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One-pot regioselective synthesis of substituted pyrazoles and isoxazoles in PEG-400/water medium by Cu-free nano-Pd catalyzed sequential acyl Sonogashira coupling–intramolecular cyclization†

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Catalyst efficacy of *in situ* generated Pd-nanoparticles (PdNPs) in the regioselective one-pot synthesis of 3,5-di & 3,4,5-trisubstituted pyrazoles and 3,5-disubstituted isoxazoles in environmentally benign PEG-400/H_2O medium, which involves the sequential (i) Cu-free acyl-Sonogashira coupling (ASC) and (ii) intramolecular ynone–amine cyclization under PTC conditions was described. The results of controlled experiments support the operation of two sequential catalytic cycles (ASC/cyclization) and achievement of complementary/opposite regioselectivity *via* ynone-bound palladium in a one-pot approach. Moreover, the *in situ* PdNPs recovered after the first catalytic cycle of the one-pot reaction sequence have been reused again five times successively. Besides, prior to the above studies, the efficacy of some common Pd–N-heterocyclic carbene (Pd–NHC) complexes in catalyzing the same one-pot two-step reaction sequence (Cu-free ASC/cyclization) both in water and organic solvents was also optimized. *In situ* generation of PdNPs from above Pd–NHCs in water was also identified, but they are not reusable due to their large size distribution.

Introduction

α,β-Unsaturated ynones (α,β-acetylenic ketones) are practical electrophilic three-carbon building blocks for diverse cyclization reactions to obtain bioactive *N*,*O*-heterocycles.[1] Besides, this approach could be a promising alternative to Huisgen 1,3-dipolar cycloaddition for the regioselective synthesis of 3,5-disubstituted azoles. Classical syntheses of ynones involve reactions of various metal acetylides with carbonyls or their derivatives, which however require harsh reaction conditions.[2] Thus, a variety of catalytic methods have been explored to synthesize ynones such as (i) propargylicalcohol oxidation,[3] (ii) acyl-Sonogashira coupling,[4] (iii) carbonylative-Sonogashira coupling,[5] (iv) acyl-Negishi coupling,[6] (v) alkynylation of activated esters[7] and (vi) direct aldehyde C–H alkynylation.[8] Among all, the Pd-catalyzed acyl-Sonogashira coupling reaction *i.e.* coupling between acid-chlorides and alkynes is relatively a facile route to obtain ynones and subsequent *N*,*O*-cyclization in a one-pot approach.

Previously, the ASC reaction was investigated using different homogeneous/heterogeneous Pd-catalysts in the absence[4f–l] or presence of copper as a co-catalyst.[4a–e] In addition, the Pd-free Cu-catalyzed ASC reaction was also reported.[4m,n] Nevertheless, the choice of a solvent and a copper catalyst/co-catalyst seems to be an important consideration in the Pd-catalyzed ASC reaction to deal with the objectives of green chemistry. Although Cu-mediated alkyne-transmetalation is beneficial to the increase of the reactivity of the entire ASC system, the reason for the Cu-free ASC reaction is suggested to prevent the potential simultaneous Glaser type oxidative dimerization of alkynes in the presence of air or other oxidizing agents. Moreover, the presence of a Cu-cocatalyst may complicate the sequential transformation of *in situ* generated ynones in one-pot in the presence of a Pd-catalyst under aerobic conditions. Considering the solvent factor, although the ASC reaction can carry on smoothly even in less polar solvents to produce ynones, the use of highly polar solvent/co-solvents was suggested for the subsequent *N*,*O*-cyclization.[4d,9] Previously, we have reported the efficacy of palladium(II)–N-heterocyclic

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carbenes (Pd–NHCs) in catalyzing the Sonogashira coupling to synthesize internal alkynes under copper-free conditions in dichloromethane (DCM).[10] As emphasized in the literature, due to their special steric and electronic properties the NHC ligands can increase the efficacy of Pd-catalysts in almost all cross-coupling reactions as compared to phosphines.[11] Nevertheless, a homogeneous or heterogeneous Pd-catalyzed Cu-free ASC reaction followed by *N*,*O*-cyclization that was performed entirely in pure water in a one-pot approach has not been reported yet.

Herein, we report the development of a regioselective one-pot synthesis of substituted pyrazoles and isoxazoles with a broad substrate scope in environmentally benign polyethylene glycol (PEG)-400/H_2O medium that involves the two-step reaction sequence of (i) the *in situ* generated PdNP catalyzed Cu-free ASC reaction to produce *in situ* ynones and (ii) intramolecular cyclization of *in situ* ynones with hydrazines and hydroxyl amine. The possibility of recovery and reuse of the above *in situ* PdNPs for the next catalytic cycles was also optimized. As well, prior to the above studies, we have also obtained the results on the efficacy of some common Pd–NHCs as homogeneous catalysts in catalyzing the same one-pot two-step reaction method both in organic and pure water media.

Results and discussion

The results of following three studies are discussed in a sequence:

i) Optimization of the Pd–NHC catalyzed Cu-free ASC reaction for the synthesis of 1,3-diphenylprop-2-yn-1-one (**4a**) in organic solvents.

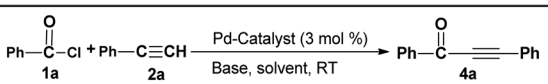
ii) Optimization of the Pd–NHC catalyzed Cu-free one-pot sequential ASC reaction and cyclization in organic solvents as well as in pure water for the synthesis of 3,5-diphenyl-1*H*-pyrazole (**6a**).

iii) Optimization of the recyclable *in situ* PdNP catalyzed Cu-free one-pot sequential ASC reaction and cyclization in PEG-400/water for the synthesis of 3,5-di & 3,4,5-trisubstituted pyrazoles and 3,5-disubstituted isoxazoles and achievement of complementary regioselectivity thereof.

Firstly, we explored the Pd–NHC (**3a**) catalyzed Cu-free ASC reaction of benzoyl chloride (**1a**) with phenylacetylene (**2a**) in DCM using pyrrolidine base as a model reaction to optimize the synthesis of corresponding 1,3-diphenylprop-2-yn-1-one (**4a**). The details of reaction conditions and the results are presented in Table 1. The Pd–NHC catalyst **3a** was derived from the NHC precursor (L_1) shown in Fig. 1. According to the results listed in Table 1, the Pd–NHC (**3a**) catalyzed Cu-free ASC reaction that was conducted in DCM has provided 93% yield of ynone **4a** at RT after 2 hours (Table 1, entry 1). The Pd–NHCs (**3b**–**3f**) derived from other NHC-precursors (L_2–L_6, Fig. 1) have also shown ability in catalyzing the same ASC reaction in DCM in the presence of pyrrolidine to provide high yields (82–89%) of **4a** (Table 1, entries 2–6). Specifically, those Pd–NHCs containing *N*-aryl substituents on the NHC ring are found to be relatively effective (Table 1, entries 1 & 3). Besides, it is also noticeable that there was no ASC reaction in the absence of a catalyst (Table 1, entry 7), but low yields of **4a** was obtained when $PdCl_2$ and $Pd(OAc)_2$ were used as catalysts (Table 1, entries 8–9).

