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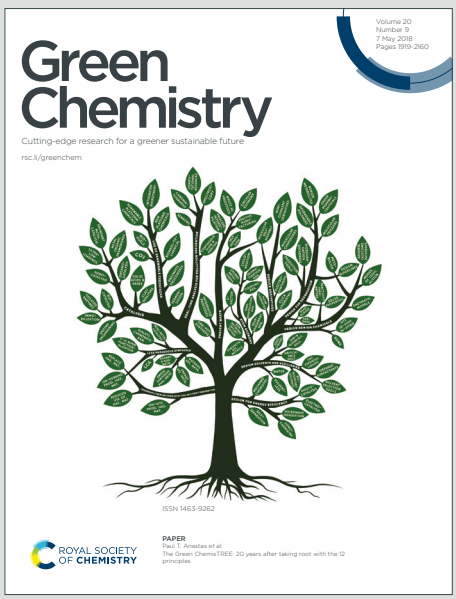

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COMMUNICATION

Solvent free and Montmorillonite K10 catalysed domino reactions for the synthesis of pyrazoles with alkynylester as a dual synthon

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Sesuraj Babiola Annes,[a] Rajendhiran Saritha,[a] Saravanan Subramanian,[b] Bhaskaran Shankar,[c] Subburethinam Ramesh*[a]

A highly regioselective, solvent free and montmorillonite K10 clay catalysed domino process with an unprecedented ring closing C-C bond formation reaction is described for the synthesis of new class of 1,3,4-trisubstituted and 1,4-disubstituted pyrazole derivatives. The reaction proceeds *via* a nucleophilic attack of enamine from an intermediate on the *β* carbon of an amino acrylate. Experimental outcome has clearly revealed that the organic solvents produce adverse effect for the pyrazole formation and oxidative condition in the presence of the reusable clay favours the 1,3,4-trisubstituted pyrazole formation. The clay in the presence of *N*-bromosuccinamide (NBS) catalyst gives the 1,4-disubstituted pyrazole after a pyrolytic cleavage at elevated temperature.

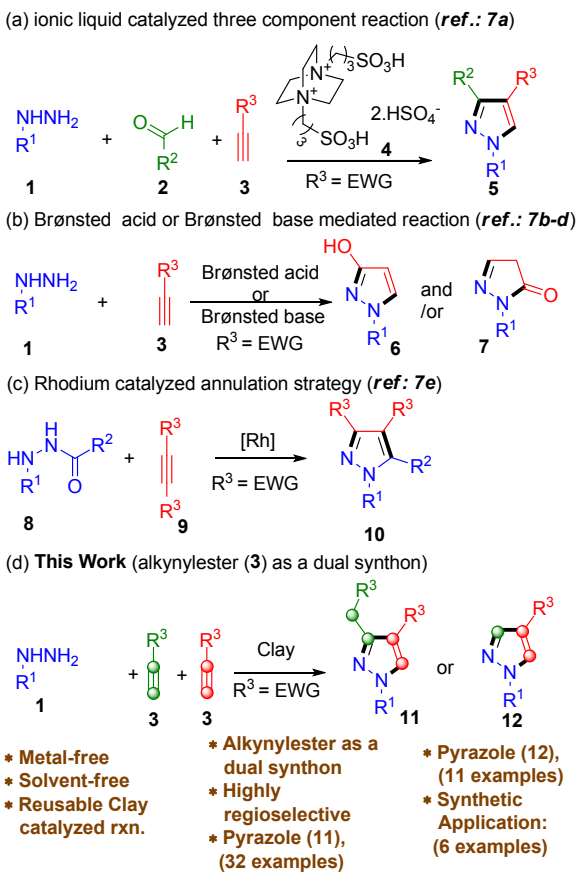
Pyrazole, a biologically interested structural motif has been extensively studied for the pharmaceutical and agrochemical applications.[1] In particular, its derivatives act as hypnotic, anti-inflammatory, sedative and analgesic agents.[2] Noteworthy examples of commercial blockbuster drug molecules possessing the pyrazole core structure are Rimonabant,[2a] Novalgin,[2b] Viagra,[2c] Celebrex,[2d] Fipronil,[2e] Difenamizole[2f] and Lonazolac.[2f] On the other hand, some of the pyrazoles with high thermal as well as hydrolytic stability were found to act as a coordinating ligand for various applications.[3] Furthermore, protonated form of pyrazole derivatives played a crucial role on self-assembly of variety of supramolecular frame work.[4]

