DOI: 10.1002/adsc.201200191

Diastereoselective Synthesis of Pyrazolines using a Bifunctional Brønsted Acidic Ionic Liquid under Solvent-Free Conditions

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Received: March 8, 2012; Revised: July 3, 2012; Published online: November 4, 2012

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200191.

Abstract: An efficient protocol for the excellent diastereoselective synthesis of pyrazolines *via* a three-component reaction of aldehydes, hydrazines and dimethyl acetylenedicarboxylate (DMAD) in the presence of a bifunctional Brønsted acidic ionic liquid as a reusable catalyst under solvent-free conditions is reported. Easy work-up, short reaction times, high yields of the products and an environmentally benign procedure avoiding toxic organic solvents are other significant features of this method.

Keywords: aldehydes; diastereoselectivity; heterocycles; ionic liquids; multicomponent reactions

Introduction

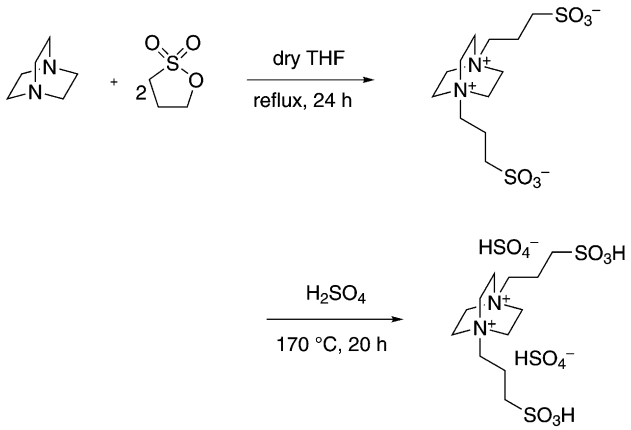
Among nitrogen-containing heterocyclic compounds, pyrazolines have attracted a great interest due to their diverse biological and pharmacological activities.[1] A great number of compounds containing pyrazoline moieties are reported to exhibit a broad range of anti-microbial,[2] anti-inflammatory,[3] anti-depressant,[4] anti-diabetic,[5] anti-cancer[6] and anti-amoebic[7] properties. These heterocyclic compounds are also utilized as insecticides, fungicides[8] and as fluorescent dyes.[9] Consequently, the synthesis of pyrazolines is an important and useful task in organic chemistry.[10]

Several methods including [3+2]cycloaddition of active 1,3-dipoles such as diazoalkanes to olefins,[11] photoactivated 1,3-dipolar cycloaddition of diaryltetrazoles to electron-deficient alkenes,[12] addition of nitrones to 1,3-enynes[13], zirconium-catalyzed enantioselective [3+2]cycloaddition of hydrazones to olefins,[14] BF_3-catalyzed intramolecular [3+2]cycloaddition of olefinic phenylhydrazones,[15] cycloaddition of nitrilimine to alkenes,[16] reaction of substituted phenylhydrazines with 3-butynol catalyzed by zinc triflate,[17] chiral phosphoric acid-catalyzed electrocyclization of α,β-unsaturated arylhydrazones,[18] and *Cinchona* alkaloid-catalyzed enantioselective amination of α,β-unsaturated ketones[19] have been reported for the synthesis of pyrazolines. Most of the reported methods, in spite of their potential utility, require expensive chiral catalysts or substrates, long reaction times, toxic organic solvents and high amounts of catalysts to provide stereoselectivity. Further, unavailability of some starting materials, use of potentially toxic dipoles and their difficult handling limit the utility of some of these methods, especially in large-scale operation, leading to serious economical and safety problems. Thus, the design of a simple, efficient, inexpensive and green approach for the synthesis of pyrazolines with excellent diastereoselectivity is highly desirable.

In recent years, the utility of ionic liquids as green media and catalyst in chemical and biochemical transformations has received much attention due to their favorable properties such as high polarity and ionic conductivity, high thermal and chemical stability, ease of recovery and reuse, non-flammability and low vapor pressure.[20] These properties make the ionic liquids as attractive alternatives to environmentally unfavorable toxic organic solvents. It is also noteworthy that the physical properties of ionic liquids such as melting point, solubility, viscosity, density and hydrophobicity can be adapted by changing their cations and/or anions, enabling the design of a useful and convenient ionic liquid for a particular purpose. Among the ionic liquids, sulfonic acid ($-SO_3H$)-functionalized Brønsted acidic ionic liquids have attracted extensive interest as they are non-volatile, non-corrosive, air and water stable, and provide easy recovery and reuse.[21] These Brønsted acidic ionic liquids

which offer the advantages of both liquid acids and solid acids, have emerged as useful alternatives to traditional mineral liquid acids such as sulfuric acid and hydrochloric acid in chemical reactions. Because of their unique properties, several organic transformations such as esterification reactions,[22] Beckmann rearrangement,[23] Ritter reaction,[24] biodiesel synthesis,[25] Pechmann condensation[26] and Biginelli reaction[27] have been reported to proceed efficiently in the presence of these Brønsted acidic ionic liquid catalysts.

As a part of our ongoing research on the development of efficient protocols for the synthesis of heterocyclic compounds,[28] herein, we report a novel, facile and environmentally benign one-pot three-component synthesis of pyrazolines from arylaldehydes, hydrazines and DMAD with excellent diastereoselectivity using a bifunctional Brønsted acidic ionic liquid as a safe, inexpensive and reusable catalyst under solvent-free conditions (Scheme 1). To the best of our knowledge, this is the first report on the use of an ionic liquid as catalyst for the one-pot three-component synthesis of pyrazolines under solvent-free conditions.

