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PMA-SiO₂ mediated MCR in PEG-400: A greener aza-Friedel-Crafts reaction leading to 3-arylmethyl/diarylmethyl indoles

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Abstract

A greener approach for the synthesis of 3-arylmethyl/diarylmethyl indoles has been achieved *via* a PMA-SiO₂ mediated three-component reaction (the aza-Friedel-Crafts reaction) involving indoles, aldehydes and *N*,*N*-disubstituted anilines in PEG-400. A variety of indole derivatives were prepared by using this operationally simple and straight forward methodology in acceptable yields.



20 examples; 60-68% yield

KEYWORDS: indole, aldehyde, aniline, MCR, PMA-SiO₂, PEG-400.

INTRODUCTION

Multicomponent reactions (MCRs) due to their well-known ability of creating diversity around a particular scaffold have attracted continuing interest in organic synthesis and medicinal / pharmaceutical chemistry.^[1-3] In fact MCRs can deliver library of molecules for various uses by saving time, energy and cost and are considered as preferred techniques not only in green chemistry but also for drug discovery efforts. However, all MCRs are not green and therefore improving the greenness of existing MCRs has become a major goal of both academic and industrial R&Ds.

While some limited pharmacological properties of 3-diarylmethyl indoles were studied^[4] way back in 1974 by Whitehead and Whitesitt, not much progress has been made thereafter to evaluate this class of compounds further. In 2004, 3-[(4fluorophenyl)(1*H*-imidazol-1-yl)methyl]-1-ethyl-2-methyl-1*H*-indole that is related to this class of indoles has been reported by Borgne *et al* as a potent, selective and nonsteroidal inhibitor of enzyme aromatase.^[5] The selective inhibition of COX-2 (cyclooxygenase-2) by 3-arylmethyl indoles have been reported by Campbell *et al* in the same year.^[6] One of the possible reasons for the lack of further pharmacological studies on this class of indoles is perhaps their limited access. Indeed, the synthesis of 3-arylmethyl/diarylmethyl indole from indole and aldehyde/ketone was not straightforward due to the high nucleophilicity of indole towards azafulven intermediate formed during the reaction leading to the formation of

bis(indolyl)methane.^[7] To overcome this difficulty Et₃SiH /TFA (trifluoroacetic acid) was utilized by Steele et al in 2004 for a rapid donation of hydride ion to the azafulven intermediate to form 3-arylmethyl indole.^[7] Similarly, TMSOTf/Et₃SiH was used to synthesize 3-arylmethyl indoles.^[6] In 2006, the reaction of indole, N,Ndimethylanilne and aromatic aldehyde (or its equivalent) termed as aza-Friedel-Crafts reaction was performed in the presence of copper(II)bis(trifluoromethanesulfonate) / 2,2'-bis-(diphenylphosphino)-1,1'-binaphthyl to give the 3-diarylmethyl indole derivative.^[8] Recently, TFA,^[9] HClO₄-SiO₂ (in MeOH),^[10] FeCl₃,^[11] binuclear Downloaded by [Dicle University] at 14:03 05 November 2014 complex of bis(ethylcyclopentadienyl)zirconium perfluorooctanesulfonate (in 1,2dichloroethane)^[12] and ZnCl₂^[13] have been utilized for aza-Friedel-Crafts reaction leading to the synthesis of 3-arylmethyl/diarylmethyl indoles. While many of these methods are efficient and useful, most of them however involved the use of nonenvironmental friendly catalyst or solvent. In some cases, in addition to their cumbersome preparation, catalysts are either air- or moisture-sensitive (thereby required strictly anhydrous reaction conditions) and cannot be recycled. Thus, development of more environmental friendly method for aza-Friedel-Crafts reaction leading to the synthesis of 3-arylmethyl/diarylmethyl indoles is highly desirable.

