J. Braz. Chem. Soc., Vol. 19, No. 6, 1230-1233, 2008.
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0103 - 5053 $6.00+0.00

Short Report

Synthesis of Imidazole Derivatives from β-Lapachone and Related Compounds using Microwave and Supported Reagents

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Naftoimidazóis inéditos foram preparados por reação, ativada por microondas, entre paraformaldeído, β-lapachona (ou *o*-quinonas correlatas) e acetato de amônio suportado em montmorilonita k-10, ou em alumina básica. O uso do suporte básico forneceu os melhores rendimentos, superiores a 80%. Isso foi confirmado para a reação com β-lapachona e piperonal.

New naphthoimidazoles were prepared by reaction, activated by microwave irradiation, between paraformaldehyde, β-lapachone (or related *o*-quinones) and ammonium acetate supported on montmorillonite k-10, or on basic alumina. Use of the basic support gave the best results, with yields above 80%. This was confirmed for the reaction with β-lapachone and piperonal.

Keywords: imidazole, microwave, basic alumina, lapachone

Introduction

β-Lapachone (**1a**) is an *ortho*-naphthoquinone present in small amounts in trees of the *Tabebuia* species (Bignoniaceae), commonly called "ipê" or "pau d'arco" in Brazil. In addition, it can be obtained by the isomerization of lapachol, a quinone that is more abundant and more readily extracted from the same sources. The biological activities of these compounds and simple derivatives, have been investigated since the 1940's (anti-malarial[1]) up to the present (anti-tumor,[2] anti-microbial,[3] anti-inflammatory[4] and anti-parasitic[5]) and were recently reviewed.[6]

The use of β-lapachone and some semi-synthetic derivatives as chemotherapic agents in the treatment of American trypanosomiasis (Chagas disease) has been investigated,[7] and five imidazole derivatives, prepared from this quinone and aromatic aldehydes, have shown expressive action over the tripamastigote form of *Trypanosoma cruzi*.[8,9] These imidazole derivatives were prepared by conventional methods.[9]

As part of an ongoing study into the use of microwave activation and the use of supported reagents, in this case ammonium acetate, we investigated the preparation of the previously unknown simple imidazole derivatives of β-lapachone and related *ortho*-quinones with formaldehyde.

Microwave activation has provided significant improvement on heterocyclic synthesis,[10] including imidazoles, with[11-13] or without support,[14,15] with reduction/elimination of solvents, decreased reaction times and equal or improved yields.

Results and Discussion

Imidazole synthesis from α-diketones has a long history[16] and was initially plagued by low yields and by-products (such as oxazoles). Improvements occurred by the use of acidic conditions, e.g., glacial acetic acid reflux.[17] The availability of microwave technology for synthetic purposes has allowed the efficient preparation of 2,4,5-trissubstituted and 1,2,4,5-tetrassubstituted imidazoles. Further observed benefits, that were occasionally associated with solid supports such as silica, alumina, clays, amongst others,[11-13] included improved yields, and dramatic reductions in reaction time and quantities of solvent used (AcOH).[14,15] Interestingly, the best supports found in these studies were always the acidic in nature.

Based on these findings, the preparation of the previously unreported imidazole derivatives **2a**-**c** was attempted. By starting from β-lapachone (2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromene-5,6-dione, **1a**), *nor*-β-lapachone

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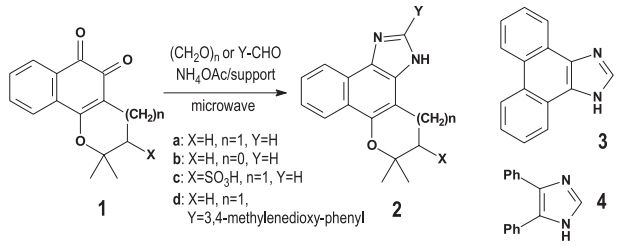
(2,2-dimethyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione, **1b**) or β-lapachone-3-sulfonic acid (2,2-dimethyl-5,6-dioxo-3,4,5,6-tetrahydro-2*H*-benzo[*h*]chromene-3-sulfonic acid, **1c**), and by using ammonium acetate supported on montmorillonite k-10, and paraformaldehyde, with microwave activation, (Scheme 1), the expected products (**2a-c**) were obtained in yields that varied from fair to poor (Table 1).



Scheme 1. Imidazole synthesis using supported ammonium acetate and microwave activation.