The common strategy for the construction of pyrazole ring is based on the condensation reaction between phenylhydrazine (**1**) and 1,3-dicarbonyl compound[5a] or enone derivatives.[5b,c] However, these reactions involve multistep precursor synthesis, harsh reaction condition, use of transition metal sources and poor regio-selectivity. Besides, many other methods for the synthesis of pyrazoles have also been reported.[6] In particular, reaction of alkynyl or alkenylester with the bifunctional nucleophilic[7b] compound phenylhydrazine (**1**) has been demonstrated in the following few synthetic strategies such as (i) ionic liquid **4** catalyzed three component domino reaction using hydrazine (**1**), aldehyde (**2**) and *α*-alkynylester (**3**) to produce 1,3,4-trisubstituted pyrazole derivatives (**5**) (Scheme 1a),[7a] (ii) Brønsted acid or base mediated two component strategy for the *aza*-Michael reaction using hydrazine (**1**) and alkynylester (**3**) followed by an intramolecular amide formation reactions to synthesize 1-phenyl-1*H*-pyrazol-5-ol (**6**)[7b,d] or pyrazol-5(4*H*)-one (**7**)[7c,d] respectively (Scheme 1b), (iii) rhodium catalysed annulation of phenylacetohydrazide (**8**) derivative of phenylhydrazine (**1**) with alkynylester (**3**) to produce pyrazole **10** (Scheme 1c),[7e] (iv) indium(III)/silver(I) catalyzed [2 + 2 + 1] annulation strategy with hydrazine and enaminoester (alkenylester) for the 1,3,4-trisubstituted pyrazole diester.[7f] To date, the reported methodologies for pyrazole synthesis use toxic organic solvents and/or transition metals which are in noncompliance with the need of green chemistry aspects.[8] Along this line, a domino reaction involving a phenylhydrazine (**1**) and an alkynylester (**3**) as dual synthon for the synthesis of new class of polysubstituted pyrazoles (**11** and **12**) is not known in the literature (Scheme 1d). Also, highly selective catalysts with added advantage of recyclability are crucial for the development of sustainable process. Therefore, environmentally benign, and cost effective reaction with readily available starting materials to construct new class of pyrazole derivatives are highly needed. As part of our interest in developing new methods for the synthesis of pyrazole and its derivatives,[9] here in, we report solvent free and recyclable montmorillonite K10[10a-i] clay catalyzed domino reaction for the synthesis of pyrazole derivatives. We found that the precursor phenylhydrazine (**1**) and alkynylester (**3**) undergoes double *aza*-Michael reactions and an unprecedented C-C bond formation reaction.

[a] *Department of Chemistry, School of Chemical and Biotechnology, SASTRA Deemed University, Thanjavur 613401, Tamil Nadu, India.*
[b] *Discipline of Inorganic Materials and Catalysis, Central Salt and Marine Chemicals Research Institute (CSMCRI), Council of Scientific and Industrial Research (CSIR), G.B. Marg, Bhavnagar - 364 002, Gujarat, India.*
[c] *Department of Chemistry, Sethu Institute of Technology, Kariapatti-626115, Tamil Nadu, India.*

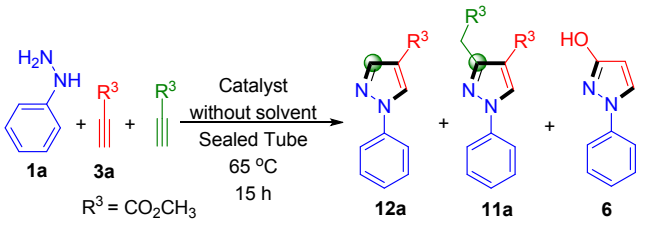
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Scheme 1. Different reactivity of phenylhydrazine (**1**) with α-alkynylester (**3**) for the synthesis of pyrazoles (**5-7**, **10-12**).



