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Catalyst-free tandem Knoevenagel-Michael reaction of aldehydes and pyrazolin-5-one: fast and convenient approach to medicinally relevant 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ol)s

Abstract: Catalyst-free tandem Knoevenagel-Michael reaction of aryl aldehydes and two equivalents of 3-methyl-1-phenyl-2-pyrazolin-5-one results in fast (5 min) formation of medicinally relevant 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ol)s in excellent 93%–99% yield.

Keywords: 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ol)s; catalyst-free; Knoevenagel reaction; Michael addition; pyrazolin-5-one; tandem reaction.

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Introduction

Continuously growing interest in convenient and green techniques motivates chemists to increase the tools of their arsenal [1]. In recent years, tandem reactions have emerged as a very attractive method giving access to complex molecules in a facile and efficient manner [2].

Tandem Knoevenagel-Michael reaction is well known in classic organic chemistry [2–6]. Recently, we have published several variants of either chemically or electrochemically induced tandem Knoevenagel-Michael reaction [7–9]. Now we wish to report the fast tandem transformation of aryl aldehydes and two equivalents of 3-methyl-1-phenyl-2-pyrazolin-5-one into substituted 4,4′-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s, which proceeds under catalyst-free conditions.

4,4′-(Arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s have a broad spectrum of biological activities, such as anti-inflammatory [10], antipyretic [11], gastric secretion stimulatory [12], antidepressant [13], and antibacterial [14] properties. Moreover, the analogous 4,4′-(arylmethylene) bis(1*H*-pyrazol-5-ols) are used as fungicides [15], pesticides [16], insecticides [16], dyestuffs [17], and chelating and extracting reagents for different metal ions [18, 19].

The most common method for the synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ol)s involves one-pot pseudo-three-component condensation of aldehydes with 3-methyl-1-phenyl-2-pyrazolin-5-one. Several catalysts have been used for this transformation, including $LiOH{\cdot}H_2O$ [20], 1,3-disulfonic acid imidazolium tetrachloroaluminate [21], sulfuric acid ([3-(3-silicapropyl) sulfanyl]propyl)ester [22], melamine trisulfonic acid [23], nano *n*-propylsulfonated γ-Fe_2O_3 [24], and silica-bonded *N*-propyltriethylenetetramine [25]. However, most of these synthetic methods suffer from several drawbacks such as moderate yields, long reaction times, complex and expensive catalysts, or tedious workup procedures. Furthermore, the previously mentioned techniques require additional purification steps of target compounds, for instance, crystallization [20–23, 25] or flash chromatography [24].

Taking into consideration the basic principles of "green chemistry", catalyst-free procedures are particularly welcome [26]. Two catalyst-free methods for synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ol)s have been reported. In the first method, a mixture of an aldehyde and 3-methyl-1-phenyl-2-pyrazolin-5-one is heated under reflux in ethanol for 4 h [27], but the yields and melting points of the resultant 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ol)s thus prepared have not been reported [27]. Recently, another solvent-free method has been published (heating to 120°C for 10 min) [28]. Unfortunately, aldehydes are easily oxidized under this high temperature conditions, which results in the formation of many by-products. Crystallization from ethanol is necessary to isolate pure 4,4′-(arylmethylene) bis(1*H*-pyrazol-5-ol)s from the bulk solid obtained by this reaction [28]. When we repeated this experiment with benzaldehyde and 3-methyl-1-phenyl-2-pyrazolin-5-one, the expected product was formed in 83% yield by NMR data, but it was isolated in 71% yield only after crystallization.

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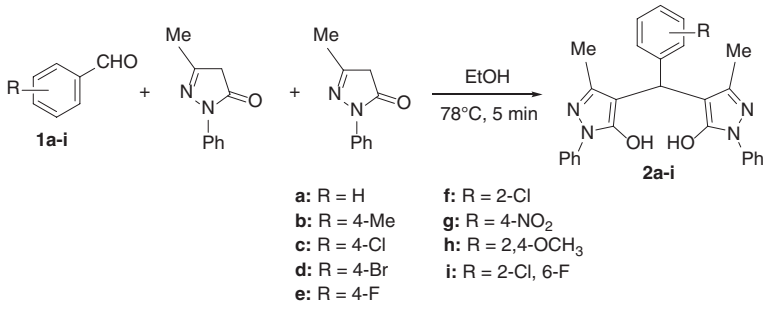


Scheme 1

Taking into consideration the basic principles of "green chemistry", catalyst-free procedures are particularly welcome [28–31]. In this report, we describe a convenient, fast, and efficient catalyst-free tandem transformation of aldehydes and pyrazolin-5-ones into substituted 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ol)s **2a–i**.