Table 1. Yields (isolated products) for imidazoles **2a-d**, **3** and **4** using ammonium acetate supported on basic alumina compared with other methods

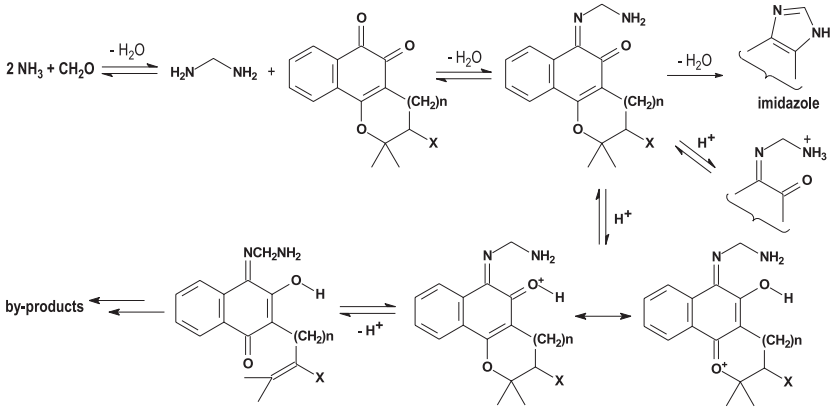
Imidazole	Yield / (%)		
	Basic alumina	other methods	
2a	81	70	thiswork
2b	85	19	thiswork
2c	81	46	thiswork
2d	82	30[b]	ref. 9
3	51	65[c]	ref. 18
4	14	80[d]	ref. 19

However, when the support was changed to basic alumina, whilst keeping the other conditions as before (Experimental), significant improvement of the yields (81-85%, Table 1) for formation of the products **2a-c** was observed. The competitive formation of oxazoles was determined to be less than 5% relative to imidazole in all cases, and these products were practically absent from the isolated product. The oxazoles could be clearly detected in the crude reaction mixture, after initial work-up, as GC peaks of smaller t_R, relative to the corresponding imidazoles. The oxazoles were identified by GC-MS and the relative amount was determined by FID-GC.

One of the possible reasons for the success of the use of basic alumina (pH 9.5) as support in the studied reactions, may be related to the nature of the *o*-quinones used, which contain an alkoxy group conjugated with one of the ketone moieties. This feature not only decreases the electrofilicity of this carbonyl, but provides a route for tautomerization in acidic media. Scheme 2 integrates these ideas and Orru's[15] mechanistic proposals on imidazole synthesis.

This synthetic method (using ammonium acetate supported on basic alumina) that was developed to prepare the previously unknown derivatives was applied to the preparation of the known imidazoles by reaction of β-lapachone with piperonal (to give **2d**), and 9,10-phenanthrenequinone and benzil with paraformaldehyde (to give **3** and **4** respectively). Yields are given in Table 1 together with yields from previously reported synthesis. The low yields for **3** and **4** are in accordance with literature data, where acidic conditions afforded better results.[11-13,17]

In addition, it was also investigated whether these reactions could occur efficiently without a support or microwave energy (other conditions kept equal). The experiments were carried out for the synthesis of compound **2a**. With microwave irradiation but no support, TLC analysis of the crude product revealed the presence of imidazole in much reduced yield, with most of the quinone left unreacted. With alumina as support but no microwave irradiation, no conversion was detected after 24 h at room temperature.



Scheme 2. Imidazole formation and competition with by-products in acidic media.

Conclusions

The method described above, with ammonium acetate supported on basic alumina and microwave activation, which does not use solvents at the reaction stage, seems to be an appropriate alternative for synthesis of imidazoles from some 4-alkoxy-substituted 1,2-quinones. But it does not displace previously known methods for other 1,2-dicarbonyl substrates. Preliminary biological tests with compounds **2a-c** detected promising activity against *T. cruzi*, specially for **2a**.[24]

Experimental

A domestic microwave oven (Panasonic Piccolo, model NN-S42BH, 2.45 GHz and 800 W) was used, at power setting 1 (P1). Oven calibration was performed according to known procedures,[20] and determined that P1 = 81.4 W (P2 = 162.8, P3 = 221.0, P6 = 290.7, P8 = 372, and P10 =535.0 W); the oven performance was found to be very reproducible.

The solid supports in this investigation were basic alumina (Aluminiumoxid S, Riedel-de-Haën; grade II activity (Brockman), pH (10%, 20 °C) = 9 ± 0.5, mesh >130) and montmorillonite k-10 (Aldrich). Melting points: Büchi 510; UV spectra: Shimadzu 1240; IR: Perkin-Elmer 1605; NMR: Bruker AC200, Advance 400 and 500; MS: Varian Saturn 2000 or Agilent 6890N/5973, and Micromass ZQ.

The montmorillonite k-10 supported reagent was prepared by adding 9.3 g of the solid support to a 100 mL solution of 4.3 g of ammonium acetate in methanol (the solvent was used to alleviate mixing problems due to the montmorillonite being a very fine powder, adhering to the mortar and pestle), and vigorously stirred for 2 h; the solvent was then evaporated under reduced pressure. With basic alumina, the supported reagent was prepared by grinding 9.3 g of solid support and 4.3 g of ammonium acetate in a mortar, until homogeneous. The supported reagents were stored in a dessicator.

The quinones **1a-c** were prepared by known methods.[21-23] Benzil and 9,10-phenanthrenequinone were commercial products (Aldrich).

