# Multicomponent reactions of 1,3-disubstituted 5-pyrazolones and formaldehyde in environmentally benign solvent systems and their variations with more fundamental substrates<sup>†</sup>

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Many multicomponent reactions (MCRs) of 1,3-disubstituted 5-pyrazolones and formaldehyde were developed in environmentally benign solvent systems. Styrenes, vinylferrocene and 2-phenylindoles could easily react, under solvent-free conditions or in glycerol solvent, with 1,3-disubstituted 5-pyrazolones and paraformaldehyde in the absence of any catalyst to afford a variety of complex skeletons in moderate to excellent yields. Particularly, these MCRs are proved to be combinable with the synthesis of 1,3-disubstituted 5-pyrazolones from phenylhydrazines and  $\beta$ -ketone esters in glycerol or a carboxylic acid-functionalized ionic liquid, [MIm-CO<sub>2</sub>H]BF<sub>4</sub>. Therefore, some two-step sequential reactions of phenylhydrazines,  $\beta$ -ketone esters, formaldehyde and styrenes or indoles were developed for the first time. All these MCRs were conducted in environmentally benign solvent systems that not only minimize generation of wastes but also simplify the work-up procedure.

#### Introduction

The study of multicomponent reactions (MCRs) is a promising, hot field of chemistry, since they allow complicated molecules to be created by using one reaction in a fast, efficient and time-saving manner.<sup>1</sup> Because of these advantages, developing new MCRs with environmentally benign methods has been recognized as one of the most important topics of green chemistry.<sup>2</sup> In a MCR, a product is assembled according to a cascade of elementary chemical reactions. The challenge is to conduct a MCR in a suitable way that allows the pre-equilibrated elementary reactions to channel into the main product and not yield side products.<sup>3</sup> For this purpose, many efforts have been devoted to optimization of reaction conditions.

Formaldehyde is a very active substrate frequently used in MCRs.<sup>4</sup> Most of MCRs using formaldehyde involve fundamental reactions such as aldol and Mannich type reactions. In some cases, methylenation of electron-rich carbons with formaldehyde that generates active methylene compounds (or methides) was also observed. The generated methylene compounds could be used as chemical platforms for the creation of various C–C, C– O, C–N bonds, among others.<sup>5</sup> Thanks to the great contributions of Tietze<sup>6</sup> and the others,<sup>7</sup> hetero-Diels–Alder reaction of oxo-dienes has been well described, and today this reaction is frequently used for developing new MCRs. However, in MCRs of formaldehyde, hetero-Diels-Alder reaction has been rarely involved. The reasons mainly stem from instability and high reactivity of the active methylene compounds generated from formaldehyde. Despite these facts, some promising results have been achieved quite recently. For example, Tietze and co-workers have successfully designed a novel three-component tandem Knoevenagel/hetero-Diels-Alder reaction involving nitroacetone, formaldehyde and alkyl vinyl ether for the total synthesis of (+)-D-forosamine.<sup>8</sup> We have also reported a three-component reaction of 1,3-dicarbonyl compounds, formaldehyde and styrenes that generates substituted dihydropyran derivatives in fair to excellent yields using water or glycerol as solvents.<sup>9</sup> In these reactions, formation of a methylene intermediate is the key to construct the MCR because it can act as an oxo-diene to react with styrenes through hetero-Diels-Alder cycloaddition. Interestingly, it was also found that replacing water with an aqueous solution of acetic acid allows successful use of some other substrates, such as 2-naphthol, 2-hydroxy-1,4-naphthoguinone, 4-hydroxycoumarin and 4-hydroxy-6-methyl-2-pyrone, in these MCRs.<sup>10</sup> All these results indicated that: (i) trapping the active methylene intermediate is a fundamental method for developing new MCRs of formaldehyde; (ii) although many substrates might be applicable in these MCRs, in order to maximize the reactivity, reaction conditions have to be carefully optimized.

