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Montmorillonite K-10 supported palladium nanoparticles: A catalyst for the preparation of α-aminoynones employing copper free acyl Sonogashira reaction

Roopesh Kumar L, Nanda H Alavandimat & Vommina V Sureshbabu*
Peptide Research Laboratory, Department of Studies in Chemistry, Bangalore University, Jnana Bharathi, Bangalore 560 056, India
E-mail: sureshbabuvommina@rediffmail.com; haricc b@gmail.com

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Palladium nanoparticles supported by Montmorillonite K-10 (MMT K-10) are utilized for the synthesis of α-amino ynones using amino acid chlorides and a mild base at room temperature. All the compounds were obtained in good yields. Furthermore, the catalyst is also utilized for the deprotection of protecting groups operating in peptide chemistry.

Keywords: α-Amino ynones, Montmorillonite K-10 clay, nanoparticles, acyl Sonogashira reaction, hydrogenation

A typical acyl Sonogashira coupling is the "ynone" formation by the reaction between acyl halide and an alkyne[1]. Ynone motif serves as a useful precursor in the multiple areas of chemistry such as polymers, dyes and multicomponent synthesis[2]. The ynone pharmacophore plays a significant role in the synthesis of plethora of bioactive heterocycles such as pyrroles[3], pyrazoles[4], isoxazoles[5], pyrrolinones[6], pyrimidines[7], quinolines[8]and 1,3-diethylnylallenes[9] as well as natural products[10].

Traditionally, ynones are synthesized by cross coupling reactions of acid halides with alkynes or metal acetylides[11]. Coupling with metal acetylides requires harsh conditions and involve time consuming procedures[12]. The most straight forward method for the synthesis of ynones is the carbonylative cross-coupling which involve a reaction of aryl triflate with phenyl acetylene in the presence of CO gas[13]. The disadvantage in the Sonogashira reaction is the necessity of use of copper salt as a co-catalyst, which makes the separation of the expected product more laborious. In addition, the combination of two metals i.e., Pd and Cu circumvents the reuse of the valuable catalyst[14].

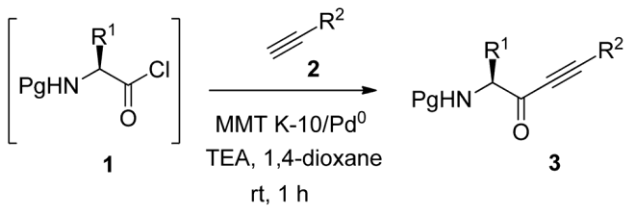
In the past few years, a number of new methods with improved catalytic systems have been explored like palladium nanoparticles (Pd NPs) supported by polyethylene glycol (PEG)[15], polystyrene[16], polyvinyl pyrrolidinone (PVP)[17] and amphiphilic-PS-PEG resin[18], for C-C bond forming reactions, dehalogenation and hydrogenation reactions.Our group had synthesized polyvinylchloride (PVC) and MMT K-10 supported Pd NPs and explored for cross coupling reactions, hydrogenation reactions,deprotection of protecting groups employed in the peptide chemistry and diarylalkynones[19].

Mandal et al., employed poly-1,4-phenylene sulphide (PPS)[20]Pd NPs, Bakherad and group engaged polystyrene supported Pd NPs [21] and silica supported zinc bromide[22], Tsai group[23] reported mesoporous silica material MCM-41 anchored palladium bipyridyl complex for copper free acyl Sonogashira reactions at elevated temperature.

Limited methodologies have been reported in the literature for the preparation of α-amino ynones. One such approach is the addition of organolithium and Grignard reagents to *N*-Boc-protected amino Weinreb amides obtained by the activation of *N*-Boc-protected amino acid at –78°C for 4h [24]. In another report, Spina et al.,used the same reagents to urethane-protected *N*-carboxyanhydrides at similar reaction conditions to obtain the products[25]. Georg et al., developed a strategy for the synthesis of β-amino ynones which are accessed via Weinreb amide formation and subsequent addition of ethyl magnesium bromide to β-amino acids[26]. These protocols, though efficient, suffer from disadvantages like time-consuming steps, multisteps, necessity of costly and hazardous reagents. We herein report a simple, mild and efficient protocol for the synthesis of α-amino ynones (Scheme I).

