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## Layered zirconium phosphate and phosphonate as heterogeneous catalyst in the preparation of pyrroles

Massimo Curini,<sup>a,\*</sup> Francesca Montanari,<sup>a</sup> Ornelio Rosati,<sup>a</sup> Eduardo Lioy<sup>b</sup> and Roberto Margarita<sup>b</sup>

<sup>a</sup>Dipartimento di Chimica e Tecnologia del Farmaco, Sezione di Chimica Organica, Via del Liceo 1, Università degli Studi, 06123 Perugia, Italy

<sup>b</sup>Bristol Myers Squibb Srl, Via del Murillo Km 2.8, 04010 Sermoneta (LT), Italy

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Abstract—Pyrroles may be prepared by condensation of alkyl and aryl amines and 1,4-diketones (Paal–Knorr reaction) under potassium exchanged layered Zirconium phosphate and zirconium sulfophenyl phosphonate catalyst in solvent free conditions. © 2003 Elsevier Science Ltd. All rights reserved.

It is well established that many acidic and basic solids can act as catalysts or promoters in liquid-phase organic synthesis.<sup>1</sup> Surface mediated solid-phase reaction are of growing interest due to their ease of set-up, mild conditions, rapid reaction, selectivity, increased yields, high purity of products and low cost, compared with their homogeneous counterpart.<sup>2</sup>

Based on our previous experience in the use of potassium exchanged layered zirconium phosphate<sup>3</sup> [ $\alpha$ -Zr(KPO<sub>4</sub>)<sub>2</sub>, surface area = 15.5 m<sup>2</sup>/g, 11<pK<sub>a</sub><11.8<sup>4</sup>] as basic catalyst and zirconium sulfophenyl phosphonate [ $\alpha$ -Zr(O<sub>3</sub>PCH<sub>3</sub>)<sub>1.2</sub>(O<sub>3</sub>PC<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>H)<sub>0.8</sub>, surface area = 24 m<sup>2</sup>/g, -5.6<pK<sub>a</sub><-8.4]<sup>5</sup> as acid catalyst in organic synthesis, we found that these catalysts were an excellent promoter for the preparation of pyrroles by condensation of alkyl and aryl amines and 1,4-diketones.

Although various methods are known for the synthesis of pyrroles by Paal–Knorr condensation<sup>6</sup> only a little attention has been paid to the use of basic or acid solids for this purpose.<sup>7</sup>

The condensation reaction was carried out by adding the acid (or basic) catalyst (in the proper % ratio) to a stirred mixture of 2,5-hexanedione (1 mmol) and amine (2 mmol) at room temperature.<sup>8</sup> The use of 2 equiv. of amine affords a valuable increase of the reactions yields, especially in the case of  $\alpha$ -Zr(CH<sub>3</sub>PO<sub>3</sub>)<sub>1.2</sub>-(O<sub>3</sub>PC<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>H)<sub>0.8</sub> where absorption effect, due to acid-base interaction, can decrease the amines availability.

The reaction takes from 30 min to 24 h and after a simple work-up affords *N*-substituted 2,5-dimethylpyrroles (Scheme 1).

As shown in Table 1, several aliphatic and aromatic amines gave the corresponding N-substituted pyrroles in good to excellent yield. It is important to note that the steric hindrance effect (entry 3, 6) of some amines decreases the reaction yield and in the case of adamantylamine (entry 12) we did not observe any reaction.

The acid or basic catalysts do not present any difference about the time and the yield of the reaction when aliphatic amines are used. Otherwise the  $\alpha$ -Zr(CH<sub>3</sub>PO<sub>3</sub>)<sub>1.2</sub>(O<sub>3</sub>PC<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>H)<sub>0.8</sub> is more efficient than  $\alpha$ -Zr(KPO<sub>4</sub>)<sub>2</sub> in the reactions of 2,5-hexanedione with less basic aromatic amines, because it is possible an activation of 2,5-hexandione, by the acid catalyst, via oxygen protonation.



Catalyst =  $\alpha$ -Zr(KPO<sub>4</sub>)<sub>2</sub> or  $\alpha$ -Zr(CH<sub>3</sub>PO<sub>3</sub>)<sub>1.2</sub>(O<sub>3</sub>PC<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>H)<sub>0.8</sub>

Scheme 1.

<sup>\*</sup> Corresponding author. Tel.: +39-075-5855106; fax: +39-075-5855116; e-mail: curmax@unipg.it

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Table	1.	Pyrroles	derivatives	produced	via	Scheme	1
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Entry	R	$\alpha$ -Zr(KPO <sub>4</sub> ) <sub>2</sub>		$\alpha\text{-}Zr(CH_{3}PO_{3})_{1.2}(O_{3}PC_{6}H_{4}SO_{3}H)_{0.8}$	
		Time (h)	Yield (%) <sup>b</sup>	Time (h)	Yield (%) <sup>b</sup>
1	<i>n</i> -Propyl	1	85	1	87
2	<i>n</i> -Butyl	1	95	1	99
3	sec-Butyl	5	72	5	76
4	iso-Butyl	2	78	2	79
5	Benzyl	2	81	2	89
6	Cyclohexyl	24	48	24	52
7	<i>p</i> -Methoxyphenyl	24	79	2	91
8	<i>o</i> -Hydroxyphenyl	24	65	20	94
9	Phenyl	24	56 <sup>a</sup>	2	$88^{a}$
10	<i>p</i> -Nitrophenyl	24	_a	20	68 <sup>a</sup>
11	2-Pyridinyl	24	_a	20	47 <sup>a</sup>
12	Adamantyl	24	_ <sup>a</sup>	24	_ <sup>a</sup>

<sup>a</sup> The reaction was carried out at 60°C.

