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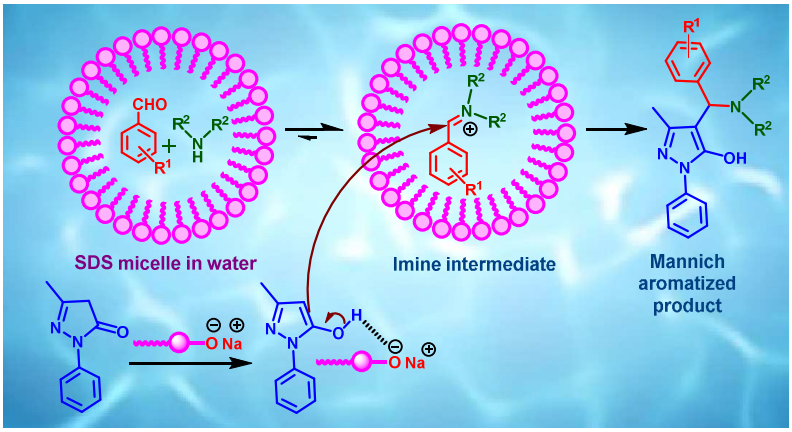
Amphiphile catalysed selective synthesis of 4-Amino alkylated-1H-pyrazol-5-ol via Mannich-aromatization prefer over Knoevenagel-Michael type reaction in water

Atul Kumar*, Shivam Maurya, Maneesh Kumar Gupta and Ratnakar Dutt Shukla



Abstract: An economic and efficient amphiphile (SDS) catalysed one pot synthesis of aromatized 4-amino alkylated-1H-pyrazol-5-ol via Mannich type preferable over Knoevenagel-Michael type reaction viz. aromatic aldehyde, secondary amine and 3-methyl-1-phenyl-5-pyrazolinone in water has been developed. In this selective Mannich aromatization, the reaction proceeds via micelle stabalized imine intermediate followed by nucleophilic addition of 3-methyl-1-phenyl-5-pyrazolinone and aromatization in water.

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An economic and efficient amphiphile (SDS) catalysed one pot synthesis of aromatized 4-amino alkylated-1H-pyrazol-5-ol via Mannich type preferable over Knoevenagel-Michael type reaction viz. aromatic aldehyde, secondary amine and 3-methyl-1-phenyl-5-pyrazolinone in water has been developed. In this selective Mannich aromatization, the reaction proceeds via micelle stabalized imine intermediate followed by nucleophilic addition of 3-methyl-1-phenyl-5-pyrazolinone and aromatization in water.

Pyrazole scaffolds have been considered as an important framework in pharmaceutical[1a,b] and agrochemical industries[1c,d].Various pyrazole substructure derivatives find application in therapeutical areas such as antimicrobials, anti-inflammatory agents, central nervous system, analgesics and oncology drugs. Various leading clinical and commericial drugs include celecoxib[2a] (Cox-2 inhibitors), rimonabant[2b] (anorectic antiobesity drug), PNU-32945[2c] (HIV-1 reverse transcriptase inhibitors), Ionazolac[2d] (NSAIDs), Zoniporide[2e] (NHE-1 inhibitors)(Fig. 1). Pyrazole also acts as a constituent & receptor in transition metal[3a] and supramolecular chemistry[3b] respectively. Therefore new approaches for the efficient synthesis of different pyrazole scaffolds with diverse substitution pattern is still a challenging task involving various synthetic steps or via multicomponent reaction[3c,d].

Out of various named multicomponent reactions, Mannich reaction provides most important and powerful synthetic methodology for the construction of novel nitrogen containing diverse biologically active organic scaffolds, reported in organic solvent[4a,b] as well as in water[4c,d].