Next, the effect of solvent and base was assessed in the same ASC reaction. It was found that the reaction conducted in toluene and MeCN can also provide relatively high yields

Table 1 Optimization of reaction conditions for the ASC between **1a** and **2a**[a]



1a 2a 4a

Entry	Catalyst	Solvent	Base	Yield[b] (%)
1	**3a**	DCM	Pyrrolidine	93
2	**3b**	DCM	Pyrrolidine	87
3	**3c**	DCM	Pyrrolidine	89
4	**3d**	DCM	Pyrrolidine	86
5	**3e**	DCM	Pyrrolidine	82
6	**3f**	DCM	Pyrrolidine	84
7	—	DCM	Pyrrolidine	N.R.
8	$PdCl_2$	DCM	Pyrrolidine	39[c]
9	$Pd(OAc)_2$	DCM	Pyrrolidine	46[c]
10	**3a**	THF	Pyrrolidine	83
11	**3a**	1,4-Dioxane	Pyrrolidine	81
12	**3a**	MeOH	Pyrrolidine	85
13	**3a**	Toluene	Pyrrolidine	89
14	**3a**	MeCN	Pyrrolidine	91
15	**3a**	DCM	Et_3N	93
16	**3a**	DCM	K_2CO_3	90
17	**3a**	DCM	Cs_2CO_3	91
18	**3a**	DCM	AcONa	89

[a] Reaction conditions: catalyst (0.03 mmol), **1a** (1.2 mmol), **2a** (1 mmol), base (2.0 mmol), 2 mL of solvent and RT. [b] Isolated yields after column chromatography. [c] Reaction time was 12 hours. [Pd–NHC] catalysts were synthesized *in situ* at RT by mixing $Pd(OAc)_2$ (0.03 mmol), NHC ligands (0.06 mmol) and DBU (0.072 mmol) in THF (1 mL) for 2 h, followed by the removal of the solvent under reduced pressure.

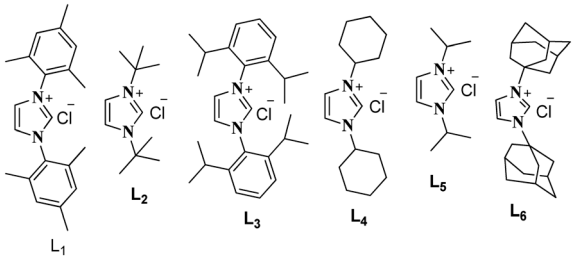
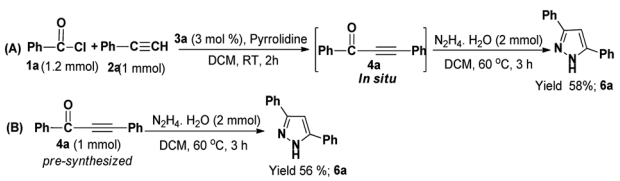


Fig. 1 NHC-ligand precursors used in the present work.

of **4a** (Table 1, entries 13–14). Concerning the results of the base effect, the use of mild organic bases is found to be beneficial in obtaining high yields of ynone **4a** under the operating conditions of this work (Table 1, entries 1 & 15).

Having the optimized conditions of the ASC reaction, ynone **4a** was then subjected for subsequent cyclization with hydrazine hydrate (**5a**) under two different conditions to produce corresponding 3,5-diphenyl-1*H*-pyrazole (**6a**). In (i), *in situ* **4a** (monitored by TLC) was reacted with **5a** in the same pot (Scheme 1A) in DCM *i.e.* without separating the catalyst **3a** after the ASC reaction. In (ii), pre-synthesized **4a** of the ASC reaction was allowed to react with amine **5a** in the absence of Pd–NHC catalyst **3a** in DCM (Scheme 1B). Since **5a** is an inorganic base, a slight excess quantity of **5a** was used to react with ynone **4a** as followed in many previous studies of cyclization.[4d,9a,d,12] It was our intention to see whether the catalyst **3a** has any decisive role also during the cyclization of **4a** with **5a** in terms of reaction times and yields. Since the substrates **4a** and **5a** are symmetrical ones, the question of complementary regioselectivity does not arise during the synthesis of **6a**, although the catalyzed and un-catalyzed cyclization paths are different as shown below. However, according to our observation, the role of Pd–NHC catalyst **3a** is not so substantial in the second step *i.e.* ynone–amine cyclization to increase the yield of **6a** in DCM as compared to the same product obtained from the un-catalyzed path.

In addition, we have also conducted few other supplementary experiments to assess the influence of solvent polarity in the above one-pot sequential process. We have noticed that the role of solvent polarity in the ASC reaction to produce ynone **4a** is not much significant (Table 1), but the role of solvents is influential during the second step *i.e.* the cyclization reaction of *in situ* ynone **4a** with amine **5a** in producing the desired pyrazole **6a**. Therefore, the entire one-pot reaction (ASC-cyclization) conducted exclusively in polar



Scheme 1 Synthesis of 3,5-diphenyl-1*H*-pyrazole (**6a**).

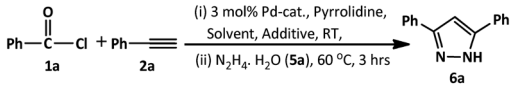
MeOH & MeCN has provided high yields (71–73%) of **6a** (Table 2, entries 3 and 5).This could be due to the increased solubility of amine **5a** in polar MeOH & MeCN compared to other solvents used in the present study. Furthermore, the addition of MeCN as a co-solvent to the DCM solvent also enhanced the rate of cyclization to provide 75% yield of **6a** (Table 2, entry 6).

The improved result of the one-pot reaction shown above was investigated further in pure water to produce **6a** to meet green chemistry protocols. In order to avoid the acid-hydrolysis side reaction, 30 mol% of tetrabutylammonium bromide (TBAB) was used as a PTC. In reality, A PTC can play multiple roles in catalyzed reactions as a co-catalyst and a stabilizing agent of intermediates and catalysts.[13,b] As a result, the one-pot reaction sequence (ASC-cyclization) shown above has occurred successfully in pure water to provide **6a** in higher yields (84%) than that conducted in organic solvents (Table 2, entry 7). However, the ASC reaction between **1a** & **2a** was unsuccessful using some Pd-sources like $PdCl_2$ and $Pd(OAc)_2$ in water even after 24 hours (Table 2, entries 8 and 9).

It was mentioned in the previous literature that Pd(II)-catalysts/pre-catalysts including Pd(II)–NHCs often exhibit heterogeneous-type catalytic behaviour generally by speciation to form PdNPs under normal experimental conditions.[13] This evidence has raised the question: which are the original catalytic species in cross-coupling reactions. It is also worth noting that homogeneously dispersed PdNPs exhibit notable ability to catalyse coupling reactions compared to Pd(II)-complex catalysts and also offer recycling advantages depending on the conditions. Hence, the one-pot reaction solutions of entries 1–7 in Table 2 were further analyzed to know the nature of the catalysts. At this point, we would like to mention that in our work, the Pd–NHC catalyzed one-pot reaction conducted in the presence of TBAB in pure water has shown the formation of some un-evenly distributed *in situ* PdNPs (Fig. S1, ESI†) during the synthesis of **6a**, where the reaction solution colour was fairly transparent brown (Table 2, entry 7). On the other hand, the Pd–NHC catalyzed one-pot reaction conducted in pure organic solvents has shown the formation of some Pd-black but not the PdNPs at the end of the reaction (Table 2, entry 1–6). When we have tried to re-use the above un-evenly distributed *in situ* PdNPs for the next cycle of the one-pot reaction, a low yield of pyrazole **6a** was obtained (Table 2, entry 10). This observation indicates that the unevenly PdNPs formed from Pd–NHC catalyst **3a** used in the present work are not well protected by either an NHC or a PTC present in the reaction solution to achieve recyclability.