All the reactions (except for **2d**) used the ratio quinone: paraformaldehyde: supported reagent = 1 mmol: 3 mmol: 5 g and were performed as follows: paraformaldehyde was mixed (with a glass rod) to the supported ammonium acetate and added to a solution of the 1,2-dicarbonyl compound in the smallest possible volume (2-3 mL $mmol^{-1}$) of the appropriate solvent (dichloromethane for **1a** and **1b**; in methanol for **1c**, and in acetone for 9,10-phenanthrenequinone and benzil) in a glass vial. For preparation of **2d**, equimolar amounts of **1a** and piperonal were used and the aldehyde was directly dissolved in the quinone solution. The solvent was allowed to evaporate and the dry material was irradiated for 10-15 min on the microwave oven (at power setting P1; in the case of **2d**, best yields were for 20 min MW irradiation). The solid mixture was then allowed to cool to room temperature and washed with ethyl acetate until complete extraction of the products (TLC). The solution was evaporated under reduced pressure and the crude product obtained submitted to column chromatography with silica gel 60 and hexane:ethyl acetate (7:3) as eluent for **2a-b**, **2d**, **3** and **4**, and methanol:acetic acid (19:1), for **2c**. Spectroscopic data for **2d**, **3** and **4** were in accordance with the literature.[9,18,19]

*6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno [5,6-d]imidazole (**2a**)*

mp 296-298°C. UV (CH_3CN; (ε)) λ_{max} /cm^{-1}: 332 nm (2700). IR (KBr) ν_{max} /cm^{-1}: 3409; 3144; 3083; 3010; 2973; 2924; 2844; 1666; 1652; 1605; 1588; 1486; 1451; 1367; 1257; 1161; 1120; 1056; 948; 770. ^{1}H NMR (CD_3OD; δ): 8.29(d, 1H); 8.21(d, 1H); 8.08(s, 1H); 7.51 (t, 1H); 7.41 (t, 1H); 3.04 (t, 2H); 2.00 (t, 2H); 1.46 (s, 6H). ^{13}C NMR (CD_3OD; δ): 146.7; 139.2; 127.2; 124.9; 123.8; 122.0; 106.0; 75.7; 33.3; 27.1; 19.8. MS (*m/z*; (%)): 252 (100); 196 (80). TOF MS ES+ (MeOH-H_2O-0.1% AcOH): 253.1262 (M+1; calc. for $C_{16}H_{17}N_2O$: 253.1341).

5,5-dimethyl-4,5-dihydro-3*H*-furo[3',2':3,4] naphtho[1,2-*d*]imidazole (**2b**): mp 246-248°C. UV (CH_3CN; (ε)) λ_{max} /cm^{-1}: 337 (3700). IR (KBr) ν_{max} /cm^{-1}: 3394; 3116; 3065; 2966; 2845; 1665; 1619; 1592; 1490; 1467; 1442; 1366; 1249; 1148; 1051; 945; 855; 757; 649. ^{1}H NMR ($CDCl_3$; δ): 8.34 (d, 1H); 8.11 (s, 1H); 7.97(d, 1H); 7.54 (t, 1H); 7.43 (t, 1H); 3.37 (s, 2H); 1.61 (s, 6H). ^{13}C NMR (CD_3OD; δ): 152.8; 139.4; 132.5; 130.0; 127.2; 125.6; 125.0; 123.6; 122.6; 120.2; 108.0; 88.9; 42.9; 28.9. MS (*m/z*; (%)): 238 (100); 223 (60); 195 (15). TOF MS ES+ (MeOH-H_2O-0.1% AcOH): 239.1065 (M+1; calc. for $C_{15}H_{15}N_2O$: 239.1184).

*6,6-dimethyl-3,4,5,6-tetrahydrobenzo[7,8]chromeno[5,- -d]imidazole-5-sulfonic acid (**2c**)*

mp 350°C (decomp.). UV (CH_3CN; (ε)) λ_{max} /cm^{-1}: 331 (3200). IR (KBr) ν_{max} /cm^{-1}: 3448; 3423; 3135; 3010; 2981; 2938; 2853; 1650; 1617; 1591; 1559; 1490; 1374; 1225; 1180; 1049. ^{1}H NMR (CD_3OD; δ): 8.35 (d, 1H); 8.20 (d, 1H); 8.12 (s, 1H); 7.55 (t, 1H); 7.43 (t, 1H); 3.50 (m, 1H); 3.42 (m, 1H); 3.34 (m, 1H); 1.93 (s, 3H); 1.49 (s, 1H). ^{13}C NMR (CD_3OD; δ): 145.9; 133.2; 127.4; 124.9; 123.8; 122.2; 104.5; 78.3; 63.2; 29.9; 24.2; 20.7. TOF

MS ES- (H_2O): 332.0798 (M-1; calc. for $C_{16}H_{15}N_2O_4S$: 331.0753).

(CD_3OD was used for most NMR spectra due to slight solubility in other solvents.)

Acknowledgments

CAPES and CNPq for financial support. Drs. Leonardo Coutada, Erika Martins and Carlos B. Bizarri and Mrs. Eliane G. Carvalho (Farmanguinhos-Fiocruz) for NMR and mass spectra includng HRMS). Drs. Marcos Eberlin e Regina Sparrapan (Lab. Thomson de Espectrometria de Massas, I.Q.-Unicamp) for HRMS.

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Received: August 20, 2007
Web Release Date: July 18, 2008