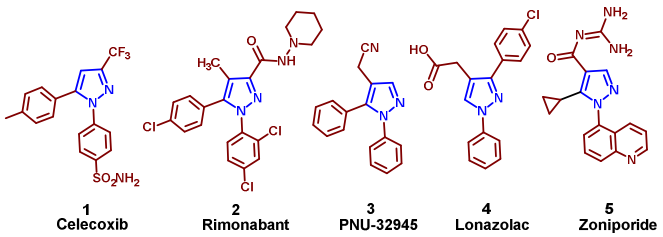
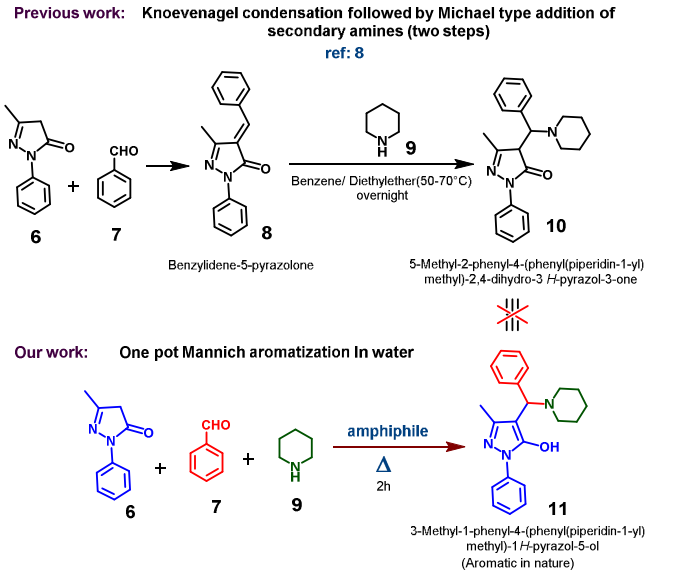


Fig. 1 Some pyrazole containing drugs

Water, essential for life, is an ultimate green solvent involved in biochemical reactions but is still not frequently used as a sole solvent for organic synthesis due to solubility issues as solubility is prerequisite for reactivity. Using amphiphile[5] is the best solution to overcome this problem. Amphiphile not only provides miceller lipophilic core for water insoluble organic reactants but also accelerates the reaction by miceller catalysis[6] in water.

One pot amphiphile catalysed Mannich aromatization involving 3-methyl-1-phenyl-5-pyrazolinone is still rare in literature whereas Knoevenagel condensation followed by Michael type addition of various nucleophiles or with itself is extensively reported[7]. Using this methodology, in 1959, Ahmed Mustafa et al[8] has reported action of secondary amines on 1-phenyl-3-methyl-4-arylidene-5-pyrazolones and synthesized 4-amino aryl methyl-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one **(10)** in moderate yield.

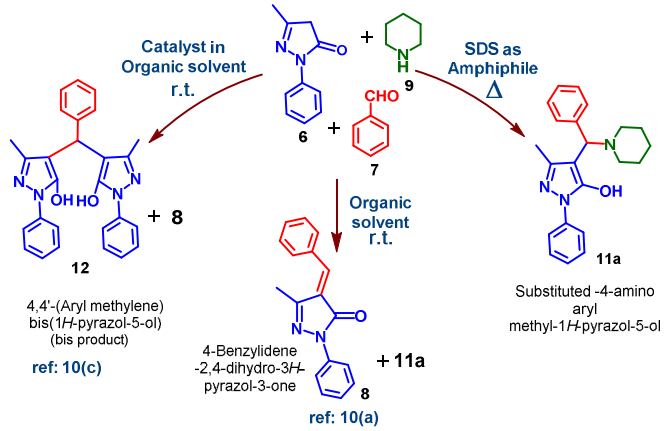


Scheme 1

We wish to report here in a highly efficient & economic procedure for the preparation of 4-amino alkylated-1H-pyrazol-5-ol derivatives via one pot three component Mannich type reaction using

amphiphile (SDS) in aqueous media in excellent yield, aromatic in nature & different from previous work (Scheme 1).

Our preliminary work was based on organocatalysis as well as multicomponent reactions (MCR's) using green approach for the synthesis of various biologically important heterocyclic compounds[9]. Inspiring from this, we attempted to synthesize 4-amino alkylated-1H-pyrozol-5-ol derivatives using SDS in water.



