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Note

A copper sulphate catalysed synthesis of derivatives of tetra substituted pyridine

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Copper sulphate has been found to be an effective catalyst in water-ethanol solvent system for the synthesis of various tetra-substituted pyridine derivatives *via* Michael addition of β-dicarbonyl compounds to α,β-unsaturated oximes and subsequent ring closure. A rapid synthesis of heterocycles by this methodology is ecofriendly in nature in addition to remarkably improved yield and reduced reaction times.

Keywords: Michael addition, copper-sulphate, unsaturated oxime solvent-system, tetra-substituted pyridine

The pyridine moiety containing scaffold is associated with diverse biological properties[1] and also present in several pharmaceutical and natural products[2]. Michael reaction is a very important and useful method of carbon-carbon bond formation, this involves the use of strong Brønsted bases like alkoxides, hydroxides catalysed conjugate addition of β-dicarbonyl compounds to activated olefins[3]. The use of strong bases is the main drawback of this reaction, because highly basic conditions cause the formation of several types of side products, and rearranged byproducts[4]. This problem could be resolved by the use of transition metals alongwith mild Lewis acid catalysts[5,6]. In recent years, copper salts as catalysts have been found to be more efficient[7,8] for the conjugate addition of β-dicarbonyl compounds with oximes to afford pyridine skeleton.

$CuSO_4.5H_2O$ is an inexpensive, water soluble and commercially available compound that can be used in the laboratory without any special precautions. This reagent has been used in important organic trans-formation processes such as synthesis of β-ketoesters *via* a diazo-decomposition process[9], conversion of aldehydes into diacetates chemoselectively[10] and in pyranylation/depyranylation[11]. But there are still only a few reports[12] describing the application of cupric sulphate pentahydrate in the synthesis of organic compounds.

Owing to the recent interest and in continuation of the work for the search of simple and practical pathways for the synthesis of bioactive heterocycle leads[13], it is wished to highlight herein the findings on the cupric sulfate pentahydrate catalyzed protocol for the synthesis of pyridine derivatives under mild conditions.

Results and Discussion

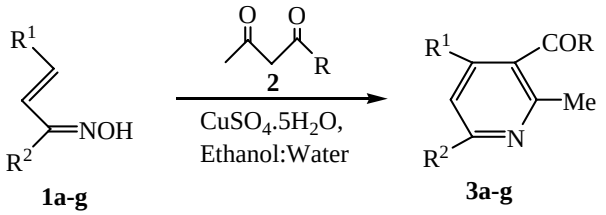
The reported literature has so far revealed that extensive studies have been carried out on the synthesis of these useful compounds. The Vilsmeier-Hack reaction[14] of conjugated oximes is a multi-step process and involves a Beckmann rearrangement of the starting oximes. In the case of oximes derived from cyclic α,β-unsaturated ketones, such a reaction is not possible. Recently amidazone was reacted with unsymmetrical tricarboxy compounds to provide a triazine, which subsequently reacted with norborn-adiene to afford pyridine derivatives[15]. Bryce and co-workers have reported the synthesis of pyridine derivatives from furan precursors[16]. Also, glutaralde-hyde can be cyclized to give pyridine in upto 53% yield by using an ammonium salt and malachite green or by iron (II) salts with halide counterions[17]. In a very recent report[18], an enamino ester and alkynone were reacted *via* Michael addition – cyclodehydration, catalysed by acetic acid / Lewis acid, but this Lewis acid catalysed cyclodehydration is found to be more sluggish and less efficient than the corresponding reaction conducted in acetic acid. Therefore, the practical application of these methods suffer from several limitations. In view of the current interest in substituted pyridine derivatives[19], there is a need for the development of a protocol using readily available and safe reagents, which leads to high yields of pyridine derivatives. A new one-pot reaction for the synthesis of tetra-substituted pyridine derivatives using $CuSO_4.5H_2O$ has now been developed and is described here. The reaction proceeds efficiently in high yields, without the formation of any by-products.

Reaction of enone oxime **1a-g** with ethylaceto-acetate **2** in the presence of $CuSO_4.5H_2O$ and

Table I — $CuSO_4.5H_2O$ mediated synthesis of various tetra-substituted pyridine derivatives **3a-g**.