Results and discussion

Synthesis of the desired products **2a–i** is easily accomplished under neutral and mild conditions by heating a mixture of an aldehyde and a pyrazolin-5-one in EtOH under reflux for 5 min (Scheme 1).

At the outset of these studies, investigations were conducted to find the optimal conditions (Table 1). The reaction between benzaldehyde **1a** and two equivalents of 3-methyl-1-phenyl-2-pyrazolin-5-one was chosen as a model. First, the experiment was performed at 80°C in water in the presence of 10 mol% of NaOAc as catalyst (Table 1, entry 1). Within 3 min, 4,4′-(phenylmethylene) bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (**2a**) was obtained in 63% yield. The replacement of water with ethanol resulted in the formation of product **2a** in 91% yield (Table 1, entry 2). The next experiment was conducted without any catalyst and solvent under heating at 100°C (Table 1, entry 3). To our surprise, even in this case, the tandem Knoevenagel-Michael reaction proceeded smoothly without noticeable changes in the yield of **2a** (90%). It became evident that the presence of NaOAc had no significant influence on the outcome of the reaction, and the effect of the solvent should be studied. It was found that the tandem reaction of benzaldehyde **1a** and two equivalents of 3-methyl-1-phenyl-2-pyrazolin-5-one proceeds better when ethanol is used as solvent (Table 1, entries 4 and 8). After increasing the reaction time from 3 to 5 min, product **2a** was obtained in 98% yield (Table 1, entry 8). Under such optimized conditions, the scope of the reaction was studied.

Table 1: Tandem Knoevenagel-Michael transformation of benzaldehyde (**1a**) and two equivalents of 3-methyl-1-phenyl-2-pyrazolin-5-one into **2a**.[a]

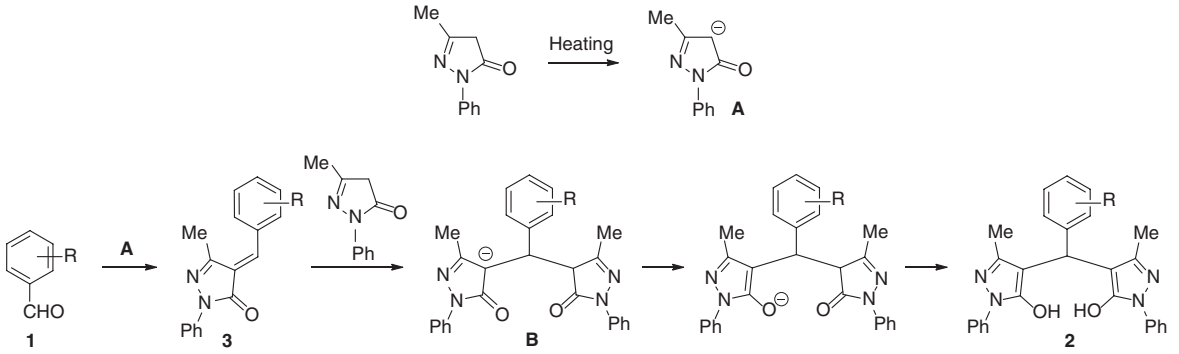
Entry	Catalyst (mol.%)	Solvent	*T* (°C)	Time (min)	Yield of 2a (%)[b]
1	NaOAc (10)	H_2O	80	3	63
2	NaOAc (10)	EtOH	78	3	91
3	–	–	100	3	90
4	–	EtOH	78	3	95
5	–	PrOH	80	3	88
6	–	MeOH	65	3	76
7	–	H_2O	80		65
8	–	EtOH	78	5	98

[a]**1a** (5 mmol), 3-methyl-2-pyrazol-5-one (10 mmol), 3 mL of solvent.
[b]Isolated yield.

Various substituted aryl aldehydes **1a–i** bearing either electron-withdrawing or electron-donating groups were allowed to react with two equivalents of 3-methyl-1-phenyl-2-pyrazolin-5-one. The tandem Knoevenagel-Michael reaction proved to be general because excellent (93%–99%) yields of 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s **2a–i** were achieved in all cases. It is also worth noting that this tandem process is performed under catalyst-free conditions within the unprecedented reaction time of 5 min and the analytically pure products are obtained by simple filtration.