Scheme 2

Previously, in the absence of catalyst, solvents using MeOH, EtOH, ACN, DMF, benzene, toluene afforded **8**[10a,b] efficiently. In heating condition, dioxane, using as a solvent also afforded **11a** in trace amount along with **8**. Considering this point of observation and to choose a better solvent-catalyst system, we carried out the reaction in dioxane by using variety of catalyst (Table 1).

Table 1 Effect of catalyst on synthesis of 11[a]

Entry	Catalyst[b]	Solvent	Yield of 12/8(%)[c]	Yield of 11a(%)[c]
1	MSA	Dioxane	60/18	12
2	PTSA	Dioxane	58/20	11
3	$BF_3.Et_2O$	Dioxane	59/24	-
4	$FeCl_3$	Dioxane	54/20	-
5	$ZrCl_4$	Dioxane	70/21	-
6	Copper(II)triflate	Dioxane	53/21	-
7	Zinc(II)triflate	Dioxane	57/22	-
8	PMA	Dioxane	70/11	-
9	SiO_2-Cl	Dioxane	52/24	trace
10	$HClO_2$-SiO_2	Dioxane	62/22	trace
11	CellSA	Dioxane	72/11	9
12	StarSA	Dioxane	70/12	10
13	SSA	Dioxane	74/10	9
14	DBSA[d]	Water	42/-	28

[a] Reaction conditions: The reaction was conducted with benzaldehyde (1 mmol), 3-methyl-1-phenyl-5-pyrazolinone (1 mmol), piperidine (1.2 mmol) in solvent (2 ml) at r.t. [b] 10 mol% were used. [c] isolated yield. [d] Reaction mixture was heated to 80°C. Abbreviations used in table: MSA = Methane sulphonic acid; PTSA = p-Toluene sulfonic acid; PMA = Phosphomolybdic acid; CellSA = Cellulose sulphuric acid; StarSA = Starch sulphuric acid; SSA = Silica sulphuric acid; DBSA = p-dodecylbenzenesulfonic acid.

Starting from the catalytic amount of brønsted acid using MSA and PTSA did not improve the yield of desired product (**11a**). The bis-product[10c,d] (**12**) was obtained in this case as major product (Table 1, entries 1 & 2). All the non-metal/metal/heteropoly lewis acids ($BF_3.Et_2O$, $FeCl_3$, $ZrCl_4$, Copper(II)triflate, Zinc(II)triflate and PMA) used in the reaction gave only bis-product (**12**) (Table 1, entries 3, 4, 5, 6, 7 & 8). The addition of catalytic amount of silica-supported acids (SiO_2-Cl & $HClO_2$-SiO_2) also did not suit for the reaction medium, afforded bis-product (**12**) with trace amount of **11a** (Table 1, entries 9 & 10). Moving towards the solid supported Brønsted acid (Cell SA, Star SA & SSA), eco-friendly and reusable catalyst, also leaded the reaction to achieve bis-product very efficiently (Table 1, entries 11, 12 & 13). Whereas when we carried out the reaction in water using DBSA (acting as surfactant as well as brønsted acid) in heating condition, surprisingly, we obtained the product (**11a**) in higher amount (28%) comparable to any another catalyst used.(Table 1, entry 14).

This result encouraged us to optimize the reaction conditions by using different type of amphiphilic surfactants to improve the yield of desired product. In order to study the effect of surfactants (non-ionic, cationic, anionic), the reaction was carried out in water using benzaldehyde, 3-methyl-1-phenyl-5-pyrazolinone, and piperidine (summarised in Table 2).