Results and Discussion

Initially, we reacted N^{α}-Fmoc-alanyl-chloride **1a** [27](1.0 mmol)with phenyl acetylene **2a**(1.2 mmol)in



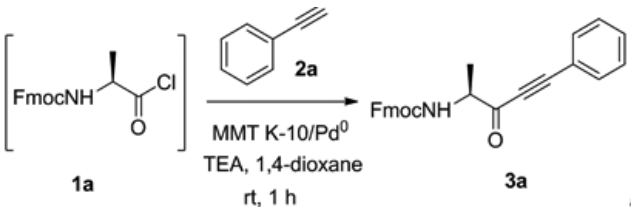
Pg = Fmoc or Boc group
R^1 = amino acid side chain
R^2 = Ph or Substituted Ph or alkyl

Scheme I — Schematic representation for the synthesis of α-amino ynones catalyzed by MMT K-10/Pd(0)

the presence of MMT K-10 Pd NPs(5 mg) and TEA (1.0 mmol) in 1,4-dioxane at room temperature, afforded only a modest yield of 55% of the desired product **3a**. We then performed a stoichiometric quantity of base and catalyst screening to optimize the reaction conditions for the coupling of **1** and **2**. In another reaction, when the stoichiometry of base and catalyst was increased to 2.0 mmol and 10 mg respectively, we obtained the corresponding amino ynone**3a** in 70% of yield. Further, when the catalyst loading was increased to 15 mg and base to 3.0 mmol, afforded the corresponding product **3a** in 88% of yield and the yield was same when catalyst loading was increased to 20 mg. Furthermore, on screening the reaction with different solvents *viz*. THF, 1,4-dioxane, DMF, ACN, toluene, ethanol and methanol. It was found that 1,4-dioxane was the optimum solvent and the desired α-amino ynone was obtained with 88% yield in the span of an hour duration of reaction time (Table I).

After the completion of reaction, as analyzed by TLC, the reaction mixture was filtered, washed with ethyl acetate. And, the filtrate was washed with water and brine solution, dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the crude was subjected to column chromatography using hexane and ethyl acetate as eluent to obtain the pure title compounds in good yield (Table II). The MMT K-10/Pd(0) was recovered and reused further for three cycles without palladium leaching. The XRD pattern of the catalyst after 3 cycles, showed peaks at 2θ values of 40°, 46° and 68°, that are related to (111), (200) and (220) facets of Pd(0), which indicates no deterioration of the catalyst.The ICP-OES analysis of the recycled catalyst after three cycles was found to be 15.8%.But, there was a slight decrease in the yield after three cycles. It took longer duration of reaction

Table I — Optimization of coupling reaction



Entry	Solvent	Time (h)	Yield (%)
1	THF	5	55
2	1,4-dioxane	3	88
3	1,4-dioxane	>6	Trace[a]
4	DMF	6	40[b]
5	ACN	6	56
6	Toluene	6	Trace
7	Ethanol	5-6	Trace
8	Methanol	5-6	Trace

