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# Potassium exchanged layered zirconium phosphate as catalyst in the preparation of 4*H*-chromenes

Massimo Curini,[a,*] Francesco Epifano,[a] Stefano Chimichi,[b] Francesca Montanari,[a] Morena Nocchetti[c] and Ornelio Rosati[a,*]

[a]*Dipartimento di Chimica e Tecnologia del Farmaco, Sezione Chimica Organica, Via del Liceo, 06123 Perugia, Italy*
[b]*Dipartimento di Chimica Organica 'Ugo Schiff', Via della Lastruccia 13, 50019 Sesto F. no, Italy*
[c]*Dipartimento di Chimica, Sezione Chimica Inorganica, Via del Liceo, 06123 Perugia, Italy*

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**Abstract**—Substituted 4*H*-chromenes were easily prepared by reaction of salicylaldehydes and ethylcyanoacetate in solvent free conditions using potassium exchanged layered zirconium phosphate as catalyst.


In recent years, there has been an increasing emphasis in the use of acidic and basic solids in liquid organic synthesis.[1] Many examples exist which demonstrate achieving better yields, higher selectivity and shorter reaction times as a result of a reaction carried out with heterogeneous catalysts under milder reaction conditions than those employed in conventional synthetic methods. In previous years we reported that layered potassium exchanged zirconium phosphate [$Zr(KPO_4)_2$] is an excellent heterogeneous catalyst for Michael addition, Henry and Knoevenagel reactions, respectively.[2] In continuing our research into the development of new methods for the formation of carbon–carbon bonds using heterogeneous catalysts, we decided to investigate the use of $Zr(KPO_4)_2$ in the reaction of salicylaldehydes with cyanoacetates for the preparation of 4*H*-chromenes. Our interest for this class of compound derived from biological consideration: recently Huang and coworkers[3] reported that 4*H*-chromene derivatives bind Bcl-2 protein and induce apoptosis in tumour cells. To our knowledge, 4*H*-chromenes were prepared from salicylaldehydes and cyanoacetates in heterogeneous liquid phase catalysis using only $Al_2O_3$[4,5] and molecular sieves.[6]

The reaction was carried out by addition of salicylaldehyde (1 mmol) to a well stirred mixture of ethylcyanoacetate (2 mmol) and $Zr(KPO_4)_2$ (50 mg/mmol aldehyde) at 40 °C (Scheme 1).[7] The reaction takes from 0.5 h to 10 h and after a simple work-up affords a good yield of 4*H*-chromenes (Table 1). The reaction product consists of a mixture of two diastereoisomers with different molar ratios. It is important to note that during the purification of 4*H*-chromenes by crystallization, spontaneously conversion produces the more abundant diastereoisomer. The existence of an equilibrium between the two diastereoisomeric forms has been confirmed by leaving the crystallized product in $CDCl_3$ solution and analyzing its rate of conversion by $^1H$ NMR analysis. For the reaction of salicylaldehyde with ethylcyanoacetate (entry 1b), it was found that the structure of the prevalent diastereoisomer can be attributed to an *erythro* configuration by comparison with the data reported in the literature.[5,8]

This methodology is also applicable to the 2-hydroxy-1-naphthaldehyde which affords more complex 4*H*-chromene models (Scheme 2) in good yield (R = methyl: 15 h, 72%;[6] R = ethyl: 3 h, 67%).

The efficiency of $Zr(KPO_4)_2$ in the synthesis of *4H*-chromene is more favourable than alternative reagents reported in the literature. For example entries 1a, 5a and 7b provided in our case 95%, 72% and 94% yield, respectively, instead of the reported 75%,[6] 66%[6] and 86% yield,[3] respectively. This method offers several

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* Corresponding authors. Tel.: +39 075 585 5106; fax: +39 075 585 5116 (M.C.); tel.: +39 075 585 5103; fax: +39 075 585 5116 (O.R.); e-mail addresses: curmax@unipg.it; ornros@unipg.it

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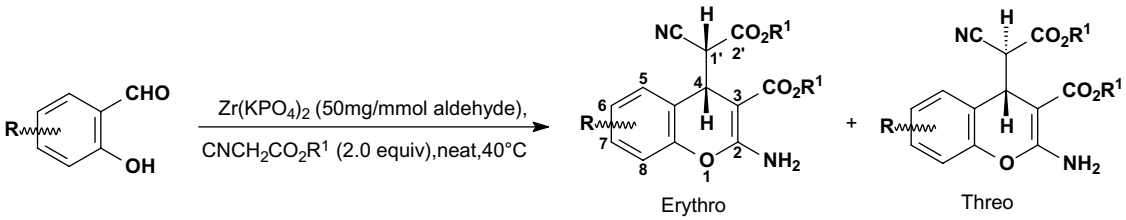
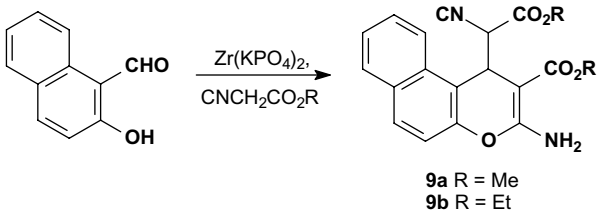