Recently the use of phosphomolybdic acid (PMA or $H_3PMo_{12}O_{40}$) that belongs to the class of heteropolyacids (HPA) has been explored as a reagent/catalyst in various organic transformations. Being several times stronger than the common acids such as H_2SO_4 , TsOH, BF_3 ·Et₂O and ZnCl₂, heteropolyacids can facilitate the reaction at lower concentration and temperature^[14] and therefore became key catalysts in the

development and commercialization of several synthetic methods.^[15-19] The use of PMA in combination with SiO₂ (e.g. silica supported phospomolybdic acid or PMA-SiO₂) in a MCR involving the reaction of arylaldehyde, *N*-methyl aniline and indole leading to 3-substituted indole derivatives i.e. *N*-((1*H*-indol-3-yl)arylmethyl)aniline (Scheme 1) has been reported earlier.^[20] We have observed that the use of *N*,*N*-disubstituted anilines (**3**) in place of *N*-methyl aniline in a similar MCR afforded the aza-Friedel-Crafts reaction products (**4**) in good yields (Scheme 1). It is evident that the *N*-monosubstituted aniline reacted though its amine nitrogen in the previously reported catalytic process whereas the *N*,*N*-disubstituted aniline reacted through its C-4 atom in the present reaction. Herein we report the preliminary results of this green synthesis.

RESULTS AND DISCUSSION

At first the MCR of indole (1a), benzaldehyde (2a) and *N*,*N*-dimethyl aniline (3a) was carried out using a range of catalysts, and solvents at various temperatures and the results are summarized in Table 1. When the reaction was carried out in the absence of any catalyst in PEG-400 at 120 °C, the product 4a was isolated in 15% yield (entry 1, Table 1). However, the yield of 4a was increased to 30% when Amberlite was used as a catalyst (entry 2, Table 1). A further increase in product yield was observed when Amberlite was replaced by PMA-SiO₂ (entry 3, Table 1). We were delighted with this observation as both PMA-SiO₂ and PEG-400 are considered as environmental friendly catalyst and solvent, respectively. This encouraged us to continue our study further. In the quest of improving the product yield further we examined the use of

other catalysts such as indian resin, clay (montmorillonite k10) and SiO₂. However, none of them were found to be effective (entries 4-6, Table 1). We also examined the use of other solvents like MeOH, i-PrOH, MeCN and water but were found to be less effective (entries 7-10, Table 1). We then examined the effect of variation of reaction temperature and the amount of catalyst used. After carrying out the reaction at various temperatures (entries 11- 14, Table 1), the range 90-95 °C (entry 3, Table 1) was found to be optimum though a slight increase of product yield was observed at 110-115 °C (entry 13, Table 1). Similarly, the use of 15 mol% (15 mg of catalyst for 100 mmol of indole **1a**) of catalyst was found to be optimum (entry 3, Table 1) as the decrease or increase in catalyst amount did not afford better yields (entries 15-18 and 3, Table 1). It is mention worthy that 3,3'-(phenylmethylene)bis(1*H*-indole) was obtained as a side product in these cases. To test the recyclability of the catalyst

used, PMA-SiO₂ was recovered by simple filtration and reused in the same reaction when **4a** was isolated without significant loss of its yield (entry 3, Table 1). Overall, a combination of PMA-SiO₂ (15 mol%) and PEG-400 was appeared to be optimal for the preparation of **4a** and was used further to expand the scope and generality of this methodology.

A range of indoles (1), aldehydes (2) and *N*,*N*-disubstituted anilines (3) were employed under the optimized reaction conditions and results are summarized in Table 2. While groups like Br or Me were tolerated on the indole ring (1), various electron-donating / withdrawing groups e.g. Cl, Br, OMe, NO₂ and CN present on the benzene ring of the reactant aldehyde **2** were found to remain unaffected under the condition employed (entries 2-8, Table 2). The use of heteroaromatic (entries 9, 10 and 19, Table 2) and aliphatic aldehydes (entry 20, Table 2) as well as formaldehyde (entries 11 and 15, Table 2) were also successful and afforded the desired indole derivatives (**4**) in acceptable yields. Notably, the corresponding bis(indolyl)methane derivative was isolated in 7-10% yield in all these cases.

Based on the previous findings^[13] a plausible mechanism for the present PMA-SiO₂ mediated MCR leading to the 3-arylmethyl/diarylmethyl indoles is shown in Scheme 2. The initial step involved the reaction of aldehyde **2** with indole **1** in the presence of PMA-SiO₂ leading to the formation of the azafulven intermediate **E-2** via **E-1** (in general, indole is known to reacts through its C-3 carbon due to the higher nucleophilicity of C-3 over C-2 caused by resonance). Subsequent reaction of **E-2** with the aniline **3** afforded **E-3** which on deprotonation yielded the desired product **4** with the regeneration of the catalyst. It is evident from this proposed reaction mechanism that the proton released from PMA-SiO₂ is the actual catalytic species in the present reaction. While the *N*,*N*-disubstituted amine moiety of **3** facilitated the attack through its C-4 atom (*via* positive mesomeric effect) in the present case, the *N*monosubstituted aniline however reacted though its amine nitrogen leading to a different type of indole derivatives.^[20]