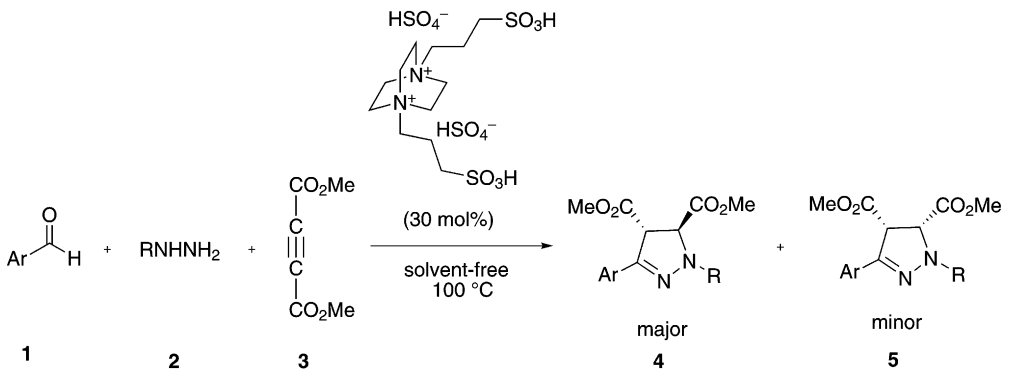


Scheme 2. Synthesis of the bifunctional Brønsted acidic ionic liquid.

Results and Discussion

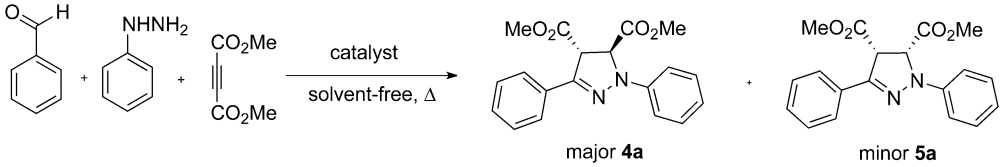
The bifunctional Brønsted acidic ionic liquid was easily prepared in two steps. First, 1,4-diazabicyclo-[2.2.2]octane (DABCO) was reacted with 1,3-propanesultone in THF to produce a white solid zwitterion. Then, treatment of this zwitterion with sulfuric acid afforded the desired ionic liquid in quantitative yield (Scheme 2).

In order to optimize the conditions, the reaction of benzaldehyde, phenylhydrazine and DMAD was selected as a model. A control experiment demonstrated that the reaction did not proceed in the absence of catalyst (Table 1, entry 1). Then, the model reaction was performed in the presence of Lewis acids such as $InCl_3$, $ZnCl_2$, $ZrOCl_2{\cdot}8H_2O$ and $Bi(TFA)_3$. Under these conditions, the desired product was obtained in low yield and poor diastereoselectivity (Table 1, entries 2–5). Performing the reaction in the presence of stronger Lewis acids such as $Bi(OTf)_3$ and $Zn(OTf)_2$, and *p*-TSA as Brønsted acid afforded the desired product in high yield but still with insignificant diastereoselectivity (Table 1, entries 6–8). To improve both the yield and diastereoselectivity, we examined this reaction using different ionic liquids. The reaction catalyzed by ionic liquids such as $[Hmim]HSO_4$, $[Bmim]BF_4$, $[Bmim]PF_6$ or $[mim(CH_2)_3SO_3H]HSO_4$ provided the corresponding product in low yield and excellent diastereoselectivity (Table 1, entries 9–12). It is noteworthy that, even in the presence of 60 mol% of monofunctional ionic liquid, $[mim(CH_2)_3SO_3H]HSO_4$ (equal to 30 mol% of bifunctional Brønsted acidic ionic liquid), the corresponding product was obtained in 70% yield (Table 1, entry 13). But, interestingly, the bifunctional Brønsted acidic ionic liquid revealed exceptional catalytic activity, affording the desired product in excellent yield and excellent diastereoselectivity (Table 1, entry 14). Encouraged by this result, we then focused on optimiz-



Scheme 1. Diastereoselective synthesis of pyrazolines.

Table 1. Optimization of the reaction conditions for diastereoselective synthesis of pyrazoline **4a**.[a]



Entry	Catalyst	Time [h]	Yield [%][b]	*dr* (**4a:5a**)[c]
1	no catalyst	10	–	–
2	$InCl_3$	1	52	56:44
3	$ZnCl_2$	1	44	57:43
4	$ZrOCl_2{\cdot}8H_2O$	1	46	60:40
5	$Bi(TFA)_3$	1	42	57:43
6	$Bi(OTf)_3$	1	88	55:45
7	$Zn(OTf)_2$	1	87	60:40
8	p-TSA	1	73	55:45
9	$[Hmim]HSO_4$	1	30	97:3
10	$[Bmim]BF_4$	1	32	96:4
11	$[Bmim]PF_6$	1	28	97:3
12	$[mim(CH_2)_3SO_3H]\ HSO_4$	1	47	97:3
13[d]	$[mim(CH_2)_3SO_3H]\ HSO_4$	1	70	97:3
14	present catalyst	1	90	98:2
15[e]	present catalyst	1	82	98:2
16[f]	present catalyst	1	90	98:2
17[g]	present catalyst	1	72	98:2
18[h]	present catalyst	1	90	98:2
19[i]	present catalyst	1	83	98:2
20[j]	present catalyst	1	90	98:2

[a] Benzaldehyde (1 mmol), phenylhydrazine (1 mmol) and DMAD (1.2 mmol), catalyst (30 mol%), under solvent-free conditions, at 100 °C.
[b] Isolated yield.
[c] The *dr* (*trans:cis*) was determined by ^1H NMR analysis of the crude reaction mixture.
[d] Reaction was performed in the presence of 60 mol% of catalyst.
[e] Reaction was performed in the presence of 20 mol% of catalyst.
[f] Reaction was performed in the presence of 40 mol% of catalyst.
[g] Reaction was performed at 80 °C.
[h] Reaction was performed at 110 °C.
[i] Benzaldehyde (1 mmol), phenylhydrazine (1 mmol) and DMAD (1 mmol), catalyst (30 mol%), under solvent-free conditions, at 100 °C.
[j] Benzaldehyde (1 mmol), phenylhydrazine (1 mmol) and DMAD (1.4 mmol), catalyst (30 mol%), under solvent-free conditions, at 100 °C.

ing the reaction conditions using this novel bifunctional Brønsted acidic ionic liquid catalyst.

To optimize the catalyst loading, the model reaction was performed in the presence of different bifunctional Brønsted acidic ionic liquid percentages (20 mol%, 30 mol%, and 40 mol%, Table 1, entries 14–16); 30 mol% loading provided the maximum yield. Higher loading of the catalyst did not affect the yield or the reaction time, whereas, reducing the catalyst loading decreased the product yield. In examining the reaction temperature in the range of 80–110 °C (Table 1, entries 14, 17, 18), 100 °C was found to be the optimum temperature. Finally, the influence of the molar ratio of the starting materials was evaluated (Table 1, entries 14, 19, 20); the best result was achieved employing 1.2 mmol of DMAD per mmol of benzaldehyde and phenylhydrazine. Consequently, the optimum conditions were found to be a 1:1:1.2:0.3 molar ratio of benzaldehyde, phenylhydrazine, DMAD and catalyst at 100 °C under solvent-free conditions.