Table 2 Effect of amphiphilic surfactants on synthesis of 11[a]

Entry	Surfactant[b]	Time (h)	Yield of 11a/12(%)[c]
1	Triton X-100	8.5	53/trace
2	Tween 80	8.5	52/trace
3	Tween 20	8.5	48/trace
4	Triton CF-10	8.5	41/trace
5	CTAB	5.0	52/trace
6	TBAB	5.5	54/trace
7	TBAF	5.5	53/trace
8	$Sc(DS)_3$	6.5	41/12
9	SDS	2.0	68/-
10	SDS/PMA[d]	4.5	55/30
11	SDS/DBSA[d]	4.5	58/33
12	SDS/XSA[d]	4.0	57/27
13	SDS[e]	4.5	42/10
14	SDS[f]	2.0	52/-
15	SDS[g]	2.0	78/-
16	SDS[h]	2.0	91/-

[a] The reaction was conducted with benzaldehyde (1 mmol), 3-methyl-1-phenyl-5-pyrazolinone (1 mmol), piperidine (1.2 mmol) in water (2 ml) at 80°C. [b] 10 mol% were used. [c] isolated yield. [d] 10:12 mol% were used. [e] the reaction was conducted at r.t. [f] 5 mol% catalyst. [g] 15 mol% catalyst. [h] 20 mol% catalyst. Abbreviations used in table: Triton-X-100 = [$C_{14}H_{22}O(C_2H_4O)_n$] where n = 9-10; Tween 80 = Polyoxyethylene(20)sorbitanmonooleate (Polysorbate 80); Tween 20 = Poly oxyethylene(20)sorbitanmonolaurate (Polysorbate 20); Triton CF-10 = Benzyl-polyethylene glycol tert-octylphenyl ether; CTAB = Cetyltrimethylammonium bromide; TBAB = Tetra-n-butylammonium bromide; TBAF = Tetra-n-butylammonium fluoride; $Sc(DS)_3$ = Scandium tris(dodecyl sulphate); SDS = Sodium dodecyl sulphate; PMA = Phosphomolybdic acid; DBSA = p dodecylbenzenesulfonic acid; XSA = Xanthan sulphuric acid.

Non-ionic surfactants (Triton-X-100, Tween 80, Tween 20 and Triton CF-10) were not found very much effective and provided poor to average yield of required product (41 to 53%) (Table 2, entries 1, 2, 3 & 4). It has been seen that in case of non-ionic surfactants, on increasing the temperature, decrease in head-group hydration occurs. Thus these surfactants separate out as a pure phase from aqueous solution, finally affects the yield of product. The product **11a** was also obtained but in poor yield, when cationic surfactants for example CTAB, TBAB & TBAF (acting as phase transfer catalyst[10e]) were employed (Table 2, entries 5, 6 & 7). A lewis acid surfactant; $Sc(DS)_3$ also did not suit for the reaction medium (Table 2, entries 8). Fortunately when we used SDS as a anionic surfactant in water on heating condition, both the yield and reaction time were improved (Table 2, entry 9). But the product formation and time factor were not adequate, when SDS was employed at r.t. (Table 2, entry 13). Considering this point of observation, we increased the amount of SDS to 15 to 20 mol % &

also decreased to 5 mol% at 80°C and demonstrated that the yield of product **11a** increased 78 to 91% (Table 2, entries 15 & 16) and decreased to 52% (Table 2, entry 14) respectively. Meanwhile, we also employed the combination of anionic surfactant along with various acids by using SDS/PMA, SDS/DBSA and SDS/XSA (Table 2, entries 10, 11 &12) but the product formation was not satisfactory. Therefore SDS was proved to be the best amphiphile for the formation of substituted 4-amino alkylated-1H-pyrazol-5-ol derivatives using solvent as water (Table 2, entry 16) (Scheme 2).

Amphiphilic properties of surfactant largely depends upon HLB values[11] for its hydrophilic and lipophilic character. A high HLB value of the surfactant indicates strongly hydrophilic character while a low value is an indication of a strong hydrophobic nature. According to HLB scale, the classification of used surfactants in Table 2 are shown in Fig 2. The large HLB value of SDS shows that it is readily soluble in water relative to other and again being an ionic surfactant its CMC is also not much affected with increase in temperature employs its use in organic synthesis.[12]