Based on the above observations, we intend to re-investigate the above one-pot reaction sequence using well dispersed *in situ* PdNPs obtained from $PdCl_2$ in PEG-400/H_2O medium. PEGs are known as effective, inexpensive and soluble polymeric stabilizing agents and reducing agents for well/homogeneously dispersed PdNPs.[14] PEGs are also known as effective solvents for certain organic transformations.[15]

Table 2 Optimization of reaction conditions for the one-pot synthesis of **6a**[a]



Entry	Cat. Pd	Solvent	Time (h) step-i/step-ii	Yield[b] (%)
1	**3a**	THF	2/3.5	61
2	**3a**	1,4-Dioxane	2/3.5	64
3	**3a**	MeOH	2/3	71
4	**3a**	Toluene	2/4	41
5	**3a**	MeCN	2/3	73
6	**3a**	DCM	2/3	75[c]
7	**3a**	H_2O	3/3	84[d]
8	$Pd(OAc)_2$	H_2O	24/–	NR[d]
9	$PdCl_2$	H_2O	24/–	NR[d]
10	Isolated PdNPs	H_2O	3/3.5	53[e]
11	$PdCl_2$	PEG-400/H_2O	2.5/3	87[f]
12	$Pd(OAc)_2$	PEG-400/H_2O	4/6	64[f]
13	$PdCl_2$	PEG-400	2.5/3.5	82[g]
14	Pre-prepared PdNPs	PEG-400/H_2O	3/4	79[h]

[a] Reaction conditions: step 1: cat. Pd (0.03 mmol), **1a** (1.2 mmol), **2a** (1 mmol), pyrrolidine (2.0 mmol), 2 mL solvent, RT and 2 h. Step 2: 2 mmol (**4a**), 60 °C and 3 h. [b] Isolated yields after column chromatography. [c] In step 2, 1 mL of MeCN was added. [d] TBAB (0.3 mmol) was added. [e] *In situ* PdNPs obtained from **3a** in the presence of TBAB were isolated and then reused. [f] 6 mL of PEG-400/H_2O (2 : 1) and TBAB (0.3 mmol). [g] 4 mL of PEG-400. [h] Pre-prepared PdNPs. NR = no reaction.

Therefore, we thought that the combination of PEG-400 and H_2O would provide a synergistic effect *i.e.* effective stabilization of PdNPs and a green reaction medium. It was mentioned in the literature that the polar capping agent forms a more open structure in water and in turn facilitates an easy contact between reactants and the metal surface.[16] Indeed such a situation is complementary in catalysis since strong encapsulation could lead to loss of catalytic activity.

The one-pot reaction of **1a**, **2a** and **4a** conducted in the presence of $PdCl_2$/PEG-400/H_2O under PTC conditions has generated *in situ* PdNPs, which have catalyzed the ASC/cyclization sequence effectively to produce **6a** in 87% yield (Table 2, entry 11). The formation of uniformly dispersed *in situ* PdNPs (7–8 nm) after the first catalytic cycle was confirmed by a TEM study (Fig. S2, ESI†). When $Pd(OAc)_2$ was used as a precursor for *in situ* PdNPs to catalyze the one-pot reaction of **1a**, **2a** and **4a**, only 64% yield of **6a** was obtained indicating that $Pd(OAc)_2$ was not an effective source for *in situ* PdNPs in PEG-400/H_2O (Table 2, entry 12). Besides, it is interesting to observe that the *in situ* PdNP (obtained from $PdCl_2$ only in PEG-400) catalyzed system has provided a slightly less yield of **4a** compared to the *in situ* PdNP (obtained from $PdCl_2$ in PEG-400/H_2O) catalyzed system (Table 2, entry 13). We have also conducted an additional experiment for the one-pot synthesis of **4a** using pre-prepared PdNPs that were obtained from $PdCl_2$/PEG-400 *i.e.* without the combination of H_2O according to a literature procedure.[17] This time 78% yield of **6a** (Table 1, entry 14) was obtained from the one-pot sequence. These results suggested that the *in situ* generated Pd nanoparticles are slightly more active catalysts than the pre-formed Pd nanoparticles. Further, the effect of reaction parameters such as temperature, the nature of PEG & PTC and the stoichiometric amount of nitrogen bases was also investigated using *in situ* PdNPs and the results are presented in the ESI.†

Substrate scope and possibility of achieving complementary regioselectivity

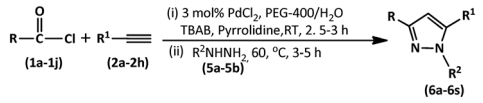
The catalytic conditions optimized with the *in situ* PdNPs in PEG-400/water for the one-pot synthesis of **6a** have been extended further to make use of different acid halide and alkyne substrates to generate symmetrical/unsymmetrical ynones (*in situ*) and their subsequent cyclization with hydrazines and hydroxyl amine to produce corresponding substituted pyrazoles (Table 3) and isoxazoles (Table 4).

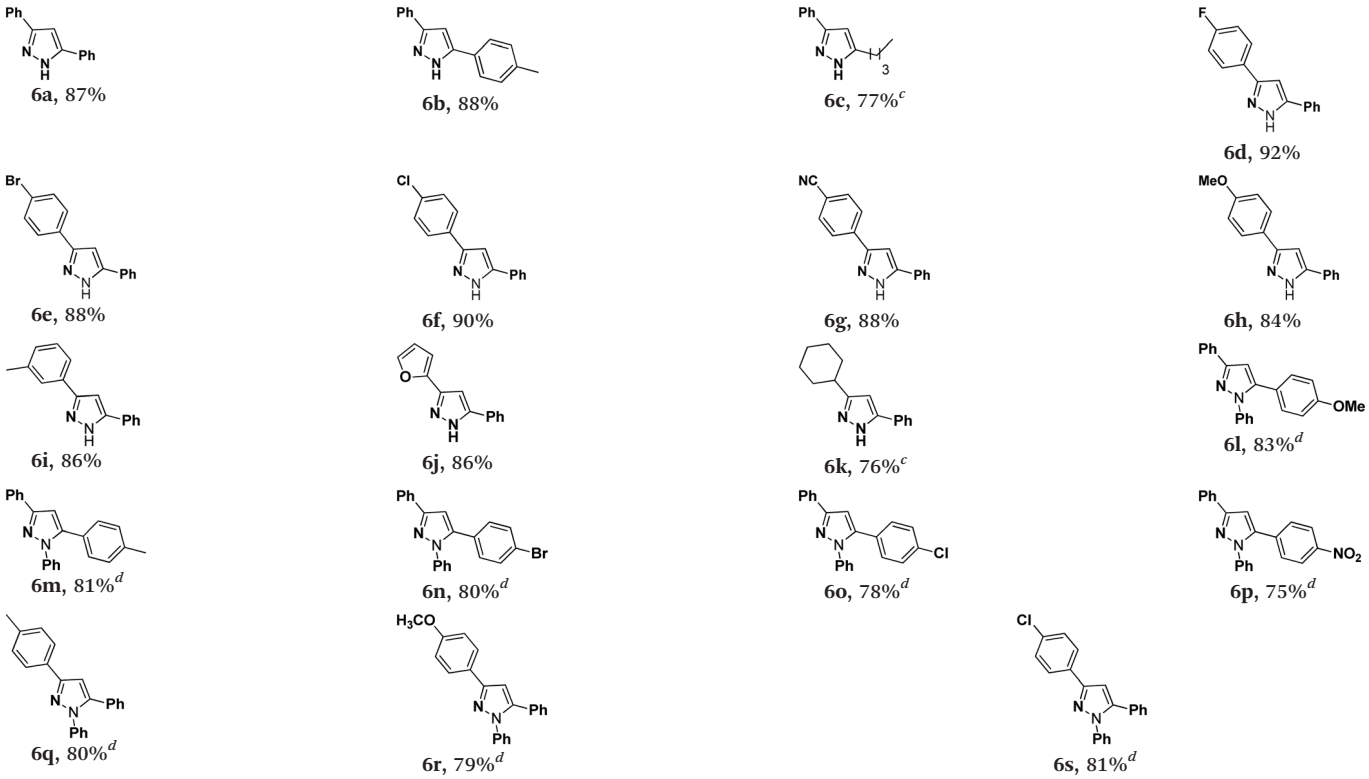
Depending on the types of substrates (ynones/hydrazines/hydroxyl amine), we have also observed the achievement of complementary regioselectivity in the above substituted pyrazole and isoxazole products. The results in Tables 3 and 4 reveal that specifically the reaction of unsymmetrical ynones with phenyl hydrazine and hydroxyl amine has provided the complementary regioselectivity in the corresponding pyrazole (Table 3, entries **6l–6s**) and isoxazole products (Table 4, entries **8b–8n**) as compared to the products obtained from the un-catalyzed reaction.[9b,12a,18a]