CONCLUSIONS

In conclusion, we have described the first use of PMA-SiO₂ in the synthesis of 3arylmethyl/diarylmethyl indoles *via* a three-component reaction (the aza-Friedel-Crafts reaction) involving indoles, aldehydes and *N*,*N*-disubstituted anilines in PEG-400. The methodology does not require the use of any expensive catalyst, reagent or solvent. The catalyst PMA-SiO₂ can be recovered and reused. A variety of indole derivatives were prepared by using this operationally simple and straight forward methodology in acceptable yields. The curent methodology represents a greener and safer alternative to the existing methods leading to 3-arylmethyl/diarylmethyl indoles and may find usage towards the synthesis of more complex indole derivatives of chemical / pharmacutical interest.

EXPERIMENTAL

Preparation²¹ Of PMA-Sio₂

To a solution of $H_3PMo_{12}O_{40}$ (1.0 g, 0.1 equiv by wt) in Methanol (50 mL) was added silica gel (9.0 g, 0.9 equiv by wt, 60-120 mesh), and the mixture was stirred at room temperature for 4-5 hr. Evaporation of methanol under reduced pressure gave a dry yellowish powder which contained 10% w/w of PMA.

General Procedure For The Preparation Of 3-Arylmethyl/Diarylmethyl Indoles (4) A mixture of indole (1) (1.0 equiv), aldehyde (2) (1.2 equiv), *N*,*N*-dimethyl aniline (3) (1.3 equiv) and PMA-SiO₂ (15 mol%) in PEG-400 (4 mL) was stirred at 90-95 °C for time indicated in Table 2. After completion of the reaction, the mixture was cooled to room temperature, diluted with EtOAc (5 mL) and filtered. The filtrate was washed with water (10 mL) and the aqueous layer was extracted with EtOAc (2 x 5 mL). The organic layers were collected, combined, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate-hexane to give the desired product.

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SUPPORTING INFORMATION

Full experimental detail and spectral data for this article can be accessed on the publisher's website.

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Table 1. Effect of reaction conditions on the MCR of 1a, 2a and



Entry	Catalyst	Solvent	Temp (°C)	Yield (%) ^b
1	No catalyst	PEG-400	90-95	15
2	Amberlite (15 mol%)	PEG-400	90-95	30
3	PMA-SiO ₂ (15 mol%)	PEG-400	90-95	65 (64, 65, 63, 64 62) ^c
4	Indion resin (15 mol%)	PEG-400	90-95	32
5	SiO ₂ (15 mol%)	PEG-400	90-95	15
6	Montmorillonite k10 (15 mol%)	PEG-400	90-95	17
7	PMA-SiO ₂ (15 mol%)	МеОН	65	20
8	PMA-SiO ₂ (15 mol%)	i-PrOH	80-85	30
9	PMA-SiO ₂ (15 mol%)	MeCN	80-85	15
10	PMA-SiO ₂ (15 mol%)	H ₂ O	90-95	40
11	PMA-SiO ₂ (15 mol%)	PEG-400	65	30
12	PMA-SiO ₂ (15 mol%)	PEG-400	80-85	42
13	PMA-SiO ₂ (15 mol%)	PEG-400	110-115	67
14	PMA-SiO ₂ (15 mol%)	PEG-400	130-135	65
15	PMA-SiO ₂ (5 mol%)	PEG-400	90-95	48
16	PMA-SiO ₂ (10 mol%)	PEG-400	90-95	55

17	PMA-SiO ₂ (20 mol%)	PEG-400	90-95	67
18	PMA-SiO ₂ (30 mol%)	PEG-400	90-95	68

^{*a*}All the reactions were carried out using 1a (1.0 equiv), 2a (1.2 equiv) and 3a (1.3 equiv)

in a solvent.

^bIsolated yield.

^cThe catalyst was recovered and reused for an additional five runs and the figures within

parentheses indicate the corresponding yield for each run.



















mol%) in PEG-400 at 90-95 °C.

^bIsolated yield.

^cThe reaction was carried out at 40–60 °C for 11h.

^dThe reaction was carried out at 60–70 °C for 11h.



Scheme 1. PMA-SiO₂ catalyzed MCR of indole, arylaldehyde, and aniline derivative.