The generality and synthetic scope of this novel catalytic method for the preparation of pyrazolines have been investigated and the results are shown in Table 2. A series of aromatic aldehydes and arylhydrazines with electron-donating as well as electron-withdrawing substituents reacted smoothly with DMAD to afford the corresponding pyrazolines in high yields and excellent diastereoselectivity (Table 2, entries 1–13). It is noteworthy that in some cases, the *trans*-diastereomer was produced as the sole product (Table 2, entries 4, 5, 8–11). Also, as an acid-sensitive

Table 2. Diastereoselective synthesis of pyrazolines catalyzed by Brønsted acidic ionic liquid under solvent-free conditions.[a]

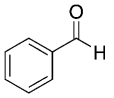
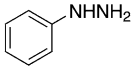
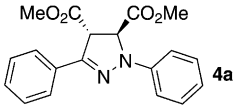
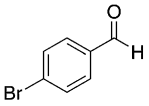
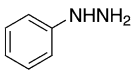
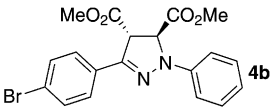
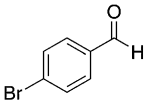
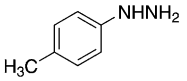
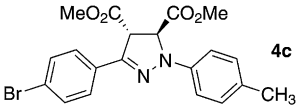
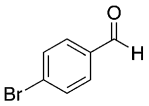
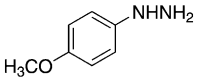
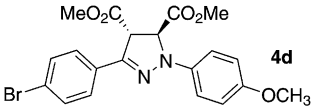
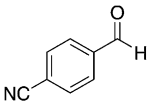
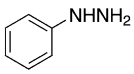
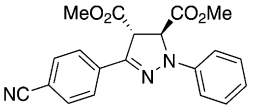
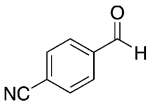
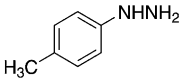
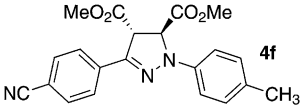
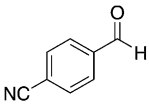
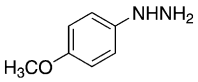
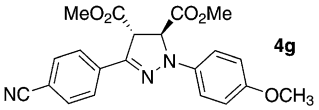
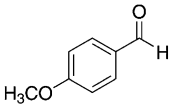
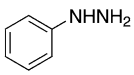
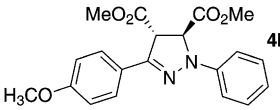
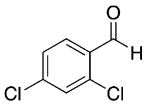
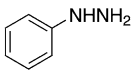
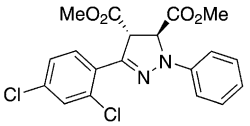
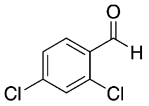
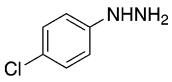
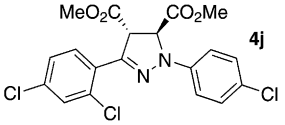
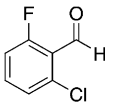
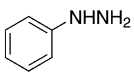
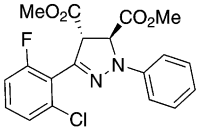
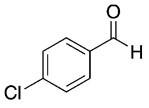
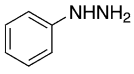
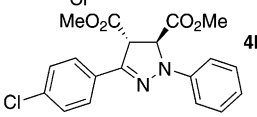
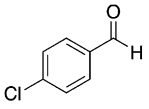
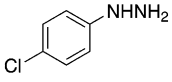
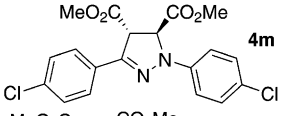
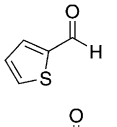
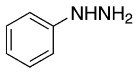
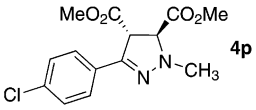
Entry	Aldehyde (**1**)	Hydrazine (**2**)	Product (**4**)	Time [min]	Yield [%][b]	*dr* (**4**:**5**)[c]
1			 **4a**	60	90	98:2
2			 **4b**	60	85	94:6
3			 **4c**	60	91	94:6
4			 **4d**	45	92	100:0
5			 **4e**	75	87	100:0
6			 **4f**	75	93	98:2
7			 **4g**	60	90	99:1
8			 **4h**	30	93	100:0
9			 **4i**	60	87	100:0
10			 **4j**	60	83	100:0
11			 **4k**	60	85	100:0
12			 **4l**	60	90	98:2
13			 **4m**	60	86	97:3
14			**4n**	60	66	98:2
15		CH_3NHNH_2	**4o**	60	90	100:0

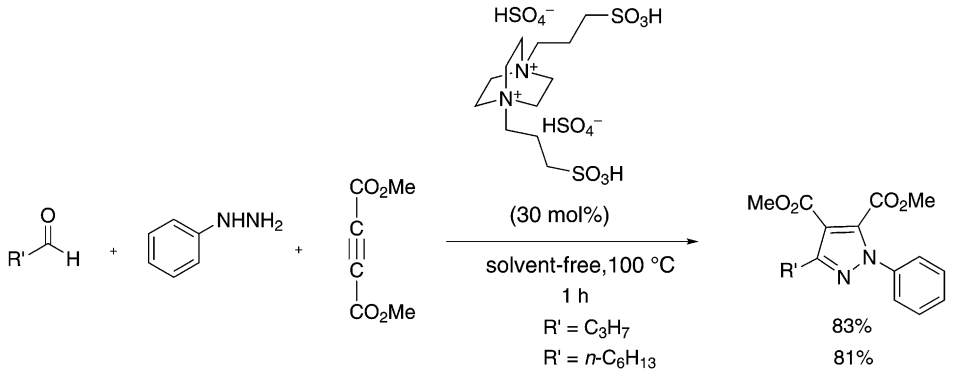
Table 2. (Continued)