Other important observations concerning the substrate scope experimentation areas shown below;

(i) When the ynones obtained from aromatic acid halides/alkynes are used as substrates for cyclization, relatively better yields of respective pyrazoles (Table 3, entries **6a** and **6b** & **6d–6j**) and isoxazoles (Table 4, entries **8a–8l**) were obtained as compared to ynones obtained from aliphatic acid halides and alkynes.

Table 3 Synthesis of di- and tri-substituted pyrazoles[a,b]





[a] Reaction conditions: step 1: $PdCl_2$ (0.03 mmol), 6 mL of PEG-400/H_2O (2 : 1), TBAB (0.3 mmol), **1a** (1.2 mmol), **2a** (1 mmol), pyrrolidine (2.0 mmol), RT and 2.5 h. Step 2: 2.0 mmol (**5a**), 60 °C, 3 h. [b] Isolated yields after column chromatography. [c] In step 1 the reaction time was 3 h. [d] In step 2 the reaction time was 5 h.

(ii) The presence of an electronic withdrawing group on phenylacetylenes (Table 3, entries **6b** & **6l–6m** and Table 4, entries **8b** and **8c**) and an electron releasing group and benzoyl chlorides (Table 3, entries **6e–6h** & **6s** and Table 4, entries **8h** and **8i**) has increased yields of corresponding azoles from the ASC-cyclization sequence.

(iii) The aryl bromide functionality remained unchanged (*i.e.* no coupling with terminal alkyne) during the ASC-cyclization (Table 3, entry **6e**).

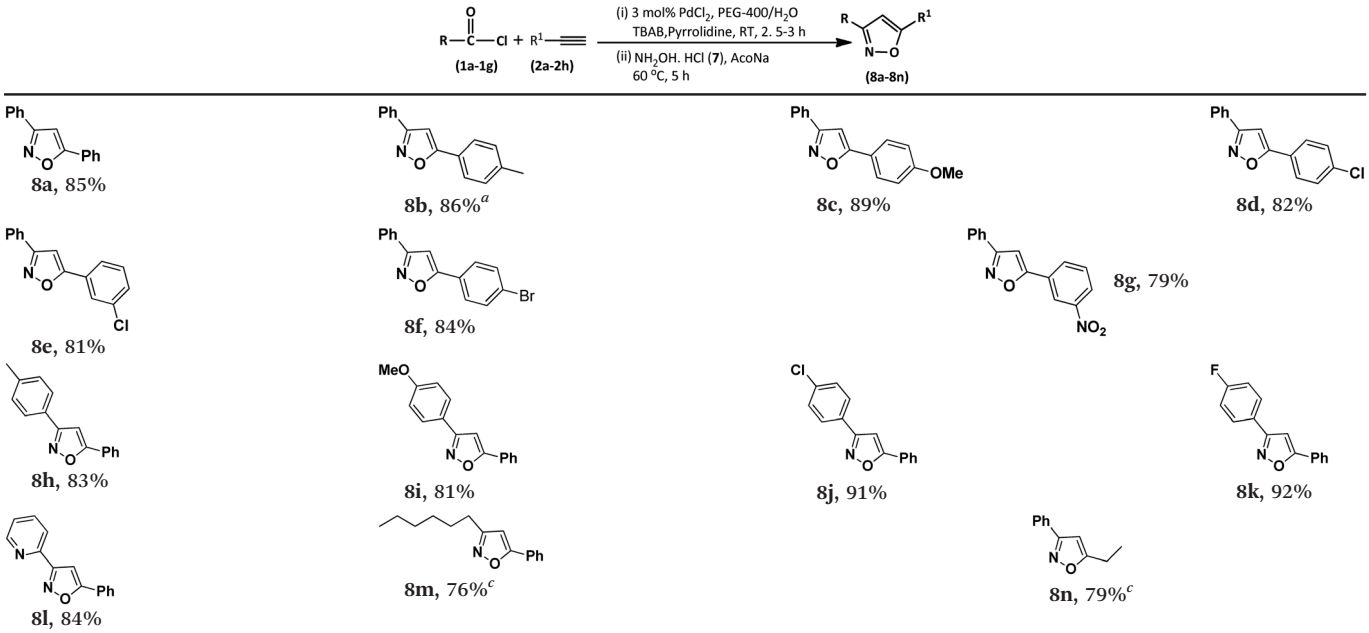
(iv) The reactivity of phenyl hydrazine was low as compared to hydrazine hydrate with ynones and hence a slight decrease in the yields of corresponding tri-substituted pyrazoles has been found (Table 3, entries **6b** & **6l** and **6m** and Table 4, entries **6l–6s**).

Mechanism

Previously, the mechanism of the Cu-free Pd-catalyzed ASC reaction was described.[4f,h–i] Pd-Catalyzed activation of symmetrical/un-symmetrical ynone–oxime involved in intramolecular cyclization to form the isoxazoles was also reported.[18a,19] Besides, a Cu-catalyzed activation of symmetrical/un-symmetrical ynone–hydrazones involved in intramolecular cyclization to form tri-substituted ones was reported.[18b] However, the role of a metal-catalyst including PdNPs in catalyzing the sequential ASC and intramolecular cyclization in one-pot to produce pyrazoles and isoxazoles has not been described yet.