Product	R	R^1	R^2	Reaction time (hr)	Yield[a] (%)
3a	OEt	Ph	Ph	4.0-4.5	82
3b	OEt	*p*-$CH_3OC_6H_4$	Ph	4.5-5.0	90
3c	OEt	*p*-ClC_6H_4	Ph	4.5-5.0	80
3d	OEt	thiophen-2-yl	Ph	4.0-4.5	85
3e	OEt	3-$NO_2C_6H_4$	Ph	5.0-5.5	80
3f	OEt	benzo[1,3]dioxol-5-yl	Ph	5.0-5.5	85
3g	OEt	2-OHC_6H_4	Ph	4.5-5.0	87

[a] isolated and unoptimized yields.



R: OEt
R_1: Ph, *p*-$CH_3OC_6H_4$, *p*-ClC_6H_4, thiophen-2-yl, 3-$NO_2C_6H_4$, benzo[1,3]dioxol-5-yl, 2-OHC_6H_4
R_2: C_6H_5

Scheme I

water:ethanol (1:1 v/v) solvent system produced the corresponding tetra-substituted pyridine **3** as a pale yellow viscous oil in 80-90% yield (**Table I**, **Scheme I**). Analysis of the crude product did not indicate the formation of any other products. This methodology is fairly general and the reaction conditions are tolerant towards the ether group. Attempts to perform the pyridine synthesis proved fruitless even when a large excess of $CuSO_4.5H_2O$ was used. Increasing the reaction time further did not improve the yields but instead resulted in decomposition of the starting materials. The catalyst efficacy is fairly general, 10 mole% catalyst ($CuSO_4.5H_2O$) is enough to promote the reaction effectively while the use of 5 mole% of catalyst is equieffective. The catalyst ($CuSO_4.5H_2O$) is non-corrosive non-toxic, readily soluble in taken solvent system and reaction proceeds efficiently.

The mechanism of the pyridine formation is not yet clear, although a possible scheme might be formulated firstly primary Michael addition of ethylacetoacetate **2** to the enone oxime **1** gives the adduct, which undergoes a ring closure accompanied by dehydration and subsequent migration of a proton to form the N-hydroxy derivative. Alternatively, the cyclic N-hydroxy derivative could arise from intramolecular cyclization of N-hydroxy enamine. Elimination of an extra water molecule from N-hydroxy derivative provides the formation of the substituted pyridine **3**.

The structures of the synthesised compounds **3a-g** were confirmed spectroscopically. Apart from IR, ^1H NMR and mass spectra, elemental analysis also gave satisfactorily data of the final products.

In conclusion, a novel and tunable system of catalyst and solvent has been used to integrate the reaction and facilitate the reduction of waste, with use of more benign solvents. A method has been developed which is not only more environment friendly but also has economic advantages in producing pure products with less expensive and harmful catalyst in short time periods.

Experimental Section

The temperature of the reaction-mixture was measured with a non-contact mini-gun type IR thermometer (model 8868). IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrometer using KBr pellets. ^1H NMR spectra were obtained on Bruker Avance Spectrospin 300 (300 MHz) using TMS as internal standard and chemical shift are in δ. Elemental analysis was performed on a Heraeus CHN-Rapid analyzer. Mass spectra were recorded on a TOF-MS. All reactants were purchased from Sigma-Aldrich and Lancaster and used as received. Solvents used in reaction are double distilled using vacuum distillation.

Typical experimental procedure for the synthesis of tetra-substituted pyridine, 3a-g

Ethylacetoacetate **2** (0.01 mole), $CuSO_4.5H_2O$ (0.05 mole) were added to enone oxime **1** (0.01 mole) and the reaction mixture was heated with vigorous stirring at 80-100°C for a given time (**Table I**, monitored by TLC). Thereafter, the unreacted ethylacetoacetate (traces) was removed under reduced pressure. The residue was then taken in diethyl ether (2 × 20 mL) and the resulting mixture was extracted with 1M HCl (3 × 20 mL). The combined acidic aqueous extracts were adjusted to *p*H 9 by means of aqueous ammonia and extracted with dichloromethane (2 × 20 mL). The dichloromethane extract was dried over anhydrous sodium sulphate and

concentrated on a rotary evaporator to afford the crude tetra-substituted pyridine derivative **3a-g** in 80-90% yield, which was then purified by column chromatography over silica gel using chloroform as eluent to give the pure final product **3a-g** as light yellow viscous oil.