On the other hand, the derivatives of pyrazolone are an important class of antipyretic and analgesic compounds.<sup>11</sup> As these compounds have great potential in pharmaceutical chemistry, their derivatizations by synthetic methods have gained much attention recently.<sup>12</sup> 1,3-Disubstituted 5-pyrazolone is one of the most important pyrazolone derivatives, and today it is often used in many fundamental reactions. Particularly, 1,3-disubstituted

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5-pyrazolone was proved to be applicable in the Knoevenagel reaction when some aromatic aldehydes were used as substrates.13 High reactivities of 1,3-disubstituted 5-pyrazolones gave us impetus to use 1,3-disubstituted 5-pyrazolone and formaldehyde as substrates in Tietze's domino reaction. In this paper, we will now prove the feasibility and generality of the three-component reaction of 1,3-disubstituted 5-pyrazolone, formaldehyde and styrenes, which will result in new polyheterocycles. Particularly, we will show that this MCR could be carried out under catalystand solvent-free conditions, which significantly simplifies the work-up procedure and minimizes generation of wastes. Furthermore, the MCR was proved to be combinable with synthesis of 1,3-disubstituted 5-pyrazolones from phenylhydrazines and β-ketone esters. Environmentally benign solvents, such as glycerol and a carboxylic acid-functionalized ionic liquid, [MIm-CO<sub>2</sub>H]BF<sub>4</sub>, were adopted in order to improve the reaction yield. Thus, a stepwise one-pot reaction of phenylhydrazines,  $\beta$ -ketone esters, styrenes and formaldehyde was developed, for the first time, in green media. We will also show in this paper that other substrates, such as vinylferrocene and 2-phenylindoles could assemble readily in glycerol with 1,3-disubstituted 5-pyrazolone and formaldehydes to generate some complex products in moderate yields.

#### **Results and discussion**

Initially, the three-component reaction between 1-phenyl-3-methyl-5-pyrazolone (*Ia*),  $\alpha$ -methylstyrene (*2a*) and paraformaldehyde was investigated under catalyst- and solvent-free conditions. Although both 1-phenyl-3-methyl-5-pyrazolone and paraformaldehyde are solid, because the reaction was conducted at 110 °C, the model reaction could, in fact, be performed in liquid state. At the end of reaction, a red viscous mixture was obtained. By isolation with preparative TLC, a pale yellow solid that was identified as 1,4,5,6-tetrahydro-3,6-dimethyl-1,6-phenylpyrano[2,3-c]pyrazole

(3a), was obtained. As shown in Table 1, under a ratio of Ia/HCHO/2a = 1.0/1.0/1.0, 3a was obtained in 58% yield after 11 h of reaction (entry 1). In order to improve the

**Table 1** Three-component reaction of 1a, 2a and HCHO under solvent-free condition<sup>*a*</sup>



<sup>*a*</sup> *1a*: 0.5 mmol paraformaldehyde was used as source of HCHO, 110 °C. <sup>*b*</sup> 90 °C. <sup>*c*</sup> Fformalin (37 wt%) was used instead of paraformaldehyde. <sup>*a*</sup> A side product (**II**) was also isolated in 15% yield with respect to *1a*. <sup>*e*</sup> Only trace amount of (**II**) was isolated.

reaction yield, excess amounts of paraformaldehyde and  $\alpha$ -methylstyrene have been used (entries 2 and 3). Under an optimized ratio, la/HCHO/2a = 1.0/1.5/2.0, the reaction yield was kept nearly unaltered when the reaction time was decreased from 11 h to 5 h (entry 4). Further decrease of reaction time to 2 h resulted in an incomplete reaction, and as a result, only 55% of yield was obtained (entry 5). Further investigation revealed that the reaction was also affected by temperature, and in order to achieve a higher yield, the reaction has to be carried out at 110 °C (entry 6). In addition, using paraformaldehyde as HCHO source was proved to be also crucial for the model MCR, because only 43% of yield was obtained when formalin was used (entry 7). From all the results in Table 1, we can conclude, at this stage, that three-component reaction of 1-phenyl-3-methyl-5-pyrazolone (1a),  $\alpha$ -methylstyrene (2a) and paraformaldehyde proceeded readily without any special effort, and an optimal yield, 85%, could be obtained under catalystand solvent-free conditions.