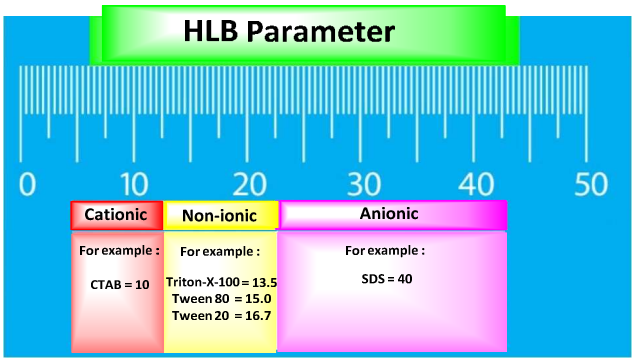
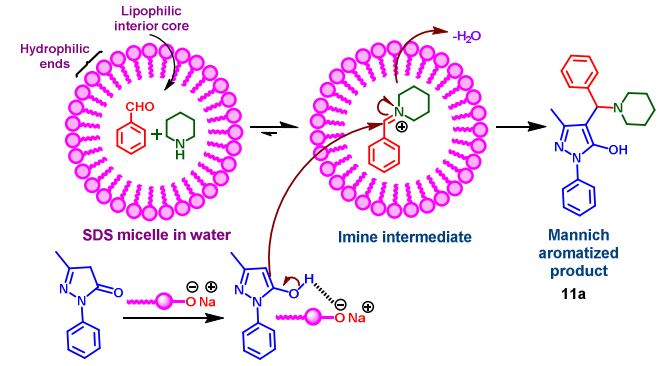


Fig. 2 A quick comparison of used surfactants on the basis of HLB values

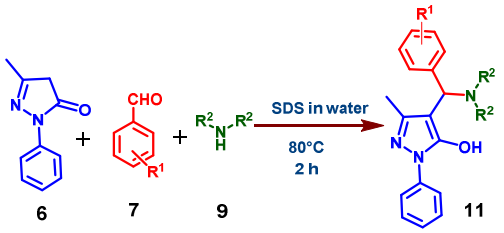


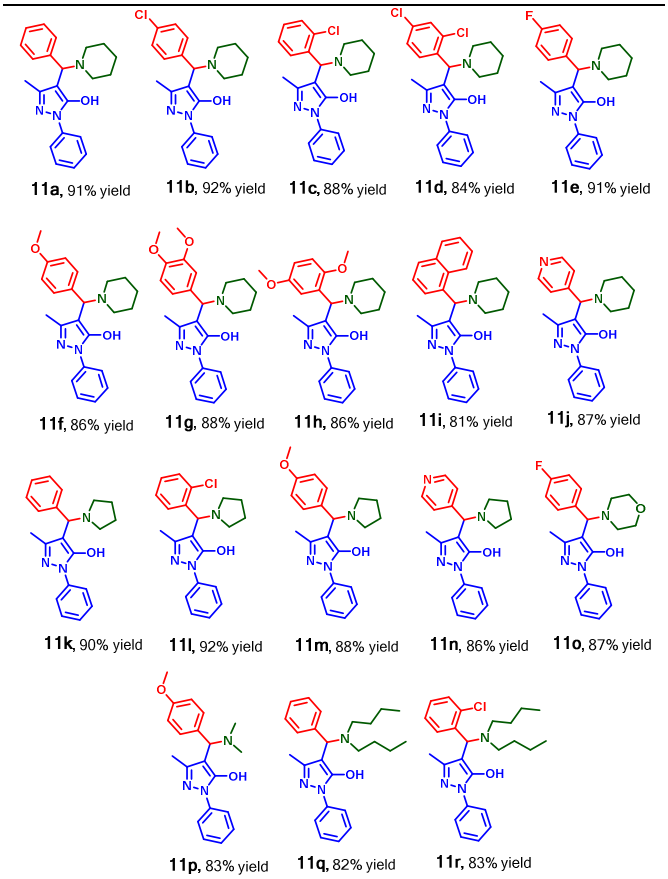
Scheme 3 Effect of SDS on reaction medium

Previously the mechanism for the direct esterification of carboxylic acids with alcohols has been reported by Kobayashi et al[13a] using a surfactant type Brønsted acid catalyst in water. Inspiring this fact, we proposed the plausible mechanism as shown in Scheme 3.