Taking into consideration the previously discussed results and the mechanistic data on the related electrocatalytic tandem transformation previously reported by us [7], the following mechanism for the catalyst-free tandem Knoevenagel-Michael reaction of aryl aldehydes **1** with 3-methyl-1-phenyl-2-pyrazolin-5-one can be proposed (Scheme 2).

The initial step of this catalyst-free tandem process begins with ionization of 3-methyl-1-phenyl-2-pyrazolin-5-one leading to anion **A**. This process can be thermally



Scheme 2

activated. Subsequent Knoevenagel condensation of **A** and aryl aldehyde **1** takes place affording the intermediate product **3**. This step is followed by Michael addition of another equivalent of 3-methyl-1-phenyl-2-pyrazolin-5-one with **3** to give rise to anion **B**. Finally, the anion **B** undergoes intramolecular tautomeric transformation with the formation of corresponding 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s **2.**

Conclusion

A novel, fast, and efficient catalyst-free Knoevenagel-Michael reaction of aryl aldehydes and two equivalents of 3-methyl-1-phenyl-2-pyrazolin-5-one leading to 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s in excellent yields was developed. Noncatalytic conditions of this cascade procedure correspond to present-day demands of "green chemistry". This tandem procedure uses simple equipment and readily available starting materials. The final compounds are isolated by simple filtration of the reaction mixture and do not need further purification. The technique described offers an efficient and convenient way to 4,4′-(arylmethylene) bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s, the prominent compounds with approved practical utilities and different biomedical applications.

Experimental

Melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded with a Bruker Avance II-300 at ambient temperature in DMSO-d_6 solutions. IR spectra were registered with a Bruker ALPHA-T FT-IR spectrometer in KBr pellets. HRMS (ESI) were run on Bruker micrOTOF II instrument; external or internal calibration was performed using Electrospray Calibrant Solution (Fluka). All starting materials were obtained from commercial sources and used without purification.

General procedure

A mixture of 3-methyl-1-phenyl-2-pyrazolin-5-one (10 mmol) and a benzaldehyde **1a–i** (5 mmol) in ethanol (3 mL) was stirred under reflux for 5 min then cooled to room temperature. The resultant precipitate was filtered off, rinsed with ice-cold ethanol (2×1 mL), and dried under reduced pressure.

4,4′-(Phenylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (2a) White solid; yield 2.14 g (98%); mp 170–172°C (lit. [22] 170–172°C); ^{1}H NMR: δ 2.33 (s, 6H, 2CH$_3$), 4.97 (s, 1H, CH), 7.15–7.29 (m, 7H, Ar), 7.44 (t, *J* = 7.9 Hz, 4H, Ar), 7.72 (d, *J* = 7.6 Hz, 4H, Ar).

4,4′-[(4-Methylphenyl)methylene)]bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (2b) White solid; yield 2.16 g (96%); mp 205–207°C (lit. [22] mp 202–204°C); ^{1}H NMR: δ 2.31 (s, 6H, 2CH$_3$), 2.51 (s, 3H, CH$_3$), 4.91 (s, 1H, CH), 7.06–7.27 (m, 6H, Ar), 7.44 (t, *J* = 7.6 Hz, 4H, Ar), 7.72 (d, *J* = 7.9 Hz, 4H, Ar).

4,4′-[(4-Chlorophenyl)methylene)]bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (2c) White solid; yield 2.19 g (93%); mp 215–216°C (lit. [22] mp 215–217°C); ^{1}H NMR: δ 2.30 (s, 6H, 2CH$_3$), 4.95 (s, 1H, CH), 7.20–7.34 (m, 6H, Ar), 7.42 (t, *J* = 7.8 Hz, 4H, Ar), 7.69 (d, *J* = 7.6 Hz, 4H, Ar).

4,4′-[(4-Bromophenyl)methylene)]bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (2d) White solid; yield 2.50 g (97%); mp 220–222°C (lit. [23] mp 183–184°C); ^{1}H NMR: δ 2.32 (s, 6H, 2CH$_3$), 4.95 (s, 1H, CH), 7.19–7.27 (m, 4H, Ar), 7.42–7.48 (m, 5H, Ar), 7.71 (d, *J* = 7.9 Hz, 4H, Ar).