formation reaction There is a constant pursuit for the efficient and environmentally benign catalytic methodologies to reduce the energy consumption as well as to achieve high atom efficiency. In this regard, montmorillonite K10, an environmental compatible and cheap the heterogeneous clay catalyst, has been utilized in discovering newer synthetic methods because of its unique catalytic properties such as distinct charge characteristics, acidity,[10a,b] surface area with Brønsted acid centres,[10a] polarity and three-dimensional pore structure.[10c,d] Thus, the development of the domino process for the construction of pyrazole was examined using phenylhydrazine **1a** and alkynylester **3a** as model substrates with montmorillonite K10 clay as heterogeneous catalyst without any solvent (Table 1, entry 1). The reaction yielded 22% of **11a** along with trace amount of **6** which is the sole product in basic condition (Scheme 1, b). To our delight, we have also observed 12% of product **12a** (Table 1, entry 1) and this could be formed after a pyrolytic cleavage from a possible intermediate. The structure of the compounds was unambiguously confirmed by HRMS, NMR and X-ray spectroscopic analysis.[11] Other reagents such as iodine and *N*-bromosuccinamide (NBS) in the absence of solvent provided compounds **11a** and **12a** with poor selectivity or poor yield (Table 1, entry 2 and 3). The domino reaction showed the adverse effect of solvent as trace amount of both the products (**11a** and **12a**) were obtained when we used the iodine or NBS in the presence of solvents (1 mL) such as ChCl:Urea an eutectic mixture, acetonitrile, toluene and dimethylformamide at 65 ºC (Table 1, entry 5-9).

Table 1. Optimization of the reaction conditions.



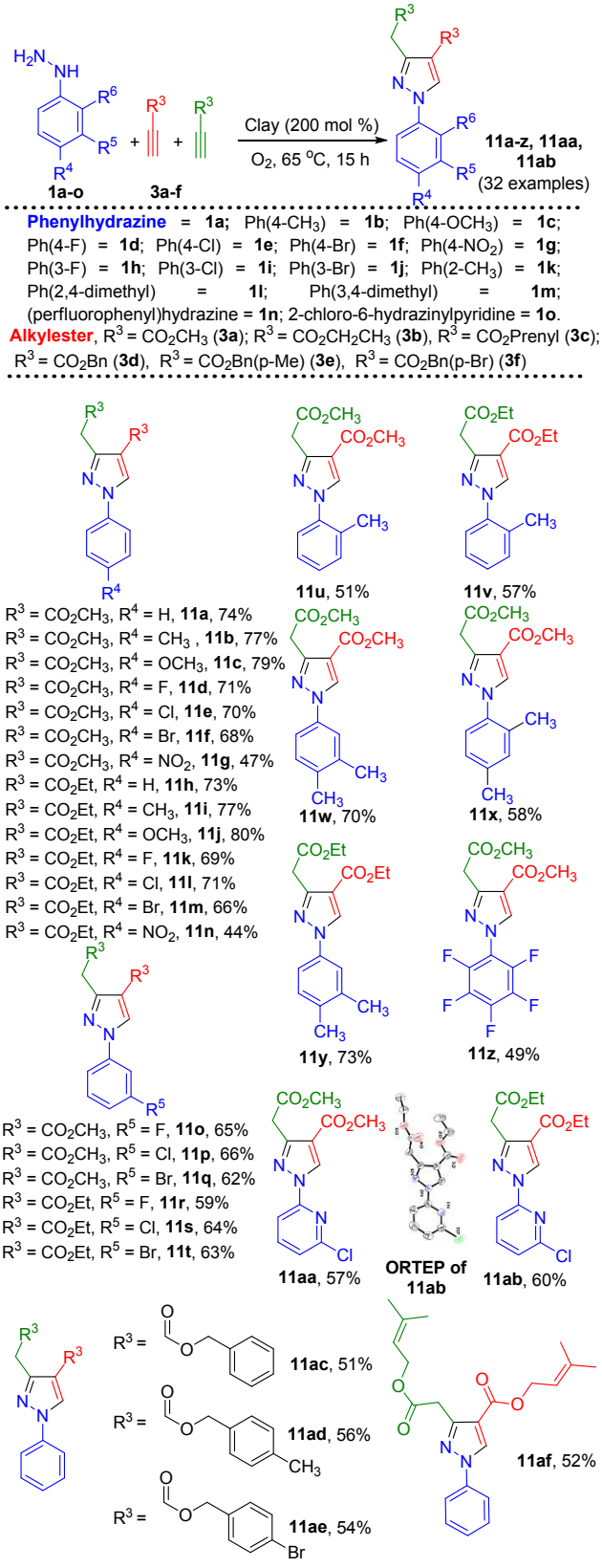
S. No	Deviation from the reaction conditions[a]	Yield %[b] 12a	11a	6
1	Clay, 25 °C, 72 h	12	22	<5
2	Iodine (100 mol %)	8	19	<5
3	NBS (10 mol %)	27	-	-
4	No catalyst, 24 h	-	-	<5
5	ChCl:Urea, Iodine (100 mol %),	-	-	12
6	CH_3CN, Iodine (100 mol %)	<5	<5	-
7	CH_3CN, NBS (100 mol %)	<5	<5	-
8	Toluene, Iodine (100 mol %),	<5	<5	-
9	DMF, Iodine (100 mol %),	<5	<5	-
10	**Sovent: tBuOH, tBuOK (1 mmol)**	**-**	**-**	**80**
11	Silica 230-400 mesh, 72 h	<5	21	-
12	Silica 60-12 mesh, 72 h	<5	22	-
13	Clay, 45 °C	17	30	-
14	Clay	19	45	<5
15	Clay, 3a = 2 mmol	10	35	-
16	Clay, 3a = 4 mmol	10	29	<5
17	Clay, 80-85 °C	27	30	<5
18	Clay, 120 °C	19	37	-
19	**Clay, O_2 atmosphere**	**<5**	**74**	**-**
20	Clay, N_2 atmosphere	15	14	-
21	Clay, NBS (10 mol %), 2 h	52	<5	-
22	Clay, NBS (5 mol %), 2 h	55	<5	-
23[c]	**Clay, NBS (5 mol %), 110 °C, 2 h**	**72**	**<5**	**-**