Entry	Aldehyde (**1**)	Hydrazine (**2**)	Product (**4**)	Time [min]	Yield [%][b]	*dr* (**4**:**5**)[c]
16		CH_3NHNH_2	 **4p**	60	83	100:0

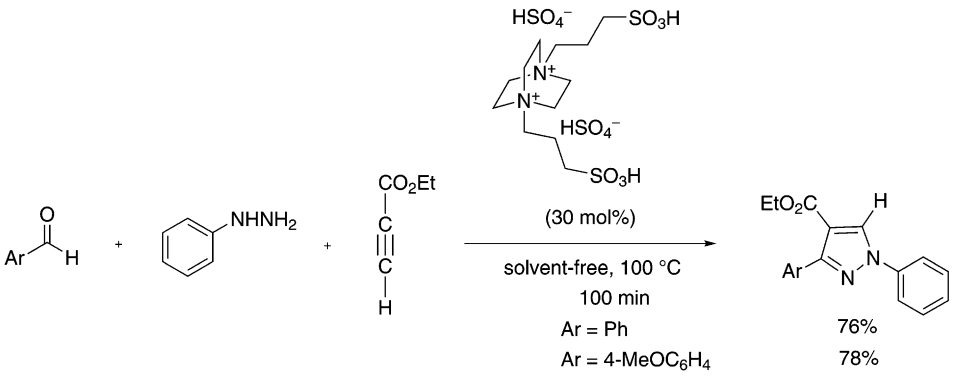
[a] Arylaldehyde (1 mmol), hydrazine (1 mmol) and DMAD (1.2 mmol), catalyst (30 mol%) under solvent-free conditions, at 100 °C.
[b] Isolated yield.
[c] The *dr* (*trans:cis*) was determined by ^{1}H NMR analysis of crude reaction mixture.

aldehyde, thiophen-2-carbaldehyde participated efficiently in this reaction to produce the desired pyrazoline in good yield and excellent diastereoselectivity (Table 2, entry 14). Under the same conditions, methylhydrazine as an alkylhydrazine took part in the reaction efficiently to give the desired pyrazoline in high yields and excellent diastereoselectivity (Table 2, entries 15 and 16). In contrast, phenylhydrazide did not give the desired product under the same reaction conditions. This may be attributed to the reduced reactivity of the hydrazide as a result of the strong electron-withdrawing effect of the acyl group in the hydrazide. It is worth noting that, when aliphatic aldehydes such as butanal and heptanal were used in place of aromatic aldehydes in these reactions, the corresponding pyrazoles were obtained in high yields (Scheme 3). Finally, two of these reactions were investigated with ethyl propiolate (an alkyne containing only one activating group) instead of DMAD. Under these conditions, the corresponding pyrazoles were also produced in high yields (Scheme 4). Therefore, the present method can be used as an efficient method for the diastereoselective preparation of pyrazolines from aromatic aldehydes, aryl- and/or alkylamines, and DMAD.

In order to check whether the observed final diastereoselectivity is due to the epimerization of the *cis* product or not, a control experiment was carried out in the presence of the bifunctional Brønsted acidic ionic liquid catalyst. For instance, the isolated mixture



Scheme 3. Synthesis of pyrazoles with aliphatic aldehydes.



Scheme 4. Synthesis of pyrazoles with ethyl propiolate.

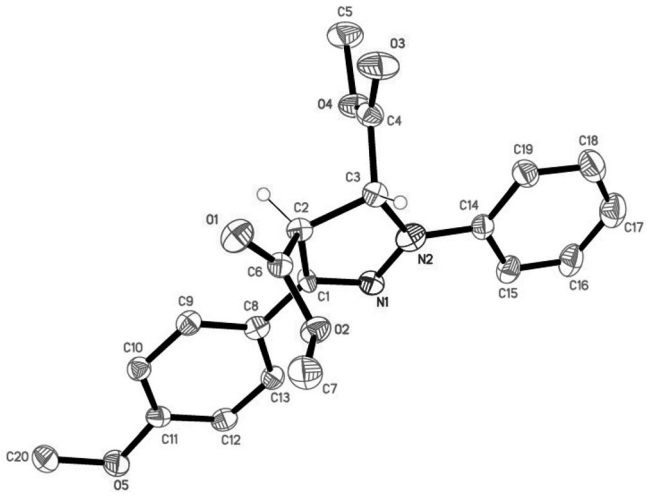


Figure 1. Crystal structure of compound **4h**.

of *cis*- and *trans*-product (from entry 2 of Table 1) was resubjected to the reaction conditions using the present catalyst; no change in diastereomeric ratio of the product was observed after 1 h, indicating that epimerization of the product did not occur during the reaction course.

The structures of new compounds were ascertained by elemental analysis and spectral (IR, ^{1}H NMR, ^{13}C NMR, and MS) data. The known compounds were identified by comparison of their mp, and IR and ^{1}H NMR spectra with authentic data.

The diastereoselectivity of the reaction and configuration of the stereogenic centers of the product **4h** were established by single crystal X-ray diffraction analysis (Figure 1).[29]

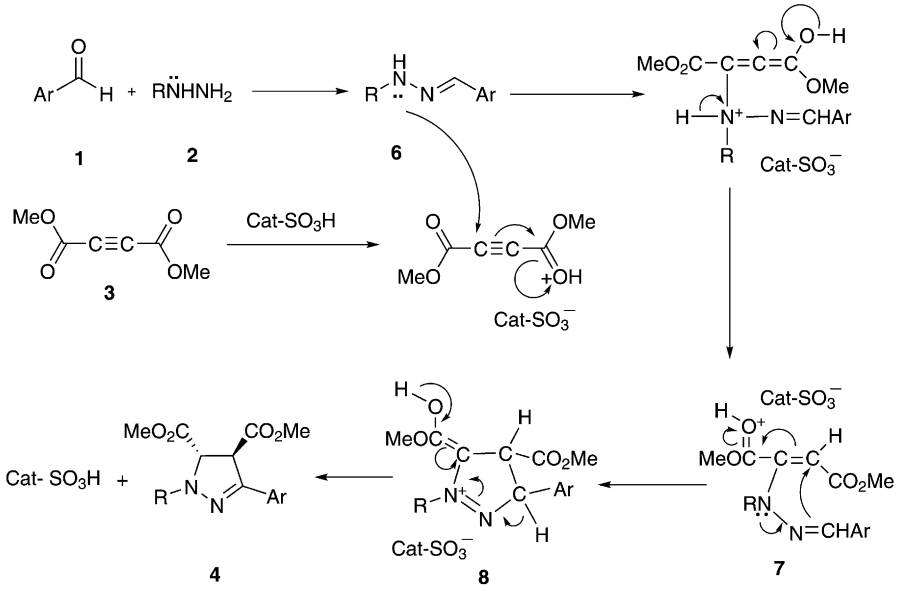
A plausible mechanism for the diastereoselective formation of pyrazoline is proposed in Scheme 5. Firstly, arylhydrazone **6** is formed by condensation of arylaldehyde **1** with hydrazine **2**. Nucleophilic attack of hydrazone to the triple bond of DMAD **3** in the presence of the catalyst provides **7** which upon cyclization gives **8**. Double bond migration in **8** affords the pyrazoline **4** as the major diastereomer and releases the catalyst for the next catalytic cycle.

