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PII: S0040-4039(14)00759-X
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.04.122
Reference: TETL 44584

To appear in: *Tetrahedron Letters*

Received Date: 28 December 2013
Revised Date: 14 April 2014
Accepted Date: 30 April 2014

Please cite this article as: Tamaddon, F., Alizadeh, M., A four-component synthesis of dihydropyrano[2,3-*c*]pyrazoles in a new water-based worm-like micellar medium, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.04.122

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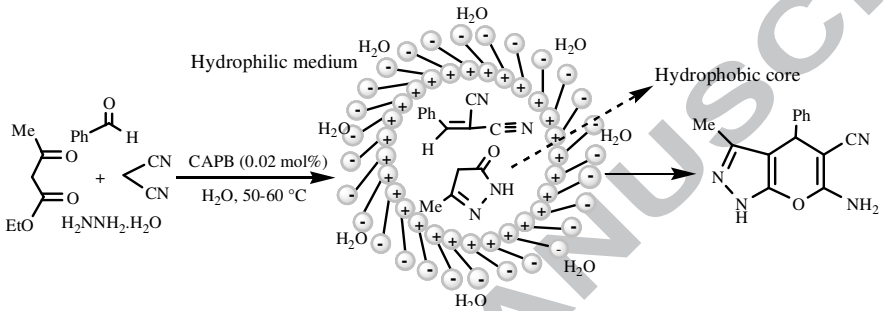

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A four-component synthesis of dihydropyrano[2,3-*c*]pyrazoles in a new water-based worm-like micellar medium

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Abstract—Cocamidopropyl betaine (CAPB) as a biodegradable surfactant produces a new worm-like micellar medium for rapid synthesis of dihydropyrano[2,3-*c*]pyrazoles via a four-component reaction of aldehydes, ethyl acetoacetate, malononitrile, and hydrazine hydrate at 50-60 °C. This zwitterionic surfactant was superior to anionic, cationic, and nonionic alternatives for accessing high yields of pure products without the use of any organic solvent. While the reaction medium was reusable, simple isolation of products, mild reaction conditions, low loading of CAPB for critical micelle concentration and short reaction times are additional advantages of this green procedure

Advances in multicomponent reactions (MCRs) have resulted in the rapid access to large libraries of bioorganic molecules, the development of molecular designs, and improvements in combinatorial chemistry.[1] Due to the benefits of MCRs, their combination with aqueous media constitutes one of the highlighted subclasses of ideal synthesis.[2]

Despite its unique properties, the instability and low solubility of organic compounds in water have restricted its use as a solvent.[3] These problems can be overcome by using organic co-solvents,[4] surfactants,[5] hydrophilic auxiliaries, and pH adjustment.[6] Among these, surfactants are very promising due to the reduction of water surface tension,[7] superior dispersion/interaction of organic compounds in water,[8] and their role as phase-transfer catalysts or micelle producers. Although surfactants are categorized as nonionic, anionic, cationic, gemini, nano, and zwitterionic,[9] the latter is more advantageous owing to the presence of both cationic and anionic regions in a molecule, large dipole moment, solubility at various pHs, salinities, and lower critical micelle concentrations (CMC). Moreover, zwitterionic surfactants create flexible micelles with various spherical, cylindrical, bilayers, vesicles, worm-like, and reverse shapes.[10]

The anti-inflammatory,[11] molluscicidal,[12] antimicrobial,[13] anticancer, fungicidal, analgesic, vasodilator, hypotensive, hypoglycemic,[14] and kinase inhibitor properties[15] of dihydropyrano[2,3-*c*]pyrazoles has resulted in the development of their synthesis as one of the important research topics of medicinal chemistry[16] (Figure 1).

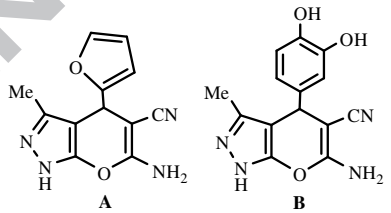

Figure 1. Biologically active dihydropyrano[2,3-*c*]-pyrazoles: (A) molluscicide, (B) inhibitor of human chk1 kinase.