Therefore, to understand this phenomenon, we have carried out some controlled experiments. As shown in Scheme 2, the reaction of pre-synthesized ynone (**4b**) with phenyl hydrazine (**5b**) and hydroxyl amine (**7**) in the absence of a Pd-catalyst at 60 °C did not form the expected pyrazole and isoxazole, but did form intermediates (**A** & **B**) only *via* *cyclo*-condensation. Upon dehydration in the presence of H_2SO_4, intermediates **A** & **B** were converted to 1,5-diphenyl-3-(*p*-tolyl)-1*H*-pyrazole (**6q**) and 5-phenyl-3-(*p*-tolyl)isoxazole (**8h**), respectively, as observed previously.[12a,18a] It is worth noting that, when the above reaction was catalyzed by PdNPs, the reaction occurred *via* intramolecular cyclization and provided 1,3-diphenyl-5-(*p*-tolyl)-1*H*-pyrazole (**6m**) and 3-phenyl-5-(*p*-tolyl)isoxazole (**8b**) as sole products. This means that the products obtained *via* the catalyzed path are complementary to the products obtained *via* the un-catalyzed

Table 4 Synthesis of di-substituted isoxazoles[b]



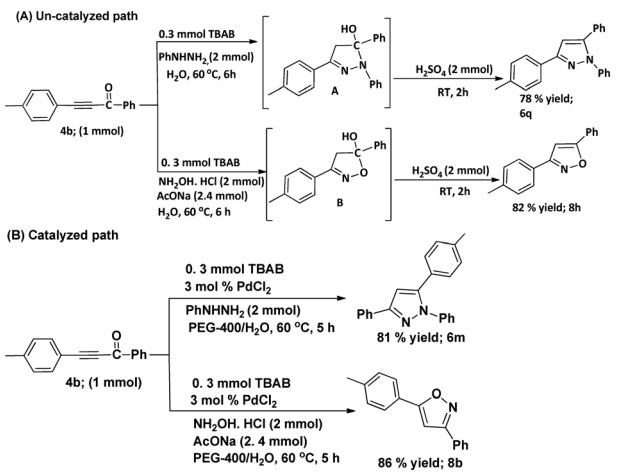
[a] Reaction conditions: step 1: $PdCl_2$ (0.03 mmol), 6 mL of PEG-400/H_2O (2 : 1), TBAB (0.3 mmol), **1a** (1.2 mmol), **2a** (1 mmol), pyrrolidine (2.0 mmol), RT and 2.5 h. Step 2: 7 (2.0 mmol), AcONa (2.4 mmol), 60 °C and 5 h. [b] Isolated yields after column chromatography. [c] Step 1: Reaction time was 3 h.

path. The structures of **6q**, **8h**, **6m** and **8b** were analysed by physical state and melting point that consistent with previous report (see experimental section).

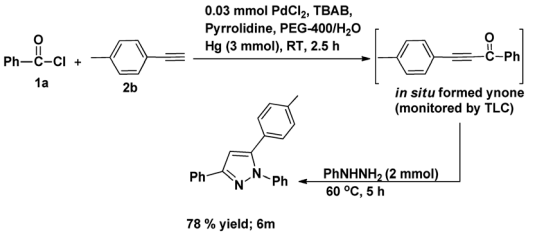
Although the *in situ* generated PdNPs have shown good catalytic activity, we didn't know whether the catalysis occurred either on the surface of the cluster or by leached Pd species.[20] Therefore, we have carried out some controlled experiments to evaluate the homogeneous/heterogeneous nature of the active PdNP catalytic system (Scheme 3). When 100 equivalents of Hg(0) (relative to palladium) was added to the one-pot two step reaction of **1a**, **2b** and **5b** under the optimized conditions there was no substantial influence on the catalytic activity.

In continuation, we have also added different quantities of carbon disulfide (0, 0.65, 1 and 1.5 equivalents to that of palladium) to the reaction mixture of Scheme 3. We have noticed that in the presence of 0 and 0.65 equivalents of CS_2, both ASC and intramolecular cyclitization reactions were still operative and gave the desired product **6m** in the range of 77–81% yields, (entries 1 and 2, Scheme 4). However, when the amount of CS_2 was increased to 1.0 and 1.5 equivalents, the ASC reaction between **1a** and **2b** was almost non-existent (entries 3 and 4, Scheme 4). These observations suggest that the active catalytic system is very likely to be homogeneous in nature.[21]

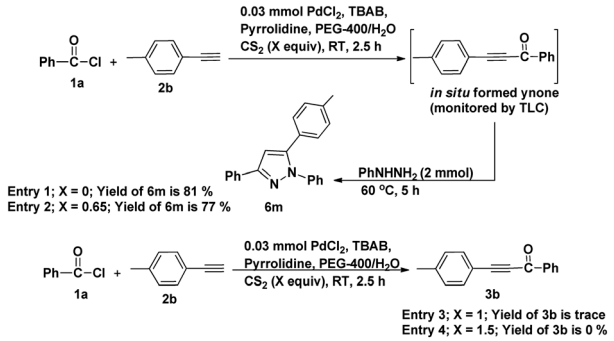
Based on the above controlled experiments and from the literature[4f,h–i,14a,b,18,19,22] a plausible catalytic cycle has been proposed. According to Scheme 5, initially, aroyl halides undergo oxidative addition with the *in situ* generated Pd(0) NPs catalytic system to form aroyl-Pd(II)–Cl intermediate **A**.



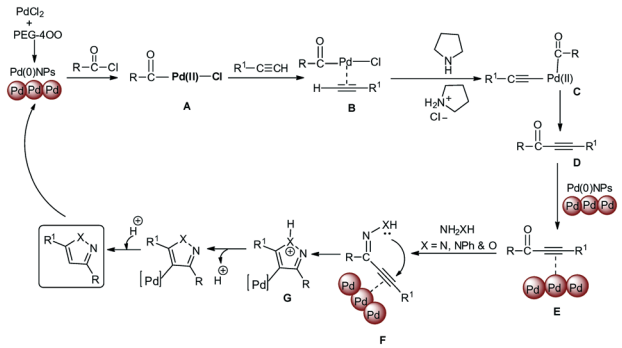
Scheme 2 Controlled experiments and achievement of opposite regioselectivity in the uncatalyzed *versus* catalyzed reaction.



Scheme 3 Hg poisoning test.



Scheme 4 CS_2 poisoning test.



Scheme 5 A plausible reaction mechanism.

Later Pd–alkyne coordination takes place in the presence of a pyrrolidine base, which in turn forms Pd–alkyne complex **C** through the transitory intermediate **B**. Finally, the reductive elimination of intermediate **C** facilitates the formation of ynone **D** and regeneration of Pd(0)NPs. These regenerated PdNPs again start the second catalytic cycle through their coordination with the C–C triple bond of *in situ* formed ynone **D**. The resulting activated ynone–palladium intermediate **E** then converts to ynone–hydrazone/ynone–oxime intermediate **F** by reacting with hydrazines/hydroxyl amine. Then, the 5-*endo-dig* cyclization of intermediate **F** occurs to form pyrazolyl–palladium/isoxazolyl–palladium intermediate **G**. Finally, the substituted pyrazole/isoxazole products were obtained regioselectively upon the subsequent deprotonation and depalladation–protonation process.

Recyclability of the *in situ* PdNP ($PdCl_2$/PEG-400) catalytic system

The reusability efficiency of the PEG-PdNPs in the one-pot synthesis of pyrazole **6l** was investigated (Fig. 2). After the formation of **6l** in the first catalytic cycle, the reaction mixture was extracted with diethyl ether (4 × 10 mL) and the solidified PdNPs were reused for the next catalytic run. It was observed that the recycled PdNPs have shown significant catalytic efficiency up to 5 successive catalytic runs. The TEM studies reveal that the PdNP sizes were increased to 20 nm

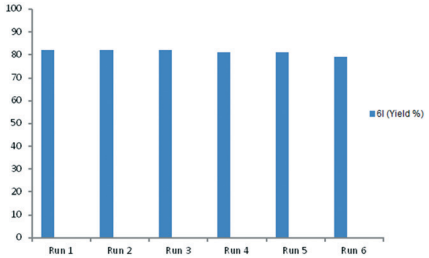


Fig. 2 Data showing the recyclability of *in situ* PdNPs.

which may be due to aggregation after the 6th catalytic run (Fig. S3, ESI†).