[a]**Reaction conditions:** phenylhydrazine **1a** (1 mmol), alkynylester **3a** (1 mmol), montmorillonite K10 clay (200 mol %), 65 °C, 15 h, [b]Isolated yield. [c]Complex reaction mixture at temp. more than 120 °C

On the other hand, the pyrazole **6** was exclusively obtained in a basic condition in alcoholic solvent (Table 1, entry 10) and the reaction proceeds *via* an amide formation followed by intra-molecular *aza*-Michael reaction. Then, the effect of other solid catalyst was studied and the obtained results indicated us that the silica gel meshes 60-120 as well as silica 230-400 were less effective than the clay (Table 1, entry 11, 12). Next, the temperature of the reaction was evaluated (Table 1, entry 13, 14, 17 and 18) and found 65 ºC as the optimal condition for better yields as well as the selectivity of the reaction at this initial stage (Table 1, entry 14). Furthermore, to improve the selectivity, we envisioned that, oxidative condition could

eliminate the reaction path for the formation of pyrazole **12a**. As expected, when we performed the reaction in the presence of oxygen gas (Table 1, entry 19), the compound **11a** was obtained in 74% yield with trace amount of **12a**. The obtained result clearly indicated us that the pyrazole **12a** is formed in a path for the formation of pyrazole **11a**, not after the formation of **11a**. Lower conversion was observed in a reaction in nitrogen atmosphere (Table 1, entry 20) and indicated the crucial role of oxidative condition for higher selectivity as well as the pyrazoles formation. The initial optimization experiment in 10 mol% NBS without any solvent (Table 1, entry 3) gave selectively **12a** with poor yield which encouraged us for further evaluation to improve the yield. As expected, when we tried the same reaction in the presence of the clay, pyrazole **12a** was obtained with improved yield of 52% with higher selectivity. Increasing and decreasing the catalytic loading of NBS (Table 1, entry 21, 22) did not improve the yield of **12a** significantly. However, the yield of the product was improved to 72% at elevated temperature which probably due to the facile elimination of an ethylacetate molecule. Complex reaction mixture was obtained at temperature more than 120 ºC and hence entry 23, table 1 was fixed as optimal condition for the selective formation of pyrazole ester **12a**. With these encouraging results, the scope of the reaction was examined (Scheme 2) with various