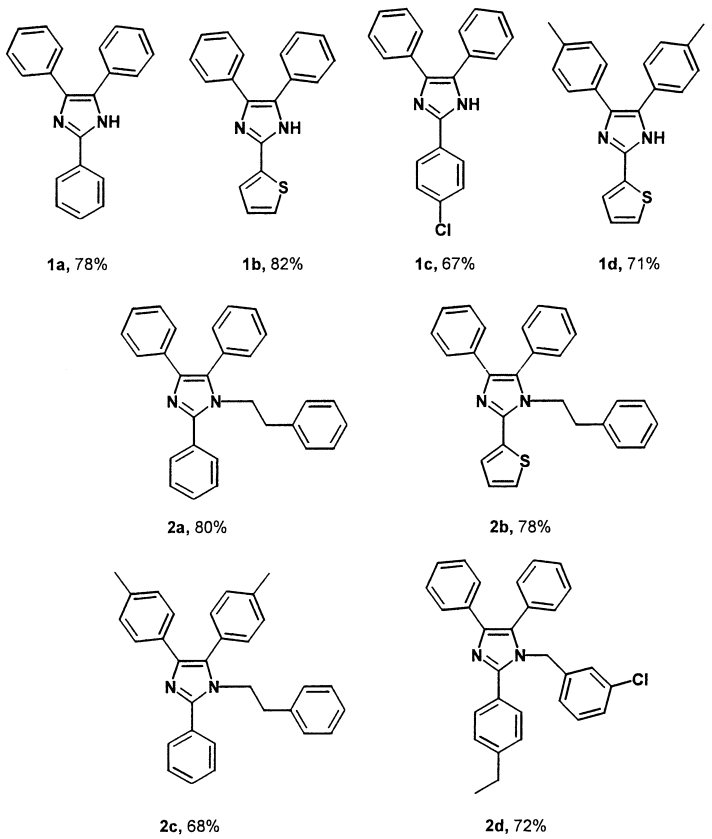


Figure 1. Structures and isolated yields of imidazoles prepared by solvent-free microwave-assisted method

Acknowledgements

We thank Dr. Ian C. Cotterill for valuable comments during the preparation of this manuscript.

References

1. (a) Caddick, S. *Tetrahedron* **1995**, *51*, 10403–10432. (b) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665–1692.
2. Cotterill, I. C.; Usyatinsky, A. Ya.; Arnold, J. M.; Clark, D. S.; Dordick, J. S.; Michels, P. C.; Khmelnitsky, Yu. L. *Tetrahedron Lett.* **1998**, *39*, 1117–1120.
3. Krieg, B.; Manecke, G. *Z. Naturforsch.* **1967**, *22b*, 132–141.
4. Sarshar, S.; Siev, D.; Mjalli, M. M. *Tetrahedron Lett.* **1996**, *37*, 835–838.
5. (a) Reddy, A. C. S.; Rao, P. S.; Venkataratham, R. V. *Tetrahedron* **1997**, *53*, 5847–5854. (b) Bougrin, K.; Soufaoui, M. *Tetrahedron Lett.* **1995**, *36*, 3683–3686. (c) Ben-Alloum, A.; Bakkas, S.; Soufaoui, M. *Tetrahedron Lett.* **1998**, *39*, 4481–4484. (d) Glas, H.; Thiel, W. R. *Tetrahedron Lett.* **1998**, *39*, 5509–5510. (e) Martin-Aranda, R. M.; Vicente-Rodriguez, M. A.; Lopez-Pestana, J. M.; Lopez-Peinado, A. J.; Jerez, A.; Lopez-Gonzales, J. D.; Banares-Munoz, M. A. *J. Mol. Catal. A* **1997**, *124*, 115–121. (f) Bogdal, D.; Pielichowski, J.; Jaskot, K. *Heterocycles* **1997**, *45*, 715–722.
6. In the original procedure the reaction is performed in refluxing acetic acid.[3]
7. Compound **1b**: ^{1}H NMR (DMSO-d_6, 360 MHz) δ (7.15, m, 2H), (7.29–7.51, m, 10H), (7.68, dd, 1H), (12.83, s, 1H). HRMS $[M+H]^+ = 303$; compound **1d**: ^{1}H NMR (CD_3OD, 360 MHz) δ (2.34, s, 6H), (7.13, m, 5H), (7.33, d, 4H), (7.45, d, 1H), (7.65, d, 1H). HRMS $[M+H]^+ = 331$; compound **2a**: ^{1}H NMR (DMSO-d_6, 360 MHz) δ (2.53, t, 2H), (4.08, t, 2H), (6.66, m, 2H), (7.14–7.53, m, 15H), (7.66, d, 2H), (8.09, d, 1H). ^{13}C NMR (DMSO-d_6, 90 MHz) δ 36.6, 45.4, 125.2, 126.0, 128.0, 128.2, 128.4, 128.6, 128.7, 129.1, 130.2, 134.6, 136.5, 145.3, 146.7. HRMS $[M+H]^+ = 401$; compound **2b**: ^{1}H NMR (DMSO-d_6, 360 MHz) δ (2.74, t, 2H), (4.17, t, 2H), (6.80, d, 2H), (7.20, m, 6H), (7.40, m, 5H), (7.55, m, 4H), (7.74, d, 1H). ^{13}C NMR (DMSO-d_6, 90 MHz) δ 35.5, 45.7, 125.9, 126.3, 126.6, 127.4, 128.1, 128.3, 128.5, 129.1, 130.2, 130.4, 131.0, 132.8, 134.2, 136.6, 140.6. HRMS $[M+H]^+ = 407$; compound **2c**: ^{1}H NMR (DMSO-d_6, 360 MHz) δ (2.23, s, 3H), (2.42, s, 3H), (2.51, t, 2H), (4.08, t, 2H), (6.67, m, 2H), (7.12, d, 2H), (7.14–7.52, m, 16H), (7.63, d, 1H), (8.07, d, 1H). ^{13}C NMR (DMSO-d_6, 90 MHz) δ 20.6, 20.9, 35.6, 45.7, 125.1, 126.0, 126.6, 128.0, 128.2, 128.4, 128.5, 128.6, 129.2, 130.7, 131.3, 131.9, 135.1, 136.5, 137.3, 138.1, 146.5. HRMS $[M+H]^+ = 429$; compound **2d**: ^{1}H NMR (CD_3OD, 360 MHz) δ (1.25, t, 3H), (2.70, q, 2H), (5.14, s, 2H) (6.64, s, 1H), (7.12–7.55, m, 15H), (7.90, d, 1H). ^{13}C NMR (DMSO-d_6, 90 MHz) δ 15.3, 27.9, 47.2, 124.3, 125.2, 126.0, 127.9, 128.4, 129.0, 130.4, 130.6, 133.0, 134.4, 139.7, 143.8, 144.7, 145.6, 147.2. HRMS $[M+H]^+ = 449$.