In order to understand the mechanism of this MCR, counter experiments were then carried out under the identical condition by using different combinations of each two substrates. No product was detected in the reactions of  $1a + (HCHO)_n$  and 1a + 2a. In the case of  $1a + (HCHO)_n$ , a product, (II) (see Scheme 1), was observed. These results suggest that the concomitant presence of 1a, 2a and paraformaldehyde in the same reaction pot is necessary for the selective formation of 3a. Tietze and others have developed an intramolecular domino Knoevenagel/hetero-Diels-Alder reaction using 1-phenyl-3-methyl-5-pyrazolone as one of the substrates.14 Two-component hetero-Diels-Alder reactions of 1,3-diphenyl-4-arylidene-5-pyrazolone and alkyl vinyl ether or 2,3-dimethylbutadiene have also been reported and used for synthesis of heterocyclic compounds.<sup>15</sup> Our previous investigations have demonstrated that styrenes are capable of trapping a o-quinone methide that was generated in situ from formaldehyde and a suitable electron-rich carbon-containing compound. On the basis of these reported results, we suspect here that the model reaction might proceed through a tandem Knoevenagel/hetero-Diels-Alder reaction (Scheme 1). Formation of intermediate (I) is the key to initiate the MCR. There are two possibilities to trap the intermediate (I): (i) with  $\alpha$ methylstyrene through a hetero-Diels-Alder reaction; and (ii) with the next 1-phenyl-3-methyl-5-pyrazolone molecule through a Michael reaction. In our experiments, products from both reaction pathways could be observed. Fortunately, formation of the



Scheme 1 Plausible reaction pathway of three-component reaction of *Ia*, paraformaldehyde and *2a*.

side product (II, obtained from tandem Knoevenagel/Michael reaction) could be significantly inhibited by using excess amount of  $\alpha$ -methylstyrene (Table 1, entris 1 and 4). It should be noted that hetero-Diels-Alder reaction could theoretically generate two regioisomers. However, only one product was obtained in our hand. This high regioselectivity deserves further investigation, and we are now working on this line.

Literature information about the skeleton of 3a shows that it is an important structure as its fragment is often involved in pharmaceutical synthesis.<sup>16</sup> However, synthesis of this kind of compound is generally not easy, because either expensive chemicals or multi-step reactions were used (see ESI<sup>†</sup>).<sup>17</sup> Our method presents an effective and a straightforward way to access such compounds. From the viewpoint of green chemistry, the model reaction in Table 1 can be considered as an ideal tool for green synthesis because of the fact that (i) the high atomeconomy of the reaction, the only by-product is water; (ii) catalyst- and solvent-free conditions that minimizes generation of wastes. All these aspects make the model MCR highly attractive to green organic synthesis.

Having these results in hand, we then investigated the scope and limitations of the model MCR. As shown in Table 2, many 1,3-disubstituted 5-pyrazolones could react readily with paraformaldehyde and  $\alpha$ -methylstyrene, and good to excellent vields were obtained under solvent-free conditions. In particular, high yields were obtained with 3-tert-butyl- or 3-aryl-substituted 1-aryl-5-pyrazolones. Aryl groups in N1-position of the pyrazolone play a key role in facilitating the reaction because of the fact that replacing the aryl groups with alkyl group, for example tert-butyl (1w), results in a decrease of the reaction vield (43%, entry 22). In order to improve the reaction of Iw, another styrene, 4-fluoro- $\alpha$ -methylstyrene (2g), was then used, and in this case, a good yield, 70%, was obtained. Limitation of this MCR was observed in the reaction of unsubstituted 1-H-pyrazolone, Ix, with which no desired product was detected (entry 24).

Table 3 shows the results of different styrenes in the model MCR. All styrene derivatives react readily with 1a and formaldehyde under solvent-free conditions affording the desired pyrano[2,3-c]pyrazoles 3x-3ae in moderate to excellent yields (54-89% yield, Table 3, entries 1-7). Styrenes with methyl group in  $\alpha$ -position (2g and 2h) afforded better yields than those without substituents (entries 5 and 7). Not only styrenes, but also vinylferrocene can be used in this MCR. For example, 3-tertbutyl substituted 1-aryl-5-pyrazolones, *Ic* and *Ij*, could react readily with vinylferrocene and paraformaldehyde to afford the corresponding ferrocene-containing heterocycles, 3af and 3ag, in moderate yields (Scheme 2). It should be noted that skeleton of the obtained ferrocene-containing product has never been reported before, indicating great ability of our MCR for creation of molecular complexity.