Pyranopyrazoles have been synthesized via the reaction of tetracyanoethylene with 3-methyl-1-phenylpyrazolin-5-one,[17] or by the three-component reaction of a pyrazolone, carbonyl compounds, and malononitrile.[18] Recently, four-component reactions of aldehydes, 1,3-dicarbonyl compounds, malononitrile, and hydrazine have been developed for the synthesis of pyranopyrazoles[19] using L-proline,[20] piperidine, morpholine,[21] triethylamine,[22] imidazole,[23] γ-alumina,[24] cetyltrimethylammonium chloride (CTACl),[25] I_2,[26] and glycine.[27] However, more efficient syntheses of pyranopyrazoles using biocompatible catalysts are desirable.

Cocamidopropyl betaine (CAPB) is a biodegradable zwitterionic surfactant with viscoelastic properties[28] that self-assembles into flexible worm-like micelles, and increases the viscosity of water via a fluid-like polymeric transient network.[29] These significant properties result from the presence of both positive and negative charges in the molecule (Figure 2). CAPB has been used as a foam booster, an emulsifier, an antistatic agent in hair conditioners,[28] and as carrier vehicles for drug delivery.[30]

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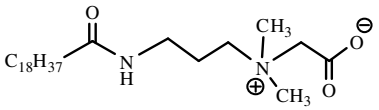
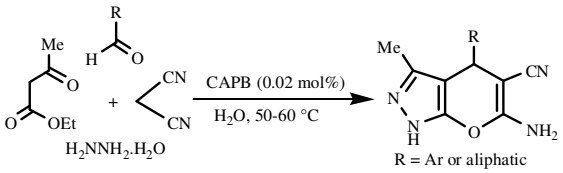


Figure 2. Cocamidopropyl betaine.

The unique properties of CAPB prompted us to use it in the green synthesis of pyranopyrazoles via the four-component reaction of aldehydes, ethyl acetoacetate, malononitrile, and hydrazine hydrate in water at 50-60 °C (Scheme 1). To the best of our knowledge, this is the first use of CAPB as a catalyst or surfactant in aqueous organic reactions.



Scheme 1. CAPB-catalyzed synthesis of dihydro[2,3-*c*]pyranopyrazoles.

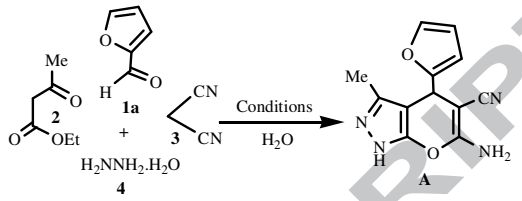
To optimize the conditions for the synthesis of the dihydropyrano pyrazole **A** as a molluscicide, condensation of furfural (**1a**), malononitrile, ethyl acetoacetate, and hydrazine hydrate in the molar ratio 1:1:1:2 in water was selected as a model reaction and screened with various types of surfactants. As Table 1 shows, the best yield of 6-amino-4-(furan-2-yl)-1,4-dihydro-3-methylpyrano[2,3-*c*]pyrazole-5-carbonitrile (**A**) was obtained after two minutes from the reaction with 0.02 mol% of CAPB in water at 50-60 °C (Table 1, entry 11). The precipitated product formed during the reaction was isolated in high purity by addition of cold water and filtration. For a reusability test, after completion of a model reaction in 10 mmol scale, the mixture was cooled and filtered. The filtrate was used as the recycled reaction medium in the second reaction run and compound **A** was isolated in the same yield without significant changes in the reaction time (Table 1, entries 11-13).

From a mechanistic point of view, condensation of hydrazine hydrate (**4**) with ethyl acetoacetate (**2**) and subsequent tautomerization results in the formation of enolate **8**, while Knoevenagel condensation of malononitrile (**3**) with furfural (**1**) provides the intermediate **6**. Michael addition of the intermediate **8** to electron-deficient alkene **6** generates intermediate **9**, which undergoes intramolecular cyclization to give the pyranopyrazole **A**. This explanation is presented in Scheme 2.

Comparison of the results of the CAPB-catalyzed reaction of benzaldehyde (1 mmol), malononitrile (1 mmol), ethyl acetoacetate (1 mmol), and hydrazine hydrate (2 mmol) with previously reported water-based methods shows the merit of the present protocol (Table 2).