Finally, the possibility for recovery and reuse of the ionic liquid catalyst was examined in the reaction of benzaldehyde, phenylhydrazine and DMAD under solvent-free conditions at 100 °C. After completion of the reaction, the mixture was cooled to room temperature and water was added. The product was separated by simple filtration and washed with water. Then water was evaporated, the catalyst was dried at 80 °C under reduced pressure for 2 h and reused for the subsequent reaction. The data shown in Table 3 illustrate that the ionic liquid catalyst can be reused at

Table 3. Reusability of catalyst for synthesis of **4a**.[a]

Run	Cycle	Yield [%][b]	*dr* (**4a:5a**)[c]
1	0	90	98:2
2	1	90	98:2
3	2	88	97:3
4	3	87	96:4
5	4	85	95:5

[a] Benzaldehyde (1 mmol), phenylhydrazine (1 mmol) and DMAD (1.2 mmol), catalyst (30 mol%) at 100 °C under solvent-free conditions.
[b] Isolated yield.
[c] The *dr* (*trans:cis*) was determined by ^{1}H NMR analysis of crude reaction product.



Scheme 5. A plausible mechanism.

least four times without significant decreases in the reaction yield and diastereoselectivity.

Conclusions

In conclusion, the present work describes a novel and efficient protocol for the preparation of pyrazolines through a three-component condensation reaction in the presence of catalytic amounts of bifunctional Brønsted acidic ionic liquid under solvent-free conditions. The non-hazardous experimental conditions, reusable catalyst, short reaction times, high yields and excellent diastereoselectivity are the remarkable features of this procedure. Thus, it provides a better and more convenient alternative to the existing methodologies for the synthesis of pyrazoline derivatives.

Experimental Section

The chemicals used in this work were purchased from Fluka and Merck chemical companies. The progress of the reaction was monitored by TLC using 0.25 μm pre-coated silica gel plates. Melting points were determined using Stuart Scientific SMP2 apparatus. ^{1}H NMR (400 and 500 MHz) and ^{13}C NMR (100 and 125 MHz) spectra were recorded on Bruker Avance 400 and 500 spectrometers, respectively. FT-IR spectra were recorded on a Nicolet-Impact 400D instrument in the range of 400–4000 cm^{-1}. Mass spectra were recorded on a Platform II spectrometer from Micromass; EI mode at 70 eV. Elemental analysis was done on a LECO, CHNS-932 analyzer.

Synthesis of Bifunctional Brønsted Acidic Ionic Liquid Catalyst

A solution of 1,4-diazabicyclo[2.2.2]octane (DABCO) (10 mmol) and 1,3-propanesultone (20 mmol) in dry THF was refluxed for 24 h to afford a white solid zwitterion. The resulting solid was washed with Et_2O in order to remove the unreacted starting materials and dried under vacuum. Then, sulfuric acid (20 mmol) was added to the solid zwitterion and the resulting mixture was stirred for 20 h at 170 °C during which time the solid zwitterion was liquefied and resulted in the bifunctional Brønsted acidic ionic liquid; yield: quantitative; mp 85 °C. IR (KBr): ν_{max} = 2924, 1471, 1398, 1222, 1051, 853, 590 cm^{-1}; ^{1}H NMR (400 MHz, D_2O): δ = 4.02 (s, 6H), 3.72 (t, J = 8.0 Hz, 2H), 2.96 (t, J = 8.0 Hz, 2H), 2.28–2.21 (m, 2H); ^{13}C NMR (100 MHz, D_2O): δ = 63.2, 51.1, 46.8, 17.8; anal. calcd. for $C_{12}H_{28}N_2O_{14}S_4$: C 26.08, H 5.11, N 5.07, S 23.21; found: C 25.92, H 5.15, N 5.14, S, 23.04.

Diastereoselective Synthesis of Pyrazolines; General Procedure

First, a mixture of arylaldehyde **1** (1 mmol) and hydrazine **2** (1 mmol) was stirred for 20 min. Then, DMAD **3** (1.2 mmol) and catalyst (0.3 mmol) were added and the resulting mixture was stirred at 100 °C under solvent-free conditions for the appropriate time according to Table 2. The progress of the reaction was monitored by TLC (eluent: *n*-hexane/ethyl acetate, 5:1). After completion of the reaction, the mixture was cooled to room temperature and water was added. The product was separated by simple filtration and washed with water. The resulting crude product was purified by recrystallization from EtOH to afford the pure product. In the case of liquid products, the purification was performed by column chromatography on silica gel.

Dimethyl 4,5-dihydro-1,3-diphenyl-1*H*-pyrazole-4,5-dicarboxylate (4a):[30] mp 150–152 °C; IR (KBr): ν_{max} = 3056, 2949, 1742, 1596, 1275, 1146, 1017, 740, 687 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.5, 2H), 7.4 (t, J = 7.3 Hz, 2H), 7.36 (d, J = 7.0 Hz, 1H), 7.31 (t, J = 7.5 Hz, 2H), 7.16 (d, J = 8.5 Hz, 2H), 6.92 (t, J = 7.5 Hz, 1H), 5.19 (d, J = 5.0 Hz, 1H), 4.58 (d, J = 5.0 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 169.3, 143.7, 143.6, 131.1, 129.2, 129.0, 128.6, 126.3, 120.3, 113.3, 65.9, 55.7, 53.2, 53.1.