<sup>b</sup> Isolated yields.

The reported procedure clearly demonstrates that layered zirconium phosphate and phosphonate are both good catalysts for the preparation of *N*-alkyl-2,5dimethylpyrroles, while the acid catalyst is preferable for the preparation of *N*-aryl-2,5-dimethylpyrroles.

The important features of our method are: mild reaction conditions, simple work-up and recyclable nature of the catalysts employed<sup>9</sup> whose preparation does not require any particular skill.<sup>10,11</sup> Furthermore, the lower quantity of  $\alpha$ -Zr(KPO<sub>4</sub>)<sub>2</sub> (12% molar) or  $\alpha$ -Zr(CH<sub>3</sub>PO<sub>3</sub>)<sub>1.2</sub>(O<sub>3</sub>PC<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>H)<sub>0.8</sub> (6% molar) required in this procedure respect to solid catalysts (e.g. Al<sub>2</sub>O<sub>3</sub>, zeolites, montmorillonites) used in analogous methods reported in literature, make ours catalysts highly efficient.

Studies for the application of our method to the synthesis of several heterocyclic compounds are under investigation in our laboratory.

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- 8. General procedure: To a mixture of amine (2 mmol) and 2,5-hexanedione (1 mmol), under stirring and at room temperature (or 60°C, see Table 1), catalyst (12% molar  $\alpha$ -Zr(KPO<sub>4</sub>)<sub>2</sub> 6% molar or for for α- $Zr(CH_3PO_3)_{1,2}(O_3PC_6H_4SO_3H)_{0,8})$  was added. After appropriate time the reaction was diluted with dichloromethane, filtered on buckner and washed with a 5% HCl solution to remove the amine excess. The organic solution was evaporated under vacuum affording the pyrrol derivative with good purity.

Analytical data for selected compounds:

**2,5-Dimethyl-1-butyl-1***H***-pyrrole**: (pale yellow oil); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  0.95 (t, J = 7 Hz, CH<sub>3</sub>, 3H), 1.36 (m, CH<sub>2</sub>, 2H), 1.58 (m, CH<sub>2</sub>, 2H), 2.19 (s, CH<sub>3</sub>, 6H), 3.69 (t, J = 8.3 Hz, CH<sub>2</sub>, 2H), 5.78 (s, pyrrolics, 2H); GC/MS (m/z) (M<sup>+</sup>) 151, 136, 122, 108, 94. Anal. calcd for C<sub>10</sub>H<sub>17</sub>N: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.38; H, 11.37; N, 9.25.

**1-Benzyl-2,5-dimethyl-1***H***-pyrrole**: (white solid, mp 42–44°C); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  2.14 (s, CH<sub>3</sub>, 6H), 5.03 (s, CH<sub>2</sub>, 2H), 5.87 (s, pyrrolics, 2H), 6.89 (m, PhH, 2H), 7.29 (m, PhH, 3H); GC/MS (*m*/*z*) (M<sup>+</sup>) 187, 170, 129, 107, 91. Anal. calcd for C<sub>13</sub>H<sub>15</sub>N: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.33; H, 8.15; N, 7.52.

**1-(4-Methoxyphenyl)-2,5-dimethyl-1***H***-pyrrole**: (pale yellow solid, mp 59–60°C); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  2.03 (s, CH<sub>3</sub>, 6H), 3.85 (s, OCH<sub>3</sub>, 3H), 5.88 (s, pyrrolics, 2H), 6.96 (m, PhH, 2H), 7.14 (m, PhH, 2H); GC/MS (*m*/*z*) (M<sup>+</sup>) 201, 186, 171, 159, 145, 129. Anal. calcd for C<sub>13</sub>H<sub>15</sub>NO: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.56; H, 7.55; N, 6.94.

**2-(2,5-Dimethyl-1***H***-pyrrol-1-yl)pyridine**: (colourless oil); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  2.13 (s, CH<sub>3</sub>, 2H), 5.89 (s, pyrrolics, 2H), 7.25 (m, PhH, 2H), 7.81 (m, PhH, 1H), 8.61 (m, PhH, 1H); GC/MS (*m*/*z*) (M<sup>+</sup>) 172, 157, 145, 130, 94. Anal. calcd for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>: C, 76.71; H, 7.02; N, 16.27. Found: C, 77.67; H, 7.05; N, 16.25.

9. The catalysts can be reused several times after washing with dichloromethane and drying at 120°C for 12 h. The reaction (entry 9) has been repeated three times with the

following yields: 54, 57, 53% ( $\alpha$ -Zr(KPO<sub>4</sub>)<sub>2</sub>) and 85, 84, 82 ( $\alpha$ -Zr(CH<sub>3</sub>PO<sub>3</sub>)<sub>1,2</sub>(O<sub>3</sub>PC<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>H)<sub>0.8</sub>).

- 10. For the preparation of  $\alpha$ -Zr(KPO<sub>4</sub>)<sub>2</sub>, see: Alberti, G.; Torracca, E. J. Inorg. Nucl. Chem. **1968**, 30, 317–318.
- 11. For the preparation of  $\alpha$ -Zr(CH<sub>3</sub>PO<sub>3</sub>)<sub>1.2</sub>(O<sub>3</sub>PC<sub>6</sub>H<sub>4</sub>-SO<sub>3</sub>H)<sub>0.8</sub>, see: Alberti, G.; Casciola, M.; Costantino, U.; Peraio, A.; Montoneri, E. *Solid State Ionics* **1992**, *50*, 315–322.