It is well known that 1,3-disubstituted 5-pyrazolone could be prepared by condensation between hydrazines and β-ketone esters.18 The reaction was normally carried out in an alcoholic solvent under mild conditions with or without assistance of acidic or basic catalyst. Easy synthesis of 1,3-disubstituted 5-pyrazolone and high efficiency of the model MCR encouraged us to combine both the condensation and the model MCR in a one-pot procedure. However, heating a mixture composed of

Table 2 Substrate scopes for three-component reactions of 1,3disubstituted 5-pyrazolones,  $\alpha$ -methylstyrene and formaldehyde<sup>*a*</sup>

(HCHO)

1

2

3

4

5

6

7

8

9

## solvent-free, 110 °C 1b-w Entry 1,3-Disubstituted 5-pyrazolone Product Yield (%) 36 88 1h 91 3c 85 31 93 3e 95 3f 55 3g 3h 85 3i 62 92 3j 10 3k 82 1k11 31 65 12 87 3m 13 3n 70





<sup>a</sup> 1,3-Disubstituted 5-pyrazolone: 0.5 mmol, α-methylstyrene: 1.0 mmol, paraformaldehyde: 0.75 mmol, reaction time: 5 h, temperature: 110 °C.
 <sup>b</sup> Reaction time: 11 h. <sup>c</sup> 4-Fluoro-α-methylstyrene was used.

phenylhydrazine (4*a*), paraformaldehyde, ethyl benzoylacetate (5*a*) and  $\alpha$ -methylstyrene (2*a*) generates a messy product without predominant selectivity (Table 4, entry 1). In view

Table 3Three-component reactions between 1a, HCHO and differentstyrenes<sup>a</sup>



" Ia: 0.5 mmol, alkene, 1.0 mmol; paraformaldehyde: 0.75 mmol; 110 °C, 5 h.



Scheme 2 Three-component reaction of 1,3-disubstituted 5-pyrazolone, vinylferrocene and paraformaldehyde (ratio of pyrazolone/ $2i/(\text{HCHO})_n = 1.0/2.0/1.5$ ).

of the fact that the use of an alcoholic solvent is beneficial for the condensation between phenylhydrazine and β-ketone ester, we then tried the two-step sequential reaction in glycerol that has been proposed as a promising, green, renewable and bio-compatible medium for organic synthesis by us<sup>19</sup> and the others.<sup>20</sup> As shown in Table 4, although direct mixing all the four components is unsuccessful for construction of 3e, a one-pot two-step reaction sequence can be realized in glycerol by a stepwise manner (entries 2 and 3). The desired product, 3e, could be prepared by the following procedures: (i) heating phenylhydrazine and ethyl benzoylacetate in glycerol that generates 1,3-diphenyl-5-pyrazolone smoothly, the reaction time in this step was marked as  $t^1$ , and (ii) mixing paraformaldehyde and  $\alpha$ -methylstyrene together with the reaction solution, and keeping the system react under the former condition to the desired reaction time,  $t^2$ . Monitoring the progress of reaction with TLC revealed that suitable reaction time should be  $t^1 = 4$  h and  $t^2 = 10$  h. The sequential reaction was also affected by temperature and solvent amount, and the optimal condition is 110 °C and 2.5 g glycerol for a reaction in 0.5 mmol scale (entries 4 and 5). Under this optimized condition, many  $\beta$ -ketone esters and styrenes were used in the one-pot sequential reaction, and the desired pyrano[2,3-c]pyrazoles were obtained in moderate to good yields by using glycerol as solvent (entries 6-14). A less-reactive arylhydrazine, 2,4,6-trichlorophenylhydrazine (4b), was also