substituted phenylhydrazine (**1a-o**) and alkynylester (**3a-f**) for the synthesis of pyrazole diester (**11**). The domino reaction using substituted phenylhydrazines with electron donating groups such as $-CH_3$ (**1b**) and $-OCH_3$ (**1c**) at *para* position progressed effortlessly and provided the respective pyrazole products (**11b, 11c**, **11i, 11j**) in very good yield. The halogen substituents in a chemical entity can be easily functionalized in a suitable coupling reaction conditions for various synthetic applications. Hence, halogen substitution such as -F, -Cl and -Br at *para* and *meta* position on phenylhydrazine (**1d-f**) were participated in the optimized reaction conditions along with alkynyl esters (**3a** or **3b**) and obtained the corresponding products (**11d-f**, **11k-m**, **11o-t**) in relatively lower yields than electron donating groups. Among the halogen substitutions, slightly lower yields were obtained for the *meta* substituted phenylhydrazines than the *para* substitution which may be due to the steric factor against the cyclization product. As expected, it was clearly reflected from reactions of *ortho* substituted phenylhydrazine (**1k**) with alkynylesters (**3a** or **3b**) and provided the corresponding products with lower yields 51% (**11u**) and 57% (**11v**) respectively. Moreover, treatment of disubstituted phenylhydrazines (**1l** and **1m**) with alkynylesters (**3a** or **3b**) found to be effective and gave the respective products (**11w-y**) in good yields. Interestingly, the (perfluorophenyl)hydrazine (**1n**) were also tolerated the cyclization reaction condition and provided pyrazole **11z** in noticeable yield of 49%. Furthermore, the heterocyclic hydrazine, 2-chloro-6-hydrazinylpyridine **1o** proceeded well with alkynylesters **3a** & **3b**, and 2-chloro-6-pyrazolyl pyridines (**11aa** & **11ab**) were isolated in 57% and 60% respectively. The ORTEP of **11ab** is shown in the Scheme 2. The scope of the reaction was then tested with prenyl (**3c**)

Scheme 2. Synthesis of pyrazolediesters (**11a-z, 11aa** and **11ab**) using phenylhydrazines (**1a-o**) and alkynylesters (**3a** and **3b**)

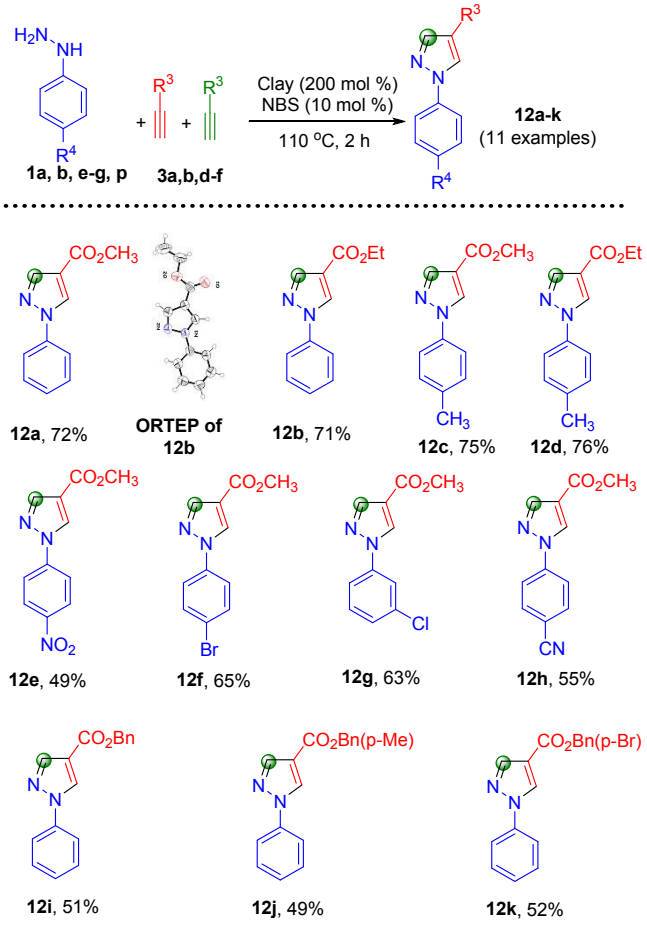


Reaction conditions: phenylhydrazine **1** (1 mmol), alkynylester **3** (1 mmol), montmorillonite K10 clay (200 mol %), 65 °C, 15h, under O_2.

and benzylated (**3e-f**) alkynyl esters and the respective pyrazoles were obtained in good yields (**11ac-11af**).