Ethyl-2-methyl-4,6-diphenyl pyridine-3-carboxylate, 3a

IR (KBr): 1710, 1570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31 (m, 10H, Ar-H), 7.07 (s, 1H), 4.13 (q, J = 7.3 Hz, 2H, OCH_2CH_3), 3.81 (s, 3H, OCH_3), 2.71 (s, 3H, CH_3), 1.03 (t, J = 7.3 Hz, 3H, OCH_2CH_3); HRMS: M^+ 316.95. Anal. Calcd. for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.45; H, 6.04; N, 4.42%.

Ethyl-4-(4-methoxy-phenyl)-2-methyl-6-phenyl pyridine-3-carboxylate, 3b

IR (KBr): 1720, 1575 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.28 (m, 9H, Ar-H), 7.05 (s, 1H), 4.11 (q, J = 7.3 Hz, 2H, OCH_2CH_3), 2.69 (s, 3H, CH_3), 1.02 (t, J = 7.3 Hz, 3H, OCH_2CH_3); HRMS: M^+ 347.24. Anal. Calcd. for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found C, 76.03; H, 6.05; N, 4.05%.

Ethyl-4-(4-chloro-phenyl)-2-methyl-6-phenyl pyridine-3-carboxylate, 3c

IR (KBr): 1705, 1575 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 9H, Ar-H), 7.08 (s, 1H), 4.15 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 2.72 (s, 3H, CH_3), 1.05 (t, J = 7.2 Hz, 3H, OCH_2CH_3); HRMS: M^+ 351.99. Anal. Calcd. for $C_{21}H_{18}ClNO_2$: C, 71.69; H, 5.16; N, 3.98. Found C, 71.63; H, 5.15; N, 3.78%.

Ethyl-2-methyl-6-phenyl-4-thiophen-2-yl-pyridine-3-carboxylate, 3d

IR (KBr): 1715, 1560 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 (m, 8H, Ar-H + thienyl), 7.09 (s, 1H), 4.16 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 2.73 (s, 3H, CH_3), 1.07 (t, J = 7.2 Hz, 3H, OCH_2CH_3); HRMS: M^+ 322.99. Anal. Calcd. for $C_{19}H_{17}NO_2S$: C, 70.56; H, 5.30; N, 4.33; S, 9.91. Found C, 70.49; H, 5.33; N, 4.30; S, 9.90%.

(Ethyl-2-Methyl-4-(3-nitrophenyl)-6-phenyl-pyridine-3-carboxylate, 3e

IR (KBr): 1722, 1568 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 9H, Ar-H), 7.08 (s, 1H), 4.16 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 2.72 (s, 3H, CH_3), 1.06 (t, J = 7.2 Hz, 3H, OCH_2CH_3); HRMS: M^+ 361.88. Anal. Calcd. for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73. Found C, 69.64; H, 5.20; N, 7.70%.

Ethyl-4-benzo[1,3]dioxol-5-yl-6-phenyl-pyridine-3-carboxylate, 3f

IR (KBr): 1728, 1575 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$: δ 7.33 (m, 8H, Ar-H), 7.10 (s, 1H), 5.94 (s, 2H, OCH_2O), 4.14 (q, J = 7.3 Hz, 2H, OCH_2CH_3), 2.70 (s, 3H, CH_3), 1.05 (t, J = 7.3 Hz, OCH_2CH_3); HRMS: M^+ 360.58. Anal. Calcd. for $C_{22}H_{19}NO_4$: C, 73.13; H, 5.26; N, 3.87. Found C, 72.99; H, 5.16; N, 3.86%.

Ethyl-4-(2-hydroxy-phenyl)-2-methyl-6-phenyl pyridine-3-carboxylate, 3g

IR (KBr): 1696, 1565 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 9H, Ar-H), 7.09 (s, 1H), 4.12 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 2.68 (s, 3H, CH_3), 1.03 (t, J = 7.2 Hz, 3H, OCH_2CH_3); HRMS: M^+ 332.68. Anal. Calcd. for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found C, 75.63; H, 5.70; N, 4.18%.

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