Table 1

Optimization of the reaction conditions

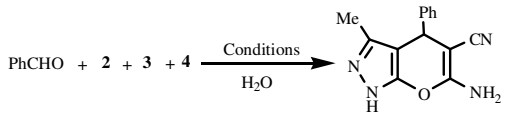


Entry	Conditions Surfactant (type/mol%)/Temp. (°C)	Time (min)	Yield (%)
1	-	260	74
2	CTAB[a] (cationic/0.05)/50-60	110	84
3	SDS[b] (anionic/0.05)/50-60	65	94
4	TritonX-100[c] (non-ionic/0.05)/50-60	25	90
5	TritonX-114[d] (non-ionic/0.05)/50-60	40	92
6	PEG-400 (non-ionic/0.05)/50-60	35	82
7	CAPB (zwitterionic/0.05)/50-60	10	98
8	CAPB (zwitterionic/0.04)/50-60	8	93
9	CAPB (zwitterionic/0.03)/50-60	8	95
10	CAPB (zwitterionic/0.02)/25-30	18	88
11	CAPB (zwitterionic/0.02)/50-60[e]	2	95
12	CAPB (zwitterionic/0.02)/50-60[f]	4	95
13	CAPB (zwitterionic/0.02)/50-60[g]	8	94
14	CAPB (zwitterionic/0.02)/70-80	12	97
15	CAPB (zwitterionic/0.02)/80-90	15	90

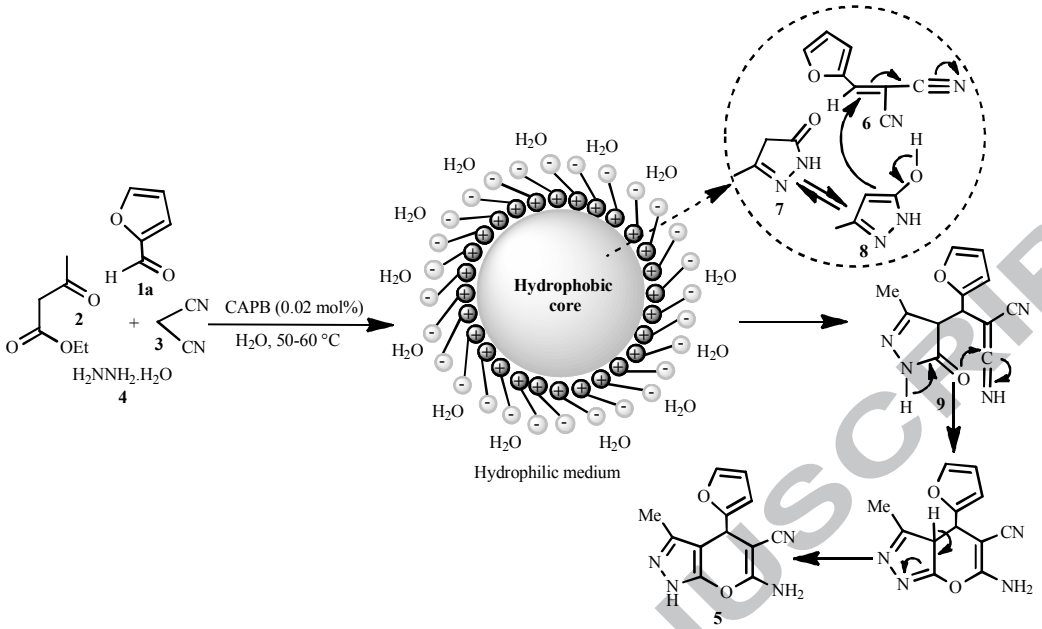
[a] Cetyltrimethylammonium bromide.
[b] Sodium dodecyl sulfonate.
[c] Polyethylene glycol *p*-(1,1,3,3-tetramethylbutyl)-phenyl ether ($C_{14}H_{22}O(C_2H_4O)_n$) with average 9.5 ethylene oxide units.
[d] $C_8H_{18}C_6H_4O(CH_2CH_2O)_{7.5}$.
[e] For the first reaction run.
[f] For the reused reaction medium in the second run
[g] For the reused reaction medium in the third run.

Table 2

Comparison of the efficiency of CAPB with other catalysts in water



Entry	Conditions Catalyst/Temp./Time/(mol%/°C/min)	Isolated yield (%)[Ref.]
1	imidazole (50/80/20)	89[23]
2	I_2 (5/25/5)	89[26]
3	L-proline (5/reflux/10)	90[20]
4	piperidine (10/r.t./5)	91[21]
5	morpholine (10/r.t./30)	62[21]
6	γ-alumina (10/reflux/50)	80[24]
7	CTACl (20/90/240)	89[25]
9	no catalyst (100/240)	76[19]
10	glycine (2/r.t./5)	90[27]
11	CAPB (0.02/50-60/4)	96 this work



Scheme 2. Cross section of the proposed worm-like micelle for CAPB in water.