		$R^{4} R^{5} R^{2}$ + (HCHO) <sub>n</sub> Ivent, 110 °C Aryl $Aryl^{1} C R^{5} R^{4}$ Time = t <sup>2</sup> $3a-ak$ $N O R^{5} R^{4}$ [MIm-CO <sub>2</sub> H]BF <sub>4</sub>			©N O BF₄ Im-CO₂HJBF₄			
	NNH <sub>2</sub>			O O OEt	O O OMe		MeO	
	4a	4b	5a 5b	5c	5d	5e	5f	
Entry	Arylhydrazine	$\beta$ -Ketone ester	Solvent	t1/h	Alkene	t²/h	Product	Yield (%)
1 <sup>b</sup>	4a	5a	solvent-free	_	2a		messy mixture	_
2 <sup>b</sup>	4a	5a	glycerol		2a		messy mixture	
3	4a	5a	glycerol	4	2a	10	3e	78
4 <sup>c</sup>	4a	5a	glycerol	6	2a	10	3e	59
5 <sup>b</sup>	4a	5a	glycerol	4	2a	10	3e	70
6	4a	5b	glycerol	4	2a	10	3a	67
7	4a	5c	glycerol	4	2a	10	3d	69
8	4a	5d	glycerol	4	2a	10	3b	69
9	4a	5e	glycerol	4	2a	10	3c	73
10	4a	5f	glycerol	4	2a	10	3f	75
11	4a	5a	glycerol	4	2b	10	3ah	48
12	4a	5a	glycerol	4	2c	10	3ai	59
13	4a	5a	glycerol	4	2h	10	3aj	47
14	4a	5a	glycerol	4	2g	10	3ak	75
15	4b	5a	[MIm-CO <sub>2</sub> H]BF <sub>4</sub>	4	2a	10	3u	48
16	4b	5e	[MIm-CO <sub>2</sub> H]BF <sub>4</sub>	4	2a	10	3t	53
17	4b	5f	[MIm-CO <sub>2</sub> H]BF <sub>4</sub>	4	2a	10	3v	56
$18^{e}$	4a	5a	glycerol	4	2a	10	3e	75
19 <sup>e</sup>	4b	5f	[MIm-CO <sub>2</sub> H]BF <sub>4</sub>	4	2 <i>a</i>	10	3v	55

**Table 4** Two-step sequential reactions of arylhydrazines, HCHO, β-ketone esters and styrenes<sup>4</sup>

<sup>*a*</sup> Arylhydrazine: 0.5 mmol,  $\beta$ -ketone ester: 0.55 mmol, glycerol: 2.5 g, paraformaldehyde: 0.75 mmol, alkene: 1.0 mmol. <sup>*b*</sup> All the four components of the reaction were added in the beginning of the reaction. <sup>*c*</sup> 85 °C. <sup>*d*</sup> 1.5 g glycerol was used. <sup>*c*</sup> Reused in the second run.

used in this reaction. And in order to improve the reaction yield, a carboxylic acid group-functionalized ionic liquid, [MIm- $CO_2H$ ]BF<sub>4</sub>, was used instead of glycerol solvent. As shown in Table 4, the desired products were obtained in moderate yields (entries 15–17). It should be noted that both glycerol and the ionic liquid are immiscible with non-polar organic solvents. Therefore, the products could be easily isolated by extraction. And the recycled glycerol and [MIm- $CO_2H$ ]BF<sub>4</sub> could be reused in the next run after a simple treatment under vacuum (entries 18 and 19). This property makes the one-pot stepwised reaction not only efficient to the synthesis of target heterocyclic compounds but also very attractive from the viewpoint of green chemistry.

Good reactivity of 1,3-disubstituted 5-pyrazolone prompts us to further explore MCRs by using this unique heterocyclic compound and formaldehyde as substrates. The next reaction we developed is a one-pot three-component reaction of indoles, 1,3disubstituted 5-pyrazolones and paraformaldehyde. As shown in Scheme 3, 1,3-diaryl-5-pyrazolones could easily react with 1alkyl-2-phenylindoles and formaldehyde in glycerol to form 1,3diaryl-2-[(1-alkyl-2-phenylindol-3-yl)methyl]-5-pyrazolone deravitives, 7a, 7b and 7c, in moderate yields. Literature information about the product showed that skeleton of the products has been proven to be active for sedation of mice.<sup>21</sup> Only a few methods are available for the synthesis of this kind of molecule.<sup>22</sup> However, either chemicals are not available or toxic reagents were used in the reported methods.23 Our MCR thus offers an effective and environmentally benign way for the synthesis of these useful pyrazole derivatives. The MCR might proceed through a tandem

Knoevenagel/Michael reaction pathway. This hypothesis can be supported by the fact that Michael reaction of 2-phenylindole and  $\alpha$ , $\beta$ -unsaturated carbonyl compounds could be performed in glycerol under catalyst-free conditions.<sup>19a</sup> Importantly, this three-component reaction can also be extended to a two-step sequential reaction in glycerol using phenylhydrazine (*4a*) and  $\beta$ -ketone ester, *5f*, as substrates (Scheme 3). This not only maximizes the synthetic efficiency but also offers a new and distinct example to promoting glycerol as reaction media.