Conclusions

In conclusion, our results have demonstrated the first example of *in situ* PdNPs catalyzed regioselective one-pot synthesis of various substituted pyrazoles and isoxazoles in an environmentally benign PEG-400/water system. A plausible mechanism has been proposed by considering the outcome of controlled experiments and literature studies explaining the operation of two sequential Pd-catalytic cycles (ASC/intramolecular cyclization) for the synthesis of ynones and the subsequent conversion to pyrazoles and isoxazoles. It is interesting to note that opposite regioselectivity was observed between the catalyzed reaction products and the un-catalyzed reaction products. The recovery of PEG-supported PdNPs obtained from the first phase of catalytic cycles has shown remarkable recyclable catalytic activity up to five successive catalytic cycles.

The results of present one-pot methodology (ASC-cyclization) are comparable or relatively better than the previous studies conducted in pure organic or mixed organic solvent systems. Besides, the optimization of Cu-free Pd-catalyzed ASC in pure water for the synthesis of various symmetric/asymmetric ynones, the first of its kind, offers a broad substrate scope for the development of other cyclization to obtain a variety of heterocycles in water. Our mechanistic studies suggest a typical heterogeneous reaction process that is unlikely to be in operation.

Experimental

General information

All commercially available reagents were used without further purification. The purity of the compounds was checked by TLC using Merck 60F254 silica gel plates. Transmission electron microscopy (TEM) analysis was performed using a PHILIPS instrument-CM 200 with an operating voltage of 20–200 kV and a resolution of 2.4 Å. ^{1}H & ^{13}C NMR spectra were recorded with a Mercury Plus spectrometer (operating at 500/400/300 MHz for ^{1}H & 125/100/75 MHz for ^{13}C) and chemical shifts were referenced to TMS.

***Ex situ* nanoparticles were synthesized according to a literature procedure.**[17] $PdCl_2$ (3 mol%) was added into PEG-

400 (4 g) present in a 25 mL round bottom flask and was allowed to stirr at room temperature for overnight. After the completion of the reaction, the colour of the solution turned from light yellow to dark, indicating the formation of palladium nanoparticles. Then, these PdNPs were used to catalyze the one-pot three-component reaction of **1a**, **2a** and **5a**.

General procedure for the synthesis of 4a & 4b

Synthesis of 1,3-diphenylprop-2-yn-1-one (4a). To a 10 mL round bottom flask containing 1 mL of dry THF, 0.03 mmol of $Pd(OAc)_2$, 0.06 mmol of NHC precursor $\mathbf{L_1}$ and 0.072 mmol of DBU were successively added under a N_2 atmosphere and the mixture was allowed to stir at room temperature for 2 h. Later the solvent was removed under reduced vacuum. Then, benzoyl chloride **1a** (1.2 mmol), pyrrolidine (2.0 mmol) and phenylacetylene **2a** (1.0 mmol) in 2 mL DCM were added and the whole reaction mixture was stirred at RT for 2 hours. The completion of the reaction was monitored by TLC, and the crude reaction mixture was extracted twice with DCM/H_2O (5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude product was further analyzed by column chromatography using (10 : 1) hexane : ethyl acetate as an eluent to give the pure product **4a**.

1,3-Diphenylprop-2-yn-1-one (4a).[4] 93% yield; white solid; M.P. 42–44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, J = 7.9, 1.5 Hz, 1H), 7.63–7.57 (m, 2H), 7.55 (t, J = 8.1 Hz, 1H), 7.33–7.25 (m, 2H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 178.5, 137.4, 134.5, 133.7, 131.4, 130.1, 129.4, 129.1, 120.1, 93.5, 87.4 ppm.

1-(4-Methylphenyl)-3-phenylpropynone (4b).[4] 91% yield; white solid; M.P. 85–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 7.6 Hz, 2H), 7.45–7.38 (m, 3H), 7.25 (d, J = 8.5 Hz, 2H), 2.35 (s, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ 177.8, 145.4, 134.7, 133.4, 131.2, 129.8, 128.7, 120.2, 93.2, 87.3, 22.7 ppm.

General procedure for the one-pot synthesis of substituted pyrazole and isoxazoles

Synthesis of 3,5-diphenyl-1*H*-pyrazole (6a). To a 25 mL round-bottom flask containing 6 mL of PEG-400/H_2O (2 : 1) solution, $PdCl_2$ (0.03 mmol), benzoyl chloride **1a** (1.2 mmol), TBAB (0.3 mmol), pyrrolidine (2.0 mmol) and phenylacetylene **2a** (1.0 mmol) were successively added and the whole reaction mixture was stirred at RT for 2.5 hours. The formation of *in situ* ynone **4a** was confirmed by TLC, and hydrazine hydrate **5a** (2.0 mmol) was then added and stirring was continued for further 3 hours at 60 °C. Then, the reaction mixture was cooled to RT and extracted with diethyl ether (4 × 10 mL). The organic layers were combined and the volatile components were evaporated under reduced pressure. Finally, the crude product was purified by column chromatography (silica gel 60–120 mesh size) using ethyl acetate/hexane (1 : 4) as an eluent to obtain 87% yield of (**6a**). A similar procedure was used to synthesize 3,5-disubstituted isoxazoles. It has been noticed that the reaction time was 5 hours in the second step.

Hg(0) poisoning test. As per the general procedure for the synthesis of **6m**, $PdCl_2$ (0.03 mmol), benzoyl chloride **1a** (1.2 mmol), TBAB (0.3 mmol), pyrrolidine (2.0 mmol) 4-ethynyl toluene **2b** (1.0 mmol) and 6 mL of PEG-400/H_2O (2 : 1) solution with the addition of elemental Hg (3 mmol, 100 equivalent to that of relative palladium) were successively added and the resulting reaction mixture was stirred at RT for 2.5 hours. After the *in situ* formation of ynone, phenylhydrazine **5b** (2.0 mmol) was added. The resulting mixture was stirred for additional 5 hours at 60 °C to achieve 78% yield of **6m** indicating that the reaction was not inhibited by introducing Hg(0).

CS_2 poisoning test. As per the general procedure for the synthesis of **6m**, $PdCl_2$ (0.03 mmol), benzoyl chloride **1a** (1.2 mmol), TBAB (0.3 mmol), pyrrolidine (2.0 mmol) 4-ethynyl toluene **2b** (1.0 mmol) and 6 mL of PEG-400/H_2O (2 : 1) solution were employed as a control. CS_2 (0 equivalent & 0.65 equivalent to that of palladium) correspondingly was added to the above reaction mixtures and stirred at RT for 2.5 h. After the *in situ* formation of ynone, phenylhydrazine **5b** (2.0 mmol) was added. The resulting mixture was allowed to stir for further 5 hours at 60 °C to afford 77–81% yield of **6m**. When we carried out the same reaction using 1.0 and 1.5 equivalents of CS_2 there was no ASC reaction. Successive investigations of the reactions recommend that the reactions are totally inhibited when we added ≥1.0 equivalents of CS_2.