**Scheme 1.**

**Table 1.** Synthesis of 4*H*-chromenes with different alkyl cyanoacetates using $Zr(KPO_4)_2$ as catalyst in solvent free condition

| Entry | Salicylaldehydes | Cyanoacetate | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | (a) $R^1$ = methyl– | | (b) $R^1$ = ethyl– | | (c) $R^1$ = butyl– | | (d) $R^1$ = allyl– | |
| | | Time (h) | Yield (%) | Time (h) | Yield (%) | Time (h) | Yield (%) | Time (h) | Yield (%) |
| 1 | — | 1 | 95 | 2 | 88[a] | 1 | 84 | 3 | 88 |
| 2 | 5-Methyl– | 2 | 97 | 2 | 94 | 2 | 96 | 10 | 93 |
| 3 | 5-Bromo-3-methoxy– | 1 | 92 | 4 | 78 | 3 | 91 | 10 | 91 |
| 4 | 5-Nitro– | 2 | 79 | 1 | 85 | 1 | 98 | 2 | 93 |
| 5 | 3-Methoxy– | 1 | 72 | 5 | 83 | 2 | 87 | 2 | 88 |
| 6 | 4-Methoxy– | 4 | 95 | 9 | 71 | 6 | 89 | 10 | 85 |
| 7 | 5-Bromo– | 1 | 72 | 3 | 97 | 3 | 91 | 10 | 90 |
| 8 | 5-Chloro– | 1 | 98 | 4 | 94 | 1 | 81 | 2 | 86 |

[a] The diastereoisomer more abundant has an *erythro* configuration.




**Scheme 2.**

advantages; such as a high rate of conversion, good reaction times and cleaner reaction profiles. It requires simple experimental and work-up procedures, which may be carried out in the absence of solvents and provide high regioselectivity. The preparation of $Zr(KPO_4)_2$, does not require any specific skills[9] and may also be recycled.[10]

In summary, we describe an efficient procedure for the synthesis of substituted 4*H*-chromenes from several salicylaldehydes and cyanoacetic esters. Potassium exchanged layered zirconium phosphate is used as the catalyst and the reaction takes place in solvent free conditions. This method could be employed in the preparation of a wide variety of 4*H*-chromene models under extremely mild conditions.

## Acknowledgments

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7. General reaction procedure: a mixture of cyanoacetate (2 mmol) and $Zr(KPO_4)_2$ (50 mg) was stirred at 60 °C under nitrogen. After 30 min, salicylaldehyde (1 mmol), was added and the reaction mixture stirred for the appropriate time (see Table 1). The mixture was diluted with dichloromethane (5 ml) and the catalyst removed by filtration. The filtrate was concentrated under vacuum and purified by crystallization. All compounds were characterized by $^1H$, $^{13}C$ NMR and GC–MS. Selected spectral data.
*Methyl 2-amino-4-(1-cyano-2-methoxy-2-oxoethyl)-6- nitro-4H-chromene-3-carboxylate* (entry 4a): pale yellow solid (ethanol), mp 156 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 3.85 (s, 3H, $OCH_3$), 3.88 (s, 3H, $OCH_3$), 4.08 (d, $J$ = 3.5 Hz, 1H, H-3), 4.82 (d, $J$ = 3.5 Hz, 1H, CHCN), 6.24 (br s, 2H, $NH_2$), 7.26 (d, $J$ = 9.0 Hz, 1H, H-8), 8.09 (d, $J$ = 2.4 Hz, 1H, H-5), 8.25 (dd, $J$ = 2.4, 9.0 Hz, 1H, H-7). $^{13}C$ NMR (100, 12 MHz, $CDCl_3$) $\delta$ = 37.1, 46.9, 52.1, 54.2, 73.1, 115.2, 118.1, 121.6, 124.7, 125.6, 144.7, 155.1, 161.9, 165.5, 168.3. GC–MS *m/z*: 305, 249, 233, 216, 200, 189, 186, 170, 158, 142, 114. 88.
*Ethyl 3-amino-1-(1-cyano-2-ethoxy-2-oxoethyl)-1H-benzo[f]-chromene-2-carboxylate* (**9b**): yellow solid (ethanol), mp 118 °C. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 1.35 (t, $J$ = 7.1 Hz, 3H, $CH_3$), 1.38 (t, $J$ = 7.1 Hz, 3H, $CH_3$), 3.84 (d, $J$ = 2.3 Hz, 1H, H-1), 4.08–4.43 (m, 4H, 2 × $OCH_2$), 5.42 (d, $J$ = 2.3 Hz, 1H, CHCN), 6.54 (br s, 2H, $NH_2$),

7.26 (d, $J = 9$ Hz, 1H, H-5), 7.54 (t, $J = 7.5$ Hz, 1H, H-8), 7.70 (t, $J = 7.5$ Hz, 1H, H-9), 7.84 (d, $J = 9$ Hz, 1H, H-6), 7.92 (d, $J = 8$ Hz, 1H, H-7), 8.19 (d, $J = 8$ Hz). $^{13}C$ NMR (100, 12 MHz, $CDCl_3$) $\delta = 14.2$, 14.8, 34.5, 46.9, 60.3, 62.9, 73.5, 115.0, 115.7, 117.1, 122.1, 125.6, 128.2, 129.5, 130.0, 130.3, 131.6, 148.7, 162.8, 165.4, 168.6. GC–MS *m*/*z*: 281, 250, 223, 207, 193, 164, 138, 126, 114, 96, 82.

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10. The catalyst was washed with dichloromethane/methanol and dried at 180 °C for 2 h. The $Zr(KPO_4)_2$ was then reused for four cycles without consistent loss of activity.