a = Yield with Pd NP's without MMT K-10, b = yield obtained at 100°C

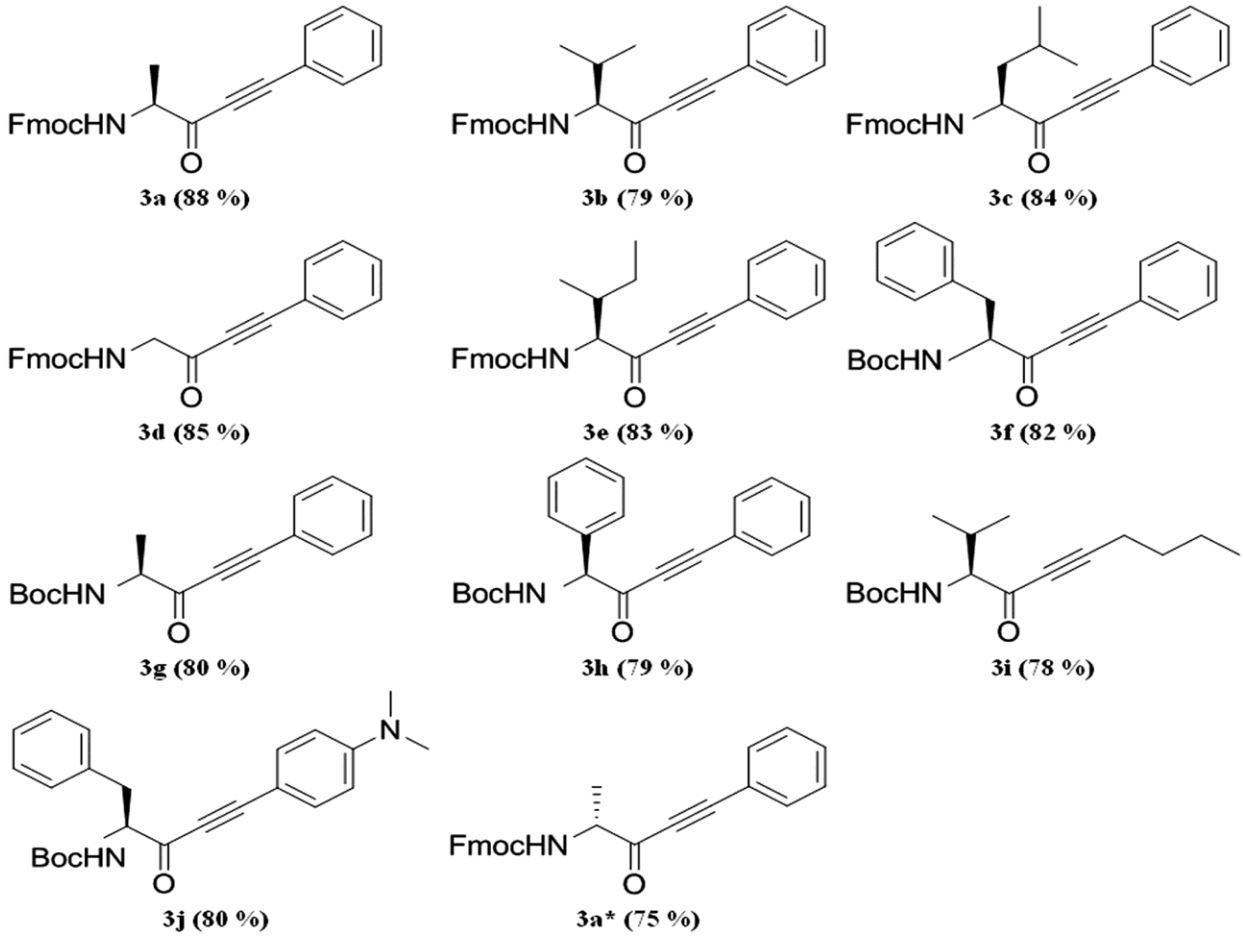
to complete the reaction when compared to the reaction using fresh catalyst. This may be due to the aggregation of metal nanoparticles within the matrix or accumulation of some organic species on the composite.

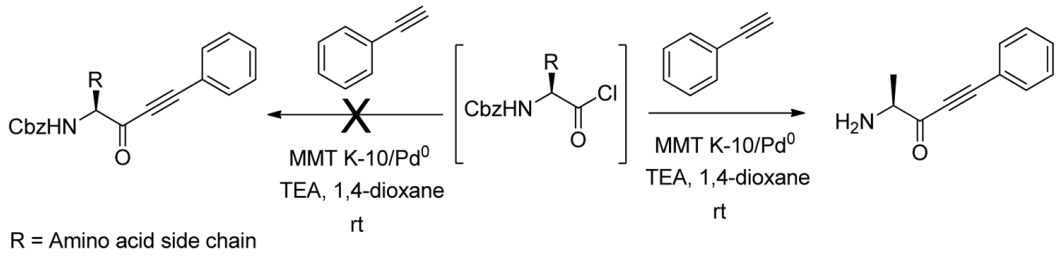
Racemization studies were carried out to investigate the optical purity of the compounds emerging from the current methodology. The RP-HPLC profiles were analyzed for the enantiomeric ynones **3a** and **3a***, which showed the single distinct peak with retention times (*Rt*) at 8.243 min and 7.189 min respectively. On the other hand, the consciously prepared equimolar mixture of **3a** and **3a*** showed the distinct peaks at (*Rt*) 8.210 min and 7.224 min respectively. These observations confirmed that the present method is racemization free and the isomers are optically pure.

The present strategy is applicable for the protecting groups employed in the peptide chemistry *viz*., Fmoc and Boc groups but subsequently failed in the Cbz protected compounds, we obtained Cbz deprotected α-amino ynone, confirmed by TLC analysis and mass spectral data (Scheme II).

With the result of Cbz deprotection, we further explored this catalyst for the deprotection of the protecting groups utilized in the peptide chemistry including Cbz, benzyl ester and benzyl ether. Our group reported the use of PVC-Pd^0 for the deprotection of protecting groups[19] whereas deprotection using MMT K-10/Pd^0 is yet to be reported. Catalytic hydrogenation is employed for deprotection and hence we employed MMT K-10/Pd^0 for the

Table II — List of N^{α}-protected amino ynones synthesized





Scheme II — Formation of unexpected Cbz deprotected α-amino ynone

deprotection of protecting groups used in peptide chemistry.