4,4′-[(4-Fluorophenyl)methylene)]bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (2e) Orange solid; yield 2.25 g (99%); mp 181–182°C (lit. mp [22] 181–183°C); ^{1}H NMR: δ 2.32 (s, 6H, 2CH$_3$), 4.96 (s, 1H, CH), 7.07–7.12 (m, 2H, Ar), 7.22–7.27 (m, 4H, Ar), 7.44 (t, *J* = 7.3 Hz, 4H, Ar), 7.71 (d, *J* = 7.6 Hz, 4H, Ar).

4,4′-[(2-Chlorophenyl)methylene)]bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (2f) White solid; yield 2.21 g (94%); mp 239–241°C (lit. [22] mp 235–237°C); ^{1}H NMR: δ 2.08 (s, 6H, 2CH$_3$), 5.04 (s, 1H, CH),

7.00–7.19 (m, 8H, Ar), 7.24 (d, *J* = 6.6 Hz, 1H, Ar), 7.38 (d, *J* = 7.9 Hz, 4H, Ar), 7.79 (d, *J* = 7.8 Hz, 1H, Ar).

4,4′-[(4-Nitrophenyl)methylene)]bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (2g) Yellowish solid; yield 2.36 g (98%); mp 230–232°C (lit. [22] mp 225–227°C); ^{1}H NMR: δ 2.35 (s, 6H, $2CH_3$), 5.13 (s, 1H, CH), 7.23–7.29 (m, 2H, Ar), 7.42–7.55 (m, 6H, Ar), 7.71 (d, *J* = 7.7 Hz, 4H, Ar), 8.17 (d, *J* = 8.6 Hz, 2H, Ar).

4,4′-[(2,4-Dimethoxyphenyl)methylene)]bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (2h) Orange solid (2.41 g, 97%); mp 198–200°C; ^{1}H NMR: δ 2.27 (s, 6H, $2CH_3$), 3.71 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.09 (s, 1H, CH), 6.46 (d, *J* = 8.4 Hz, 1H, Ar), 6.51 (s, 1H, Ar), 7.21–7.26 (m, 2H, Ar), 7.41–7.50 (m, 5H, Ar), 7.71 (d, *J* = 7.9 Hz, 4H, Ar); ^{13}C NMR: δ 11.7 (2C), 27.1, 55.0, 55.5, 98.4, 104.2, 104.7 (2C), 120.5 (4C), 123.1, 125.4 (2C), 128.9 (5C), 129.1 (2C), 137.5 (2C), 146.3 (2C), 156.8, 159.0; IR: ν 2959, 2421, 1614, 1504, 1406, 1294, 1210, 1123, 840, 758 cm^{-1}. HRMS (ESI). Calcd for $C_{29}H_{29}N_4O_4$ ([M+H]$^+$): *m/z* 497.2183. Found: m/z 497.2174.

4,4′-[(2-Chloro-6-fluorophenyl)methylene)]bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (2i) White solid; yield 2.33 g (95%); mp 215–216°C; ^{1}H NMR: δ 2.20 (s, 6H, $2CH_3$), 5.36 (s, 1H, CH), 7.09–7.16 (m, 1H, Ar), 7.21–7.29 (m, 4H, Ar), 7.43 (t, *J* = 7.6 Hz, 4H, Ar), 7.71 (d, *J* = 7.9 Hz, 4H, Ar); ^{13}C NMR: 11.9 (2C), 29.3, 102.7 (2C), 115.6 (d, *J* = 24.5 Hz, 1C), 120.1 (4C), 125.4 (d, *J* = 25.3 Hz, 1C), 127.4 (d, *J* = 14.9 Hz, 1C), 128.6, 128.8 (6C), 133.6, 137.4 (2C), 146.5 (2C), 158.2 (2C), 161.7 (d, *J* = 250.5 Hz, 1C); IR: ν 3061, 2912, 2874, 2791, 1619, 1566, 1500, 1399, 789, 748 cm^{-1}. HRMS (ESI). Calcd for $C_{27}H_{23}ClFN_4O_2$ ([M+H]$^+$): *m/z* 489.1488. Found: *m/z* 489.1480.

References

[1] Nefzi, A.; Ostresh, J. M.; Houghten, R. A. The current status of heterocyclic combinatorial libraries. *Chem. Rev.* **1997**, *97*, 449–472.

[2] Ho, T. L. Tandem Organic Reactions; John Wiley & Sons: New York, 1992.