Next, we then focussed for the NBS catalyzed selective formation of pyrazole monoester (**12a-h**) (Scheme 3). As envisioned, phenylhydrazine with electrondonating group (**1b**) was found to be effective in the formation of pyrazole monoesters (**12c** and **12d**). As indicated in the Scheme 3, halogen substitutions were little less effective than electron donating group, nevertheless commendable yields of 65% and 63% of products **12f** and **12g** were obtained respectively. Interestingly, less reactive phenylhydrazine with electron withdrawing groups such as $-NO_2$ and –CN were also tolerated the reaction condition and provided products (**12e** and **12h**) with less yields. The ORTEP of **12b** is shown in the scheme 3.

Scheme 3. Synthesis of pyrazole monoester (**12a-h**) using phenylhydrazine and alkynylester (**3a** and **3b**).



Reaction conditions: phenylhydrazine **1** (1 mmol), alkynylester **3** (1 mmol), monomorillonite K10 clay (200 mol %), NBS (10 mol %) 110 °C, 2h.

The benzylated alkynes (**3d-f**) were tolerated the NBS catalyzed reaction conditions to produce the respective benzylated monoester pyrazole derivatives in good yields (**12i-k**). As depicted in scheme 4, pyrazole carboxylates (**11a/11f**, **12a**) could be easily functionalized to other useful chemical entities such as carboxylic acid (**14** and **16**) from saponification reactions, biaryl compound **17** using a Suzuki reaction, primary alcohols (**15** and **18**) using lithiumaluminumhydride reductive conditions and finally hydroxyl amide **13** from a reaction between the ester **12a** and hydroxylamine. Note to mention that all the entities were obtained in very good yield (Scheme 4).

Scheme 4. Functionalization of pyrazole esters.

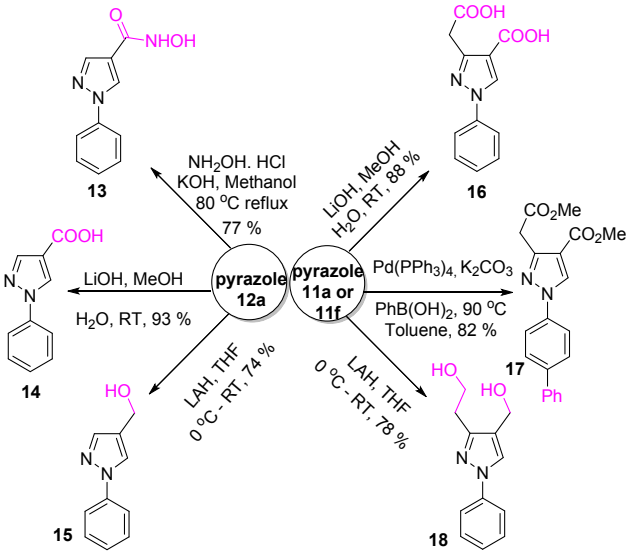
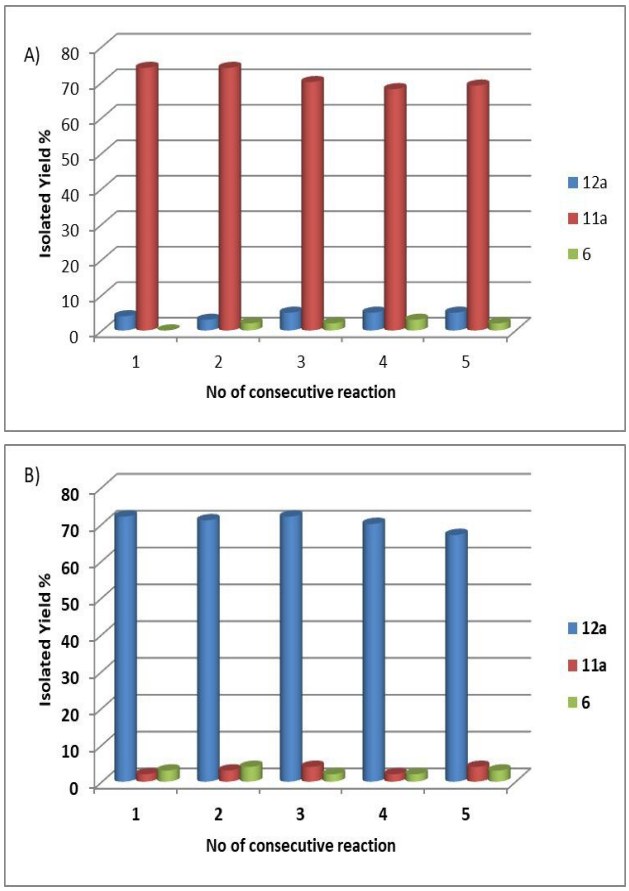