Dimethyl 3-(4-bromophenyl)-4,5-dihydro-1-phenyl-1*H*-pyrazole-4,5-dicarboxylate (4b):[31] mp 189–190 °C; IR (KBr): ν_{max} = 3092, 2951, 1739, 1597, 1502, 1207, 1145, 747, 690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 7.31 (t, J = 8.0 Hz, 2H), 7.14 (d, J = 7.5 Hz, 2H), 6.93 (t, J = 7.3 Hz, 1H), 5.21 (d, J = 5.0 Hz, 1H), 4.54 (d, J = 4.5 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H).

Dimethyl 3-(4-bromophenyl)-4,5-dihydro-1-*p*-tolyl-1*H*-pyrazole-4,5-dicarboxylate (4c): mp 151–153 °C; IR (KBr): ν_{max} = 3004, 2949, 1742, 1615, 1516, 1275, 1149, 1018, 823, 639 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 8.5 Hz, 2H), 7.05 (d, J = 8.5 Hz, 2H), 5.19 (d, J = 4.5 Hz, 1H), 4.53 (d, J = 4.5 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 2. 30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.0, 169.1, 141.9, 141.3, 138.8, 131.7, 129.7, 128.4, 127.7, 122.9, 113.5, 66.1, 55.4, 53.2, 53.1, 20.6; MS: *m/z* (%) = 432 (M^+ + 2, 33.8), 430 (M^+, 54.0), 371 (35.0), 327 (18.0), 248 (23.5), 130 (48.7), 91 (100.0), 65 (82.0); anal. calcd. for $C_{20}H_{19}BrN_2O_4$: C 55.70, H 4.44, N, 6.50; found: C 55.64, H 4.49, N 6.48.

Dimethyl 3-(4-bromophenyl)-4,5-dihydro-1-(4-methoxyphenyl)-1*H*-pyrazole-4,5-dicarboxylate (4d): mp 158–160 °C; IR (KBr): ν_{max} = 3024, 2998, 1741, 1511, 1236, 1147, 1013, 821, 786 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.31 (d, J = 4.4 Hz, 1H), 4.56 (d, J = 4.4 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 169.2, 154.4, 141.9, 137.9, 131.7, 130.2, 127.6, 122.8, 115.1, 114.7, 66.7, 55.6, 55.5, 53.2, 53.1; MS: *m/z* (%) = 447 (M^+, 8.1), 415 (16.0), 352 (6.8), 183 (20.0), 123 (39.2), 56 (100.0); anal. calcd. for $C_{20}H_{19}BrN_2O_5$: C 53.71, H 4.28, N 6.26; found: C 53.63, H 4.30, N 6.27.

Dimethyl 3-(4-cyanophenyl)-4,5-dihydro-1-phenyl-1*H*-pyrazole-4,5-dicarboxylate (4e): mp 200–201 °C; IR (KBr): ν_{max} = 3043, 2952, 2224, 1746, 1596, 1499, 1214, 1151, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.34 (t, J = 7.8 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.98 (t, J = 7.2 Hz, 1H), 5.32 (d, J = 4.4 Hz, 1H), 4.58 (d, J = 4.4 Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 168.6,

142.7, 141.1, 135.4, 132.3, 129.3, 126.5, 121.2, 118.8, 113.5, 111.6, 65.7, 54.8, 53.5, 53.3; MS: *m/z* (%) = 363 (M^+, 8.9), 304 (10.7), 260 (27.9), 244 (15.3), 143 (9.3), 116 (10.6), 92 (2.5), 77 (100.0); anal. calcd. for $C_{20}H_{17}N_3O_4$: C 66.11, H 4.72, N 11.56; found: C 66.05, H 4.80, N 11.55.

Dimethyl 3-(4-cyanophenyl)-4,5-dihydro-1-*p*-tolyl-1H-pyrazole-4,5-dicarboxylate (4f): mp 186–188 °C; IR (KBr): ν_{max} = 3035, 2955, 2225, 1742, 1516, 1278, 1150, 1014, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 9.0 Hz, 2H), 5.27 (d, *J* = 4.5 Hz, 1H), 4.55 (d, *J* = 4.5 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.7, 168.7, 140.63, 140.57, 135.6, 132.2, 130.8, 129.9, 126.4, 118.8, 113.7, 111.5, 66.1, 54.9, 53.4, 53.2, 20.6; MS: *m/z* (%) = 377 (M^+, 17.9), 318 (15.8), 274 (43.9), 130 (12.1), 91 (31.1), 59 (100.0); anal. calcd. for $C_{21}H_{19}N_3O_4$: C 66.83, H 5.07, N 11.13; found: C 66.78, H 5.09, N 11.14.

Dimethyl 3-(4-cyanophenyl)-4,5-dihydro-1-(4-methoxyphenyl)-1*H*-pyrazole-4,5-dicarboxylate (4g): mp 184–186 °C; IR (KBr): ν_{max} = 3039, 2931, 2224, 1742, 1509, 1238, 1153, 1011, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 5.26 (d, *J* = 4.5 Hz, 1H), 4.55 (d, *J* = 5.0 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.7, 168.8, 154.8, 140.5, 137.0, 135.7, 132.2, 126.3, 118.9, 115.3, 114.8, 111. 3, 66.6, 55.7, 54.9, 53.4, 53.2; MS: *m/z* (%) = 393 (M^+, 0.9), 334 (1.2), 273 (1.0), 130 (1.9), 102 (5.0), 59 (100); anal. calcd. for $C_{21}H_{19}N_3O_5$: C 64.12, H 4.87, N 10.68; found: C 64.05, H 4.90, N 10.64.

Dimethyl 4,5-dihydro-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4,5-dicarboxylate (4h):[32] mp 151–152 °C; IR (KBr): ν_{max} = 3053, 2953, 1744, 1595, 1500, 1242, 1143, 1015, 834 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.0 Hz, 2H), 7.30 (t, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.93–6.88 (m, 3H), 5.15 (d, *J* = 5.0 Hz, 1H), 4.55 (d, *J* = 4.5 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.72 (s, 3H).