[3] Sabitha, G.; Reddy, G. S. K. K.; Rajkumar, M.; Yadav, J. S.; Ramakrishna, K. V. S.; Kunwar, A. C. Iodotrimethylsilane induced diastereoselective synthesis of tetrahydropyranones by a tandem Knoevenagel-Michael reaction. *Tetrahedron Lett.* **2003**, *44*, 7455–7457.

[4] Fan, R.; Wang, W.; Pu, D.; Wu, J. Tandem Knoevenagel-Michael addition of aryl sulfonimines with diethyl malonate for synthesis of arylidene dimalonates. *J. Org. Chem.* **2007**, *72*, 5905–5907.

[5] An, Z.; Guo, Y.; Zhao, L. L-prolin-grafted mesoporous silica with alternating hydrophobic and hydrophilic blocks to promote direct asymmetric aldol and Knoevenagel-Michael cascade reactions. *ACS Catal.* **2014**, *4*, 2566–2576.

[6] Ghosh, A.; Khan, A. T. Synthesis of dihydrochromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridine-6(7*H*)-ones involving one-pot three-component tandem Knoevenagel-Michael reaction catalyzed by *n*-tetrabutylammonium tribromide (TBATB). *Tetrahedron Lett.* **2014**, *55*, 2006–2009.

[7] Elinson, M. N.; Dorofeev, A. S.; Nasybullin, R. F.; Nikishin G. I. Facile and convenient synthesis of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) by electrocatalytic tandem Knoevenagel-Michael reaction. *Synthesis* **2008**, 1933–1937.

[8] Elinson, M. N.; Dorofeev, A. S.; Nasybullin, R. F.; Fedukovich, S. K.; Nikishin, G. I. Electrocatalytic tandem Knoevenagel-Michael reaction of 3-methyl-2-pyrazolin-5-ones, aryl aldehydes and cyano-functionalized C-H acids: facile and convenient multicomponent way to substituted 3-(5-hydroxy-3-methylpyrazol-4-yl)-3-arylpropionitriles. *Electrochim. Acta* **2008**, *53*, 5033–5038.

[9] Elinson, M. N.; Nasybullin, R. F.; Nikishin, G. I. Sodium acetate catalyzed tandem Knoevenagel-Michael multicomponent reaction of aldehydes, 2-pyrazolin-5-ones, and cyano-functionalized C-H acids: facile and efficient way to 3-(5-hydroxypyrazol-4-yl)-3-arylpropionitriles. *C. R. Chim.* **2013**, *16*, 789–794.

[10] Sugiura, S.; Ohno, S.; Ohtani, O.; Izumi, K.; Kitamikado, T.; Asai, H.; Kato, K. Syntheses and anti-inflammatory and hypnotic activity of 5-alkoxy-3-(N-substituted carbamoyl)-1-phenylpyrazoles. *J. Med. Chem.* **1977**, *20*, 80–85.

[11] Behr, L. C.; Fusco, R.; Jarboe, C. H. In *The Chemistry of Heterocyclic Compounds, Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings*; Weissberger, A., Ed. Interscience Publishers: New York, 1967.

[12] Rosiere, C. E.; Grossman, M. I. An analog of histamine that stimulates gastric acid secretion without other actions of histamine. *Science* **1951**, *113*, 651.

[13] Bailey, D. M.; Hansen, P. E.; Hlavac, A. G.; Baizman, E. R.; Pearl, J.; Defelice, A. F.; Feigenson, M. E. 3,4-Diphenyl-1*H*-pyrazole-1-propanamine antidepressants. *J. Med. Chem.* **1985**, *28*, 256–260.

[14] Mahajan, R. N.; Havaldar, F. H.; Fernandes, P. S. Syntheses and biological-activity of heterocycles derived from 3-methoxy-1-phenyl-1*H*-pyrazole-5-carboxylate. *J. Indian Chem. Soc.* **1991**, *68*, 245–246.

[15] Singh, D.; Singh, D. Synthesis and antifungal activity of some 4-arylmethylene derivatives of substituted pyrazolones. *J. Indian Chem. Soc.* **1991**, *68*, 165–167.

[16] Londershausen, M. Approaches to new parasiticides. *Pestic. Sci.* **1996**, *48*, 269–292.

[17] *The Chemistry of Synthetic Dyes and Pigments*; Lubs, H. A., Ed. American Chemical Society: Washington DC, 1970.