SDS is an amphiphilic surfactant, formed micelle in water in which hydrophilic end arranges itself outward and lipophilic end arranges itself inward side of the micelle. In the lipophilic pocket of micelle, corresponding aldehyde & secondary amine easily enters forming an imine. The water molecule, generated due to imine formation easily expelled from lipophilic interior pocket to outward side of micelle[13b]. Therefore equilibrium position[14] shift towards the imine side. SO_3O^- of SDS activates 3-methyl-1-phenyl-5-pyrazolinone by formation of hydrogen bond with pyrazolic OH favouring nucleophilic addition towards imine followed by aromatization[15] (no need for further step) giving the required substituted amino alkylated-1H-pyrazol-5-ol (Mannich type of product). Supported by the computational study, the molecular volume of imine intermediate is approximately 170 Å^3 (calculated by Discovery studio 2.0) and reported hydrodynamic by Berkowitz et al[16] radii of micelle (SDS) is about 22.0 Å (volume 44620 Å^3). Therefore it reveals that imine intermediate is small enough to occupy space inside the lipophilic core of SDS micelles.

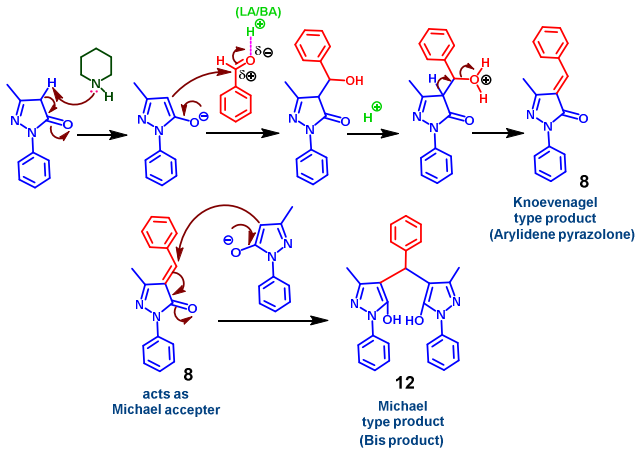
Table 3 SDS catalysed synthesis of 11[a,b]





[a] Reaction conditions: The reaction was conducted with aromatic aldehyde (1 mmol), 3-methyl-1-phenyl-5-pyrazolinone (1 mmol), secondary amine (1.2 mmol) and SDS (20 mol%) in water (2 ml) at temperature 80°C for 2 h. [b] All products are characterised by ^{1}H, ^{13}C, IR and Mass spectroscopy.

In absence of SDS, secondary amine acting as a base, abstracts a proton from 3-methyl-1-phenyl-5-pyrazolinone, position next to carbonyl finally attacks on activated carbonyl of aromatic aldehyde to form arylidenepyrazolone intermediate[10a,b] (Knoevenagel type). Again arylidenepyrazolone, acting as Michael acceptor reacts with another molecule of 3-methyl-1-phenyl-5-pyrazolinone in presence of base finally leads to the formation of 4,4'-(aryl methylene) bis (1-H-pyrazol-5-ol)[7,10c-e] (Michael type)(Scheme 4).



Scheme 4 Acid catalysed formation of bis product

Conclusions

In conclusion, we have developed an economic, efficient and green, amphiphile catalysed multicomponent reaction of aromatic aldehydes, 3-methyl-1-phenyl-5-pyrazolinone & secondary amine in aqueous media. SDS (Sodium dodecyl sulphate) is found to be very useful amphiphile to catalyse the reaction via imine intermediate through which the reaction proceeded in a more efficient and favourable manner via Mannich aromatization preferable over Knoevenagel Michael type reaction. The advantage of this method is to improve conditions for the synthesis of substituted 4-amino alkylated-1H-pyrazol-5-ol derivatives without the formation of bis product or any side product (Table 3).

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental section, characterization of all compounds, copies of ^{1}H and ^{13}C NMR spectra and Chiralpak IA HPLC for compounds. See DOI: 10.1039/b000000x/

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