Dimethyl 3-(2,4-dichlorophenyl)-4,5-dihydro-1-phenyl-1*H*-pyrazole-4,5-dicarboxylate (4i):[33] mp 107–109 °C; IR (KBr): ν_{max} = 3004, 2951, 1742, 1595, 1500, 1384, 1141, 1013, 747, 683 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.70 (dd, ^1J = 8.5 Hz , ^2J = 1.0 Hz, 1H), 7.44 (s, 1H),7.33–7.28 (m, 3H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.95 (t, *J* = 7.0 Hz, 1H), 5.26 (d, *J* = 5.0 Hz , 1H), 5.04 (d, *J* = 5.0 Hz, 1H), 3.79 (s, 3H), 3.66 (s, 3H).

Dimethyl 1-(4-chlorophenyl)-3-(2,4-dichlorophenyl)-4,5-dihydro-1*H*-pyrazole-4,5-dicarboxylate (4j): mp 144–146 °C; IR (KBr): ν_{max} = 3056, 2955, 1739, 1495, 1281, 1144, 821, 791 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.29 (dd, ^1J = 8.5 Hz , ^2J = 2.0 Hz, 1H), 7.25 (d, *J* = 9.0 Hz, 2H), 7.07 (d, *J* = 9.0 Hz, 2H), 5.24 (d, *J* = 5.0 Hz, 1H), 5.04 (d, *J* = 5.0 Hz, 1H), 3.79 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.7, 168.4, 142.4, 142.1, 135.5, 133.2, 131.7, 130.3, 129.2, 128.9, 127.3, 125.9, 114.8, 65.2, 57.2, 53.2; MS: *m/z* (%) = 444 (M^+ + 2, 24.9), 442 (M^+, 72.7), 440 (75.8), 403 (79.4), 381 (88.7), 337 (85.1), 252 (41.3), 111 (100.0), 75 (84.0); anal. calcd. for $C_{19}H_{15}Cl_3N_2O_4$: C 51.67, H 3.42, N 6.34; found: C 51.60, H 3.46, N 6.28.

Dimethyl 3-(2-chloro-6-fluorophenyl)-4,5-dihydro-1-phenyl-1*H*-pyrazole-4,5-dicarboxylate (4k): mp 89–90 °C; IR (KBr): ν_{max} = 3059, 2953, 1752, 1599, 1502, 1241, 1210, 889, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 4H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.09–7.07 (m, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 5.35 (d, *J* = 6.0 Hz, 1H), 4.73 (d, *J* = 6.0 Hz, 1H), 3.81 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.3, 167.7, 162.5, 160.5, 143.8, 136.4, 130.7 (d, $J_{C,F}$ = 9.37 Hz), 129.2, 125.72, 125.70, 120.9, 114.2 (d, $J_{C,F}$ = 22.13 Hz), 113.7, 64.5, 58.2, 53.1; MS: *m/z* (%) = 392 (M^+ + 2, 73.9), 390 (M^+, 89.5), 331 (97.7), 287 (93.2), 272 (69.5), 237 (71.5), 143 (58.2), 117 (90.4), 104 (81.5), 91 (86.8), 77 (100.0); anal. calcd. for $C_{19}H_{16}ClFN_2O_4$: C 58.39, H 4.13, N 7.17; found: C 58.33, H 4.20, N 7.19.

Dimethyl 3-(4-chlorophenyl)-4,5-dihydro-1-phenyl-1*H*-pyrazole-4,5-dicarboxylate (4l): mp 168–169 °C; IR (KBr): ν_{max} = 3095, 2952, 1740, 1602, 1501, 1269, 1209, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.33 (dd, ^1J = 8.2 Hz , ^2J = 7.2 Hz, 2H), 7.16 (dd, ^1J = 8.8 Hz , ^2J = 1.2 Hz, 2H), 6.95 (t, *J* = 7.4 Hz, 1H), 5.24 (d, *J* = 4.4 Hz, 1H), 4.56 (d, *J* = 4.4 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 168.9, 143.3, 142.3, 134.8, 129.6, 129.3, 128.8, 127.5, 120.5, 113.3, 65.7, 55.4, 53.3, 53.1; MS: *m/z* (%) = 376 (M^+ + 4, 2.7), 374 (M^+ + 2, 80.2), 372 (M^+, 100.0), 313 (99.1), 254 (83.8), 218 (48.2), 131 (40.5), 117 (76.1), 104 (86.0), 77 (98.7), 59 (93.7); anal. calcd. for $C_{19}H_{17}ClN_2O_4$: C 61.21, H 4.60, N 7.51; found: C 61.19, H 4.66, N 7.45.

Dimethyl 1,3-bis(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-4,5-dicarboxylate (4m): mp 187–190 °C; IR (KBr): ν_{max} = 3022, 2951, 1742, 1493, 1277, 1147, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 9.0 Hz, 2H), 7.08 (d, *J* = 9.0 Hz, 2H), 5.19 (d, *J* = 4.5 Hz, 1H), 4.56 (d, *J* = 4.5 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6, 168.8, 143.1, 142.1, 135.1, 129.4, 129.2, 128.9, 127.6, 125.5, 114.6, 65.7, 55.5, 53.3, 53.2; MS: *m/z* (%) = 408 (M^+ + 2, 2.4), 406 (M^+, 4.3), 287 (2.9), 149 (13.8), 111 (35.8), 57 (100.0); anal. calcd. for $C_{19}H_{16}Cl_2N_2O_4$: C 56.04, H 3.96, N 6.88; found: C 55.92, H 4.03, N 6.90.

Dimethyl 4,5-dihydro-3-(thiophen-2-yl)-1-*p*-tolyl-1*H*-pyrazole-4,5-dicarboxylate (4n): oil; IR (neat): ν_{max} = 3105, 2951, 1740, 1515, 1233, 1013, 811, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.31 (dd, ^1J = 5.0 Hz , ^2J = 1.0 Hz, 1H), 7.3 (d, *J* = 1.0 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 2H), 7.03–7.01 (m, 3H), 5.16 (d, *J* = 5.0 Hz, 1H), 4.50 (d, *J* = 5.0 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 168.9, 141.5, 138.9, 135.0, 129.7, 127.4, 127.0, 126.7, 123.2, 113.5, 66.2, 56.5, 53.2, 53.1, 20.6; MS: *m/z* (%) = 360 (M^+ + 2, 7.3), 358 (M^+, 100.0), 325 (56.3), 299 (50.9), 255 (49.7), 130 (34.2), 91 (89.7), 57 (75.9); anal. calcd. for $C_{18}H_{18}N_2O_4S$: C 60.32, H 5.06, N 7.82, S 8.95; found: C 60.26, H 5.11, N 7.88, S 8.89.