## Conclusion

Combination of 1,3-disubstituted 5-pyrazolones and formaldehyde was proved to be a useful platform for organic synthesis. Many substrates, such as styrenes, vinylferrocene and indoles could react readily with 1,3-disubstituted 5-pyrazolones and formaldehyde in the absence of any catalyst to afford the corresponding three-component adducts in moderate to excellent yields. Particularly, these MCRs are proved to be combinable with synthesis of 1,3-disubstituted 5-pyrazolones from phenylhydrazines and  $\beta$ -ketone esters in glycerol or a carboxylic acid group-functionalized ionic liquid, [MIm-CO<sub>2</sub>H]BF<sub>4</sub>. Therefore, some one-pot stepwise sequential reactions of phenylhydrazines, β-ketone esters, formaldehyde and styrenes or indoles were developed for the first time. These sequential MCRs not only open a straightforward way to synthesize the target compounds, but also maximize the synthetic efficiency significantly. Because these MCRs were conducted either under solvent-free



Scheme 3 Multicomponent reactions of 1-alkyl-2-phenylindoles, paraformaldehdye and 1,3-diaryl 5-pyrazolones and their variation with more fundamental substrates (for the three-component reaction, ratio of 6a/7a/HCHO = 1.0/1.0/1.0; for the two-step sequential reaction, ratio of 4a/5f/6a/HCHO = 1.0/1.1/1.0/1.5)

conditions or in green media, including glycerol and ionic liquid, the reaction systems possess many properties of green chemistry, such as simple work-up procedure, recyclable solvent and minimization of waste. In view of the fact that pyrazole derivatives have been widely used in pharmaceutical industry, our method might be useful for synthesis of biologically active compounds, and the investigation is underway in our group.

## **Experimental section**

All reactions were conducted in a 10 mL V-type flask equipped with triangle magnetic stirring. In a typical reaction, 1-phenyl-3-methyl-5-pyrazolone (1a, 87.0 mg, 0.50 mmol) was mixed with  $\alpha$ -methylstyrene (2a, 118.0 mg, 1.00 mmol) and paraformaldehyde (45.0 mg, 0.75 mmol) under air. The mixture was stirred for 5.0 h at 110 °C. After reaction, the mixture was mixed with ethyl acetate (3 mL), and then subjected to isolation with preparative TLC using a mixed solution of ethyl acetate and petroleum ether as eluting solvent (normally, the ratio of ethyl acetate/petroleum ether is 1/10). Product: 1,4,5,6-tetrahydro-3,6-dimethyl-1,6diphenyl-pyrano[2,3-c]pyrazole (3a): pale yellow liquid, yield = 85%, <sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.56 (s, 3H), 1.86-1.95 (m, 1H), 2.02 (s, 3H), 2.03-2.11 (s, 1H), 2.17 (dt,  $J_a = 5.2$  Hz,  $J_b = 13.6$  Hz, 1H), 2.30 (dt,  $J_a = 4.8$  Hz,  $J_b = 14.4$  Hz, 1H), 7.03-7.12 (m, 1H), 7.15 (t, J = 7.2 Hz, 2H), 7.20 (d, J = 7.6 Hz, 2H), 7.29  $(t, J = 7.6 \text{ Hz}, 2\text{H}), 7.80 (d, J = 8.0 \text{ Hz}, 2\text{H}); {}^{13}\text{C NMR}: 12.8,$ 15.7, 28.8, 33.5, 83.8, 95.8, 119.8, 124.6, 125.0, 127.3, 128.6, 129.1, 139.3, 144.2, 146.5, 150.1; IR (cm<sup>-1</sup>): 3061, 2978, 2925, 2855, 1605, 1507, 1445, 1393, 1375, 1328, 1266, 1158, 1120, 1102, 1070, 1029, 1004, 900, 866, 758, 697, 658; HRMS (ESI): calcd for  $C_{20}H_{20}N_2O$ , [M + H<sup>+</sup>]: 305.3936; found: 305.3987. Synthesis of other 1,3-disubstituted 5-pyrazolones, procedures for the other reactions and physicochemical data of the products are available in ESI.

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