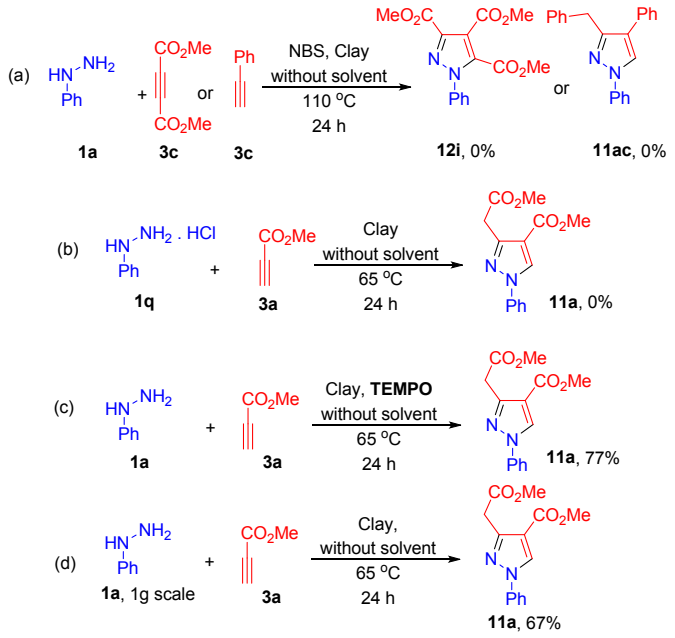
Figure 1. Activity and selectivity profile of montmorillonite K10 clay during the recycling process for the synthesis of 1,3,4-trisubstituted pyrazole (a) and the synthesis of 1,4-disubstituted pyrazole (b).



After establishing the scope of the reaction and functionalization, it is prudent to study the recyclability of the catalyst to know its stability under the reaction conditions. Therefore, reuse experiments were performed using phenylhydrazine **1a** and alkynylester **3a** as representative substrates (Figure 1). Once reaction gets completed under the optimized condition, the catalyst was collected and washed repeatedly with dichloromethane and dried in air. The recovered catalyst was reused for the five consecutive reactions without any significant loss in its activity (Figure 1).