[18] Uzoukwu, A. B.; Aljuaid, S. S.; Hitchcock, P. B.; Smith, J. D. The synthesis and crystal structures of 1-phenyl-3-methyl-4-butanoylpyrazol-5-one and of 2-pyrazolonato complexes of iron. *Polyhedron* **1993**, *12*, 2719–2724.

[19] Pettinari, C.; Marchetti, F.; Pettinari, R.; Drozdov, A.; Troyanov, S.; Voloshin, A. I.; Shavaleen, N. M. Synthesis, structure and luminescence properties of new rare earth metal complexes with 1-phenyl-3-methyl-4-acylpyrazol-5-ones. *J. Chem. Soc. Dalton Trans.*, **2002**, 1409–1415.

[20] Gouda, M. A.; Abu-Hashem, A. A. An eco-friendly procedure for the efficient synthesis of arylidenemalononitriles and 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) in aqueous media. *Green Chem. Lett. Rev.* **2012**, *5*, 203–209.

[21] Khazaei, A.; Zolfigol, M. A.; Moosavi-Zare, A. R.; Asgari, Z.; Shekouhy, M.; Zare, A.; Hasaninejad, A. Preparation of 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) over 1,3-disulfonic acid imidazolium tetrachloroaluminate as a novel catalyst. *RSC Adv.* **2012**, *2*, 8010–8013.

[22] Tayebi, S.; Baghernejad, M.; Saberi, D.; Niknam, K. Sulfuric acid ([3-(3-silicapropyl)sulfanyl]propyl)ester as a recyclable

catalyst for the synthesis of 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols). *Chin. J. Catal.* **2011**, *32*, 1477–1483.

[23] Iravani, N.; Albadi, J.; Momtazan, H.; Baghernejad, M. Melamine trisulfunic acid: an efficient and recyclable solid acid catalyst for the synthesis of 4,4′-(arylmethylene)-bis-(1*H*-pyrazol-5-ols). *J. Chin. Chem. Soc.* **2013**, *60*, 418–424.

[24] Sobhani, S.; Pakdin-Parizi, Z.; Nasseri, R. Nano *n*-propylsulphonated γ-Fe_2O_3: a novel magnetically recyclable heterogeneous catalyst for the efficient synthesis of *bis*(pyrazolyl) methanes in water. *J. Chem. Sci.* **2013**, *125*, 975–979.

[25] Niknam, K.; Habibabad, M. S.; Deris, A.; Aeinjamshid, N. Preparation of silica-bonded N-propyltriethylenetetramine as a recyclable solid base catalyst for the synthesis of 4,4′-(arylmethylene) bis(1*H*-pyrazol-5-ols). *Monatsh. Chem.* **2014**, *144*, 987–992.

[26] Wender P. A. Toward the ideal synthesis and molecular function through synthesis-informed design. *Nat. Prod. Rep*. **2014**, *31*, 433–440.

[27] Stefan S. L. Stability constants of thorium(IV) complexes with aryl-bis-(5-hydroxy-3-methyl-l-phenyl-4-pyrazolyl) methane ligands. *Monatsh. Chem*. **1994**, *125*, 859–867.

[28] Gupta A. D., Pal R., Mallik A. K. Two efficient and green methods for synthesis of 4,4′- (arylmethylene)bis(1*H*-pyrazol-5-ols) without use of any catalyst or solvent. *Green Chem. Lett. Rev.* **2014**, *7*, 404–411.

[29] Elinson M. N.; Ilovaisky A. I; Merkulova, V. M.; Belyakov, P. A.; Barba F.; Batanero B. General non-catalytic approach to spiroacenaphthylene heterocycles: multicomponent assembling of acenaphthenequinone, cyclic CH-acids and malononitrile. *Tetrahedron* **2012**, *68*, 5833–5837.

[30] Elinson, M. N.; Ilovaisky, A. I.; Merkulova, V. M.; Zaimovskaya, T. A.; Nikishin, G. I. Non-catalytic thermal multicomponent assembling of isatin, cyclic CH-acids and malononitrile: an efficient approach to spirooxindole scaffold. *Mendeleev Commun.* **2012**, *21*, 143–144.

[31] Elinson, M. N.; Ryzhkov, F. V.; Nasybullin, R. F.; Zaimovskaya, T. A.; Egorov, M. P. Non-catalytic solvent-free fast and efficient approach to substituted 5,6,7,8-tetrahydro-4*H*-chromenes from aldehydes, dimedone and malononitrlie at ambient temperature. *Mendeleev Commun*. **2015**, in press.