To start with, we used Cbz-Phe-OH as a model substrate, to this hydrogenation was carried out in the presence of MMT K-10/Pd^0 in ethanol. We successfully obtained the deprotected product H-Phe-OH within 30 minutes (Entry 1, Table III), which was adjudged by the TLC analysis. It was then isolated, filtered, evaporated the solvent and re-confirmed the product by matching the physical constants with the reported value and mass spectral data. And the Pd NPs were recovered after washings with water, ethanol, dried and reused directly in the subsequent reactions.

Catalyst worked well for the deprotection of benzyl ester in short duration in excellent yield (Entry 2, Table III); deprotection of Cbz protected di- and tetra peptides in good yields in about 35 and 100 minutes respectively (Entry 3-4, Table III). Cbz-Glu(OBzl)-OH and Boc-Thr(Bzl)-OMewere hydrogenated to Glu and Thr-OMe in good yields respectively (Entry 5-6, Table III).

Table III — Deprotection and catalytic hydrogenation reactions *via* MMT K-10/Pd^0

Entry	Protected	Deprotected	Yield (%)	Time (min)
1.	Cbz-Phe-OH	H-Phe-OH	100	30
2.	Cbz-Val-OBn	H-Val-OH	99	25
3.	Cbz-Phe-Ala-OMe	H-Phe-Ala-OMe	99	35
4.	Cbz-Ala-Asp(OBzl)-Ser-Gly-OH	Ala-Asp-Ser-Gly-OH	78	100
5.	Cbz-Glu(OBzl)-OH	H-Glu-OH	85	95
6.	Boc-Thr(Bzl)-OMe	Boc-Thr-OMe	100	50

Materials and Methods

All chemicals were used as obtained from Sigma Aldrich Company, USA. All the solvents were dried and purified using recommended procedures in the literature whenever necessary. Mass spectra were recorded on a Micromass Q-TOF micromass spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AV NMR 400 MHz and 100 MHz spectrometers, respectively, at the Indian Institute of Science, Bangalore. The RP-HPLC analysis of isomers was carried out by using an Agilent instrument at λ = 254 nm; flow rate: 0.5 mL/min; column: Phenomenex Lux Amylose-2, pore size-5 μm, diameter × length = 4.6 × 250 mm; method: gradient 0.1% TFA water-acetonitrile; Flow rate: 0.5 mL/min in 10 min. TLC experiments were performed using MERCK TLC aluminum sheets (silica gel 60 F254) and chromatograms were visualized by exposing in an iodine chamber or to a UV-lamp. Column chromatography was performed on silica gel (100–200 mesh) using ethyl acetate and hexane as the eluent.ICP-OES data were obtained from Shiva Analyticals (India) Ltd., Bangalore 562114,India using Perkin-Elmer OPTIMA 5300DV.

Experimental Section

Procedure for the preparation of MMT K-10/Pd^0 [19(c)]

A suspension of montmorillonite K-10 (500 mg) in ethanol (90 mL) was stirred for 30 min along with $PdCl_2$ (2.5 mmol). It was then refluxed for 20 min and a solution of $NaBH_4$ (3 mmol) in ethanol (6 mL) was added slowly. The initial brownish solution immediately turned colourless shows the reduction of Pd (II) to Pd (0). It was then allowed to cool to room temperature, and the black precipitate obtained was filtered. After simple washings with water and ethanol, black powder of Montmorillonite K-10/Pd^0 was obtained which was dried under vacuum and characterized.

Procedure for the preparation of N^{α}-protected amino ynones

A solution of amino/peptide acid chloride (1 mmol), aryl/alkyl acetylene (1.2 mmol), TEA (3 mmol) was stirred in 1,4-dioxane, 15 mg of MMT K-10/Pd^0 was added and the stirring was continued at roomtemperature. After the completion of the reaction (as analyzed by TLC), the reaction mixture was filtered, residue was washed with ethanol. Solvent was evaporated under *vacuo*and extractedinto ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum. The crude was subjected to column chromatography using n-hexane and ethyl acetate as eluent.

Procedure for deprotection reaction

A solution of Z-Phe-OH (200 mg) was treated with MMT K-10/Pd^0 (20 mg) in ethanol (5 mL) and the reaction mixture was stirred under hydrogen at room temperature for 30 min. After the completion of the reaction, (as identified by TLC analysis), it was filtered and evaporated under reduced pressure. And the product was confirmed by comparing the physical constants with the reported data.

Conclusion

We report a simple and efficient protocol for the preparation of α-amino ynones using MMT K-10 supported palladium nanoparticles in good yields. In addition, the catalyst was engaged for the cleavage of protecting groups Cbz (Z), benzyl esters and benzyl ethers.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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