Dimethyl 4,5-dihydro-1-methyl-3-phenyl-1*H*-pyrazole-4,5-dicarboxylate (4o): mp 65–66 °C; IR (KBr): ν_{max} = 3025, 2953, 1736, 1628, 1225, 1069, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.27 (m, 5H), 4.70 (d, *J* = 11.6 Hz, 1H), 4.53 (d, *J* = 11.2 Hz, 1H), 3.69 (s, 3H), 3.57 (s, 3H), 3.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 166.8, 138.4, 129.7, 128.8, 128.5, 126.7, 68.2, 52.6, 51.5, 44.3; MS: *m/z* (%) = 275 (M^+, 2.2), 229 (100.0), 167.0 (80.9), 149 (96.3), 127 (64.3), 105 (75.1), 77 (83.4); anal. calcd. for $C_{14}H_{16}N_2O_4$: C 60.86, H 5.84, N 10.14; found: C 60.90, H 5.88, N 10.17.

Dimethyl 3-(4-chlorophenyl)-4,5-dihydro-1-methyl-1*H*-pyrazole-4,5-dicarboxylate (4p): mp 87–89 °C; IR (KBr): ν_{max} = 3071, 2954, 1734, 1693, 1438, 1225, 1090, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 4.74 (d, J = 11.6 Hz, 1H), 4.57 (d, J = 11.2 Hz, 1H), 3.78 (s, 3H), 3.66 (s, 3H), 3.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 166.7, 138.3, 130.9, 128.8, 128.6, 127.9, 68.2, 59.5, 52.7, 51.6, 44.3; MS: *m/z* (%) = 311 (M^+, 3.0), 279 (74.5), 265 (100.0), 204 (46.7), 149 (100.0), 139 (98.8), 111 (98.0), 77 (52.6); anal. calcd. for $C_{14}H_{15}ClN_2O_4$: C 54.11, H 4.87, N 9.02, found: C 54.05, H 4.88, N 9.09.

Dimethyl 1-phenyl-3-propyl-1*H*-pyrazole-4,5-dicarboxylate (Scheme 3): oil; IR (neat): ν_{max} = 3024, 2957, 1744, 1724, 1597, 1504, 1255, 1106, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.51 (m, 5H), 3.87 (s, 6H), 2.92 (t, J = 8 Hz, 2H), 1.72–1.82 (m, 2H), 1.02 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2, 155.1, 139.1, 134.3, 131.3, 129.3, 128.8, 123.8, 114.2, 53.3, 51.73, 29.5, 22.4, 14.1; MS: *m/z* (%) = 303 (M^++1, 56.9), 302 (M^+, 82.4), 271 (84.3), 255 (4.1), 183 (67.1), 158 (88.6), 111 (74.2), 77 (100.0); anal. calcd. for $C_{16}H_{18}N_2O_4$: C 63.56, H 6.00, N 9.27; found: C 63.50, H 5.97, N 9.33.

Dimethyl 3-hexyl-1-phenyl-1*H*-pyrazole-4,5-dicarboxylate (Scheme 3): oil; IR (neat): ν_{max} = 3042, 2955, 1725, 1597, 1504, 1255, 1108, 761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.49 (m, 5H), 3.85 (s, 6H), 2.91 (t, J = 7.7 Hz, 2H), 1.68–1.74 (m, 2H), 1.26–1.32 (m, 6H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.0, 154.5, 145.7, 141.7, 134.1, 129.3, 128.7, 123.8, 100.01, 53.2, 51.7, 31.6, 29.2, 29.1, 27.6, 22.6, 14.1; MS: *m/z* (%) = 345 (M^++1, 31.1), 344 (M^+, 68.1), 313.14 (53.5), 255 (67.3), 113 (92.5), 77 (96.5), 55 (100.0); anal. calcd. for $C_{19}H_{24}N_2O_4$: C 66.26, H 7.02, N 8.13; found: C 66.32, H 7.04, N 8.16.

Ethyl 1,3-diphenyl-1*H*-pyrazole-4-carboxylate (Scheme 4): mp 102–104 °C; IR (KBr): ν_{max} = 3080, 2987, 1716, 1561, 1259, 1133, 1059, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.43 (s, 1H), 7.81 (d, J = 7.6 Hz, 2H), 7.73 (d, J = 7.6 Hz, 2H), 7.43–7.72 (m, 5H), 7.38 (t, J = 7.2 Hz , 1H), 4.31 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.0, 142.2, 132.3, 130.0, 129.6, 129.6, 129.4, 128.7, 127.9, 127.6, 127.5, 119.6, 60.5, 14.3; MS: *m/z* (%) = 293 (M^++1, 47.2), 292 (M^+, 98.6), 247 (97.2), 219 (38.0), 149 (34.3), 104 (48.2), 77 (100.0); anal. calcd. for $C_{18}H_{16}N_2O_2$: C 73.95, H 5.52, N 9.58; found: C 73.90, H 5.56, N 9.59.

Ethyl 3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carboxylate (Scheme 4): mp 92–93 °C; IR (KBr): ν_{max} = 3067, 2959, 1696, 1526, 1276, 1177, 1027, 839, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.51 (s, 1H), 7.86 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 6.8 Hz, 2H), 7.51 (t, J = 7.6 Hz, 2H), 7.37 (t, J = 7.6 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 4.32 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 139.3, 132.6, 132.2, 130.7, 129.7, 129.6, 127.4, 124.6, 120.8, 119.5, 113.3, 60.3, 55.3, 14.4; MS: *m/z* (%) = 323 (M^++1, 77.3), 322 (M^+, 100.0), 277 (82.8), 235 (38.8), 125 (49.0), 111 (73.7), 95 (78.8), 77 (83.2); anal. calcd. for $C_{19}H_{18}N_2O_3$: C 70.79, H 5.63, N 8.69; found: C 70.87, H 5.66, N 8.66.

Acknowledgements

The authors are grateful to the Center of Excellence of Chemistry and Research Council of the University of Isfahan for financial support of this work.

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