General procedure for the recyclability of PEG-PdNPs

After the first experimentation, the reaction mixture was extracted with diethyl ether (4 × 10 mL) and the solidified PdNPs were exposed to a second catalytic run using the same substrates in a 1 : 2 ratio of the PEG-400/H_2O solvent system under the optimized conditions.

3,5-Diphenyl-1*H*-pyrazole (6a).[23] 85% yield; white solid; M.P. 191–193 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (d, J = 7.2 Hz, 4H), 7.33–7.40 (m, 6H), 6.88 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 128.9, 127.9, 125.2, 99.8 ppm.

3-Phenyl-5-*p*-tolyl-1*H*-pyrazole (6b).[9a] 87% yield; white solid; M.P. 160–162 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, J = 4.2 Hz, 2H), 7.62 (d, J = 8.1 Hz, 2H), 7.23–7.46 (m, 5H), 6.84 (s, 1H), 2.39 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 129.3, 128.7, 125.05, 125.02, 99.2, 20.8 ppm.

5-Butyl-3-phenyl-1*H*-pyrazole (6c)[23]**.** 77% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.49 (m, 2H), 7.44–7.31 (m, 3H), 6.41 (s, 1H), 2.73 (t, J = 8.0 Hz, 2H), 1.66 (p, J = 7.9 Hz, 2H), 1.44–1.31 (m, 2H), 0.94 (t, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 128.6, 125.4, 100.4, 31.3, 22.1, 13.9 ppm.

3-(4-Fluorophenyl)-5-phenyl-1*H*-pyrazole (6d).[23] 92% yield; white solid; M.P. 168–170 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77–7.72 (m, 3H), 7.50–7.38 (m, 4H), 7.10 (t, J = 8.1 Hz, 2H), 6.83 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) δ 131.5, 129.7, 128.4, 127.7, 127.6, 125.6, 116.3, 116.0, 100.1 ppm.

3-(4-Bromophenyl)-5-phenyl-1*H*-pyrazole (6e).[23] 88% yield; white solid; M.P. 217–219 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.58 (m, 4H), 7.49 (d, J = 7.7 Hz, 2H), 7.47–7.41 (m, 3H), 6.82 (s, 1H) ppm; ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 132.0, 131.0, 129.9, 128.6, 127.8, 127.5, 125.9, 100.1 ppm.

3-(4-Chlorophenyl)-5-phenyl-1*H*-pyrazole (6f).[23] 90% yield; white solid; M.P. 216–218 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.72–7.64 (m, 4H), 7.56–7.48 (m, 4H), 7.38–7.30 (m, 1H), 6.83 (s, 1H) ppm; ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 128.7, 126.9, 125.0, 99.2 ppm.

4-(5-Phenyl-1*H*-pyrazol-3-yl)benzonitrile (6g).[23] 88% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (q, J = 7.8 Hz, 4H), 7.62 (dd, J = 7.6, 1.6 Hz, 2H), 7.42 (t, J = 7.6 Hz, 2H), 7.37–7.30 (m, 1H), 6.87 (s, 1H) ppm; ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 157.6, 146.8, 133.0, 130.1, 129.8, 128.9, 127.4, 125.6, 119.1, 110.1, 100.1 ppm.

3-(4-Methoxyphenyl)-5-phenyl-1*H*-pyrazole (6h).[23] 84% yield; white solid; M.P. 144–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.1 Hz, 1H), 7.60 (d, J = 8.6 Hz, 2H), 7.38–7.30 (m, 2H), 7.37–7.31 (m, 1H), 6.91 (d, J = 8.6 Hz, 1H), 6.72 (s, 1H), 3.86 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 129.4, 127.2, 125.3, 114.6, 99.6, 55.5 ppm.

5-Phenyl-3-(*m*-tolyl)-1*H*-pyrazole (6i).[12a] 86% yield; white solid; M.P. 176–178 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75–7.68 (m, 2H), 7.54 (t, J = 1.9 Hz, 1H), 7.44–7.37 (m, 3H), 7.35–7.21 (m, 2H), 6.82 (s, 1H), 2.33 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.7, 138.1, 131.3, 128.7, 128.4, 127.8, 126.2, 125.6, 122.7, 99.6, 21.4 ppm.

3-(Furan-2-yl)-5-phenyl-1*H*-pyrazole (6j).[23] 86% yield; yellow solid; M.P. 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.72 (m, 3H), 7.47–7.31 (m, 3H), 6.81 (s, 1H), 6.71 (dd, J = 7.8, 1.9 Hz, 1H), 6.49 (t, J = 7.8 Hz, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 148.4, 146.8, 142.4, 129.4, 128.7, 128.3, 125.8, 111.7, 106.5, 99.6 ppm.

3-Cyclohexyl-5-phenyl-1*H*-pyrazole (6k).[12a] 76% yield; white solid; M.P. 137–138 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (dd, J = 7.7, 1.8 Hz, 1H), 7.37–7.24 (m, 3H), 6.33 (s, 1H), 3.32–3.25 (m, 1H), 2.68–2.59 (m, 1H), 2.03–1.91 (m, 2H), 1.38–1.24 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 149.8, 132.7, 128.6, 127.9, 125.5, 99.7, 35.8, 32.7, 26.4, 26.2 ppm.

5-(4-Methoxyphenyl)-1,3-diphenyl-1*H*-pyrazole (6l).[22] 82% yield; white solid; M.P. 77–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.8 Hz, 2H), 7.42–7.20 (m, 10H), 6. 86 (d, J = 8.1 Hz, 2H), 6.75 (s, 1H), 3.82 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 151.6, 144.4, 140.1, 133.2, 130.3, 128.8, 128.1, 127.2, 125.8, 125.2, 123.1, 114.2, 104.4, 55.6 ppm.

1,3-Diphenyl-5-(*p*-tolyl)-1*H*-pyrazole (6m).[24] 81% yield; yellow solid; M.P. 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.6 Hz, 2H), 7.39–7.16 (m, 10H), 7.11 (d, J = 7.9 Hz, 2H), 6.80 (s, 1H), 2.37 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 144.4, 140.5, 138.3, 133.4, 129.1, 128.8, 128.1, 127.6, 127.3, 125.7, 125.1, 104.9, 21.4 ppm.

5-(4-Bromophenyl)-1,3-diphenyl-1*H*-pyrazole (6n).[24] 80% yield; yellow solid; M.P. 129–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 7.8 Hz, 2H), 7.46–7.17 (m, 10H), 7.05 (d, J = 7.8 Hz, 2H), 6.84 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 143.3, 139.7, 132.7, 131.6, 130.1, 129.4, 128.6, 128.2, 127.6, 125.7, 125.1, 122.3, 105.4 ppm.

5-(4-Chlorophenyl)-1,3-diphenyl-1*H*-pyrazole (6o).[24] 78% yield; white solid; M.P. 104–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.8 Hz, 2H), 7.41 (t, J = 7.2 Hz, 2H), 7.35–7.19 (m, 8H), 7.10 (d, J = 8.2 Hz, 2H), 6.84 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 143.2, 139.9, 134.4, 132.9, 130.0, 129.1, 129.0, 128.7, 128.1, 127.7, 125.9, 125.4, 105.3 ppm.

5-(4-Nitrophenyl)-1,3-diphenyl-1*H*-pyrazole (6p).[24] 75% yield; white solid: M.P. 135–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 7.8 Hz, 2H), 7.89 (d, J = 7.6 Hz, 2H), 7.45–7.25 (m, 10H), 6.94 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 147.4, 142.2, 139.8, 136.8, 132.4, 129.3, 128.7, 128.3, 125.9, 125.4, 123.7, 106.4 ppm.