The superiority of CAPB in water is reflected in the short reaction times and high product yields. The exceptional properties of CAPB are responsible for this superiority and the catalytic performance of CAPB can be due to the formation of high performance viscoelastic worm-like micelles[10] that increase the polarity and viscosity of water to provide a favorable medium to interaction of the organic reactants or intermediates.

To check the scope and efficiency of the CAPB surfactant, the reaction was performed under the optimized conditions using various substituted aromatic, heteroaromatic, and aliphatic aldehydes in water. The reactions proceeded rapidly for aromatic aldehydes with electron-withdrawing or electron-donating groups at different positions of the ring (Table 3, entries 1-16) and the desired products were isolated in excellent yields without any side product formation in very short reaction times. While a few reports are available on the synthesis of pyranopyrazoles from aliphatic aldehydes,[16,24] enolizable aldehydes such as acetaldehyde and butyraldehyde gave the desired products in excellent yields (Table 3, entries 17 and 18).

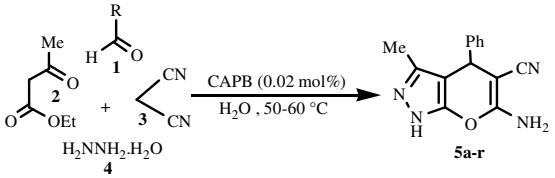
In conclusion, this protocol offers benefits for the rapid MCR synthesis of dihydropyrano[2,3-*c*]pyrazoles using cocamidopropyl betaine (CAPB) as a biodegradable surfactant in a new water-based worm-like micellar medium at 50-60 °C. This zwitterionic surfactant was superior to anionic, cationic, and nonionic surfactants for access to pure products without the use of any organic solvent. In addition, the reaction medium can be recycled.

General procedure for the preparation of 6-amino-1,4-dihydro-3-methyl-4-substitutedpyrano[2,3-*c*]pyrazole-5-carbonitriles

To a mixture of aldehyde (2 mmol), malononitrile (2 mmol), ethyl acetoacetate (2 mmol), and hydrazine hydrate (4 mmol) was added CAPB (0.02 mol%) in H_2O (1.5 mL) and the mixture was stirred at 50-60 °C for the given times (Table 3). After completion of the reaction (TLC monitoring), cold H_2O was added and the precipitated product was filtered off and washed with H_2O to give the product. The structures of the dihydropyrano[2,3-*c*]pyrazole products **5a-r** were identified by comparison of the spectroanalytical data those reported in the literature (Table 3).

Table 3

CTAB-mediated synthesis of pyranopyrazoles



Entry	R	Product	Time (min)	Yield (%)[a]	Mp (°C) (Lit.)[Ref]
1	2-furyl	**5a**	2	95	171-173 (175-177)[31]
2	C_6H_5	**5b**	4	96	244-246 (244-245)[24]
3	4-$O_2NC_6H_4$	**5c**	3	95	248-250 (251-252)[24]
4	2-$O_2NC_6H_4$	**5d**	3	91	221-225 (222-224)[32]
5	3-$O_2NC_6H_4$	**5e**	5	95	190-193 (190-192)[32]
6	4-ClC_6H_4	**5f**	5	95	234-236 (234-235)[24]
7	2-ClC_6H_4	**5g**	5	90	146-148 (145-147)[31]
8	3-ClC_6H_4	**5h**	5	89	175-178 (176-177)[33]
9	4-FC_6H_4	**5i**	4	97	171-172 (170-171)[31]
10	3-BrC_6H_4	**5j**	5	95	223-224 (223-224)[24]
11	4-$H_3CC_6H_4$	**5k**	9	87	205-208 (206-208)[24]
12	3-$H_3CC_6H_4$	**5l**	9	85	171-173 (170-172)[31]
13	4-$MeOC_6H_4$	**5m**	9	88	210-212 (210-212)[24]
14	4-HOC_6H_4	**5n**	5	94	223-225 (223-224)[13]
15	2-HOC_6H_4	**5o**	6	93	204-208 (208-209)[31]
16	3-HOC_6H_4	**5p**	5	95	225-228 (220-223)[33]
17	CH_3	**5q**	18	90	155-158 (158-160)[31]
18	$CH_3CH_2CH_2$	**5r**	15	91	140-142 (143-145)[24]

[a] All products were isolated in high purity by a simple filtration.

Acknowledgment

We acknowledge the research council of Yazd University.

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