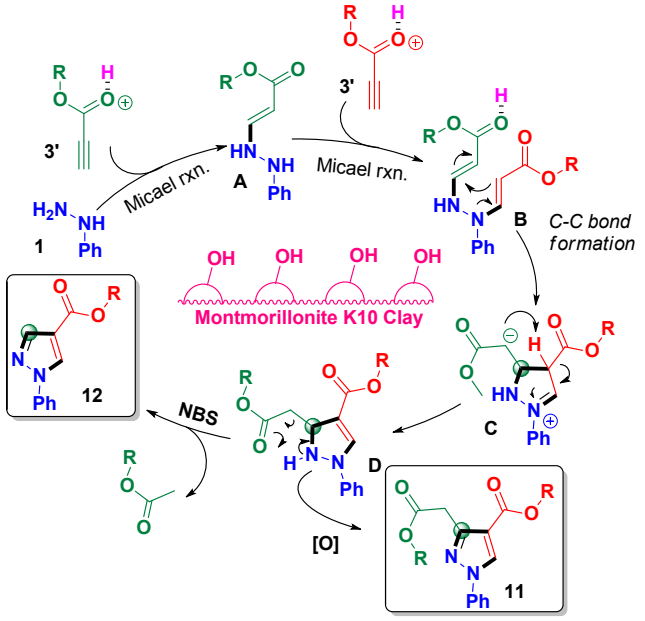
Next, we focused on the control experiments as well as to confirm the strategy whether robustic or not. From the scheme 5, a, it clearly indicated us that the electron withdrawing at R^3 of propiolate is necessary as the reaction could proceed in an *aza*-Michael reaction. We obtained a complex reaction mixture for disubstituted acetylene (**3c**, scheme 5, a) which possibly ended up in an intermediate stage as more steric crowd generation for the **12i** formation. Phenylhydrazine hydrochloride (**1q**) is not suitable for the reaction condition as strong bronsted acid (HCl) would reduce the nucleophilicity of nitrogen for *aza*-Michael reaction (scheme 5, b). Reaction in the presence of TEMPO, an oxidant as well as a radical quencher clearly indicated us that no radical path for the pyrazole formation. Finally robustic of the present synthetic strategy has been confirmed by performing 1 gram scale of **1a** in the standard condition and it provided **11a** in good yield. Based on the literature reports[10] and our experimental outcomes (Table 1) as well as the control experiments (Scheme 5) led us to propose a possible mechanism (Scheme 5) for the synthesis of pyrazole esters (**11** and **12**).

Scheme 5. Control experiments and other supporting reactions.



The heterogeneous montmorillonite K10 catalyst, a surface Brønsted acid center with unique pore size, can increase the oxophilicity by coordinating on oxygen of alkynylester (**3**) and fasten the first Michael reaction to produce intermediate **A**. The intermediate, enamine **A** undergoes another Michael reaction with protonated alkynylester (**3'**) with the help of solid Brønsted acid K10 catalyst to provide another intermediate **B**. It is noteworthy to mention here that such type of second Michael reaction under typical Brønsted acid condition is not known.[7] According to references, intramolecular C-N bond formation occurs after the first Michael reaction in the normal Brønsted acid mediated reactions.[7b-d] The distinct behavior of the K10 is probably due to the unique characteristic properties of the solid Brønsted acid.[10] Furthermore, the intermediate **B** is selectively converted into five membered intermediate **C** after an intramolecular C-C bond forming ring closed reaction through a nucleophilic attack of an enamine on a β carbon of acrylate group present in the intermediate **C**. The formed intermediate **D** after an intramolecular proton abstraction is easily oxidized to pryazole **11** without any cleavage in the oxidative condition (Table 1, entry 19). On the other hand, in presence of NBS (Table 1, entry 23) the reaction would probably undergo a retro Mannich type of cleavage[12] at elevated temperature to release pyrazole ester **12**.

Scheme 6. Proposed mechanism for the formation of pyrazole **11** and pyrazole **12**.



In conclusion, we have developed a method for the synthesis of 1,3,4-trisubstituted pyrazole and 1,4-disubstituted pyrazole derivatives from phenylhydrazine and alkynylester in montmorillonite K10 clay catalyzed domino reactions. The method utilizing alkynylester as a dual synthon for the first time can be a general approach for the selective synthesis of new class of polysubstituted pyrazole derivatives. The domino reaction requires inexpensive clay and easily available phenylhydrazine precursor. The scope of the reaction, functionalization of the pyrazoles, recyclability of the clay catalyst and possible pathway of the reaction has been demonstrated. The possible reaction pathway was explained

based on our initial experimental results. However, further experiments are in due course to gain better understanding of the reaction.

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11 For NMR spectra and data, HRMS, Melting point, Colour of the compounds: see the supporting information. Crystal information: CCDC No for the compound **11ab = 1966436**; CCDC No for the compound **12b = 1966437**.

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Solvent free and Montmorillonite K10 catalysed domino reactions for the synthesis of pyrazoles with alkynylester as a dual synthon

Sesuraj Babiola Annes,[a] Rajendhiran Saritha,[a] Saravanan Subramanian,[b] Bhaskaran Shankar,[c] Subburethinam Ramesh*[a]