1,5-Diphenyl-3-(*p*-tolyl)-1*H*-pyrazole (6q).[24] 80% yield; white solid; M.P. 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.7 Hz, 2H), 7.34–7.10 (m, 12H), 6.80 (s, 1H), 2.38 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 144.1, 140.4, 137.7, 130.6, 130.1, 129.5, 128.9, 128.4, 127.6, 125.7, 125.2, 104.8 ppm.

3-(4-Methoxyphenyl)-1,5-diphenyl-1*H*-pyrazole (6r).[25] 79% yield; white solid; M.P. 143–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.1 Hz, 2H), 7.42–7.24 (m, 10H), 6.97 (d, J = 8.1 Hz, 2H), 6.75 (s, 1H), 3.83 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 151.6, 144. 6, 140.2, 130.7, 128.9, 127.5, 125.8, 125.2, 114.3, 104.6, 55.6 ppm.

3-(4-Chlorophenyl)-1,5-diphenyl-1*H*-pyrazole (6s).[24] 81% yield; white solid; M.P. 138–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.7 Hz, 2H), 7.45–7.23 (m, 12H), 6.82 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 144.7, 139.8, 133.6, 131.5, 130.3, 129.2, 128.9, 128.3, 127.8, 127.3, 125.4, 104.9 ppm.

3,5-Diphenylisoxazole (8a).[25] 85% yield; white solid; M.P. 141–142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80–7.86 (m, 4H), 7.42–7.51 (m, 6H), 6.80 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 162.7, 130.2, 129.8, 129.1, 128.8, 128.7, 127.5, 126.8, 125.6, 97.1 ppm.

3-Phenyl-5-(*p*-tolyl)isoxazole (8b).[26] 86% yield; yellow solid; M.P. 137–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, J = 7.9, 1.9 Hz, 2H), 7.70 (d, J = 8. 1 Hz, 2H), 7.51–7.45 (m, 2H), 7.34–7.25 (m, 3H). 6.79 (s, 1H), 2.40 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 163.1, 140.9, 130.3, 129.9, 129.3, 127.6, 125.7, 124.6, 97.2, 21.7 ppm.

5-(4-Methoxyphenyl)-3-phenylisoxazole (8c).[27] 89% yield; white solid; M.P. 126–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.78 (m, 4H); 7.51–7.40 (m, 3H); 6.95 (d, 2H, J = 8.7 Hz), 6.79 (s, 1H); 3.82 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 1 70.4, 163.1, 161.3, 129.9, 129.4, 128.8, 127.4, 126.5, 120.2, 114.1, 96.9, 56.0 ppm.

5-(4-Chlorophenyl)-3-phenylisoxazole (8d).[27] 82% yield; colourless solid; M.P. 176–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.86 (m, 4H), 7.49–7.37 (m, 5H), 6. 83 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 163.2, 136.4, 130.3, 129.1, 128.6, 127.1, 126.4, 125.7, 97.9 ppm.

5-(3-Chlorophenyl)-3-phenylisoxazole (8e).[25] 81% yield; white solid; M.P. 105–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.89–7.83 (m, 3H); 7.74 (s, 1H); 7.44–7.35 (m, 5H), 6.86 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 163.4, 135.3, 130.8, 130.1, 129.2, 126.7, 125.9, 124.2, 98.2 ppm.

5-(4-Bromophenyl)-3-phenylisoxazole (8f).[25] 84% yield; white solid; M.P. 155–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.71 (m, 4H), 7.63 (d, J = 7.8 Hz, 1H), 7.49–7.42 (m, 3H), 6.82 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 163.1, 132.5, 130.3, 129.1, 127.5, 126.8, 126.4, 124.5, 97.7 ppm.

5-(3-Nitrophenyl)-3-phenylisoxazole (8g).[25] 79% yield; white solid; M.P. 167–169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.64 (d, 1H, J = 3.7 Hz), 8.11 (d, 1H, J = 7.8 Hz), 7.92–7.84 (m, 2H), 7.39–7.25 (m, 4H), 6.91 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 148.9, 132.2, 131.4, 130.7, 129.4, 128.3, 127.2, 125.4, 120.7, 100.3 ppm.

5-Phenyl-3-(*p*-tolyl)isoxazole (8h).[25] 83% yield; white solid; M.P. 141–142 °C; 7.86–7.81 (m, 2H); 7.74 (d, 2H, J = 8.2 Hz); 7.45–7.33 (m, 3H); 7.29 (d, 2H, J = 7.8 Hz); 6.81 (s, 1H), 2.36 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 163.2, 140.3, 130.4, 129.9, 129.2, 127.5, 126.9, 126.2, 125.4, 97.7, 21.8 ppm.

3-(4-Methoxyphenyl)-5-phenylisoxazole (8i).[25] 81% yield; white solid; M.P. 129–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.76 (m, 4H), 7.52–7.42 (m, 3H), 6.98 (d, 2H, J = 8.8 Hz), 6.76 (s, 1H), 3.84 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 162.6, 161.3, 130.4, 129.2, 128.5, 127.6, 125.8, 121.6, 114.2, 97.2, 55.7 ppm.

3-(4-Chlorophenyl)-5-phenylisoxazole (8j).[26] 92% yield; yellow solid; M.P. 172–174 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.75 (m, 1H), 7.48–7.11 (m, 5H), 6.84 (s,1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 162.2, 136.3, 130.3, 129.4, 128.2, 127.4, 127.1, 125.8, 97.8 ppm.

3-(4-Fluorophenyl)-5-phenylisoxazole (8k).[25] 92% yield; white solid; M.P. 165–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.88–7.81 (m, 4H), 7.45–7.34 (m, 3H), 7.17 (t, 2H, J = 8.8 Hz), 6.80 (s, 1H) ppm, ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 163.4, 161.4, 130.5, 129.3, 128.9, 127.4, 125.8, 125.4, 116.2, 116.0, 97.5 ppm.

5-Phenyl-3-(pyridin-2-yl)isoxazole (8l).[23] 84% yield; white solid; M.P. 126–127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (dd, J = 7.8, 1.8 Hz, 1H), 8.12 (d, J = 7.8 Hz, 1H) 7.86–7.75 (m, 3H), 7.46–7.25 (m, 4H), 7.21 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 163.6, 149.6, 148.4, 136.8, 130.7, 129.4, 127.7, 125.8, 124.4, 121.8, 98.7 ppm.

3-Hexyl-5-phenylisoxazole (8m).[25] 84% yield; red oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, 2H, J = 7.6 Hz); 7.51–7.36 (m, 3H), 6.38 (s, 1H), 2.75 (t, J = 7.6 Hz, 2H), 1.79–1.71 (m, 1H), 1.42–1.26 (m, 6H), 1.01–0.91 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 162.5, 129.6, 128.5, 126.6, 98.3, 31.6, 28.7, 27.4, 26.4, 22.2, 13.8 ppm.

5-Ethyl-3-phenylisoxazole (8n).[12a] 84% yield; colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.76 (m, 2H), 7.48–7.40 (m, 3H), 6.28 (s, 1H), 2.82 (q, J = 6.9 Hz, 1H), 1.33 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 162.2, 129.8, 129.3, 128.7, 126.5, 97.8, 20.3, 11.8 ppm.

Conflicts of interest

There are no conflicts to declare.

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