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AN EFFECTIVE VILSMEIER-HAACK REAGENT (TCT-DMF)FOR THE FORMYLATION OF SUBSTITUTED COUMARIN

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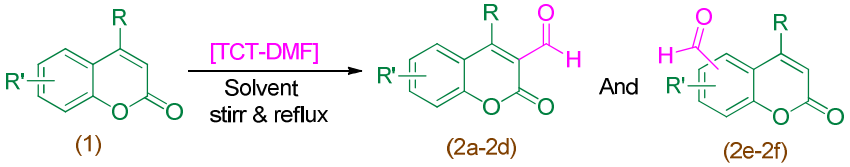
Abstract: Formylation of Coumarin derivatives have been synthesized by using effective Vilsmeier-Hack reagent [TCT-DMF] in dichloromethane under a simple stirring and reflux condition. The structures of all synthesized compounds were confirmed by IR, NMR and MassSpectrometry. This is a newly developed efficient method for the formylation of substituted coumarinusing environmentally benign reagent.

Keywords: [TCT-DMF] green reagent, formyl coumarin, conventional method.

Introduction:

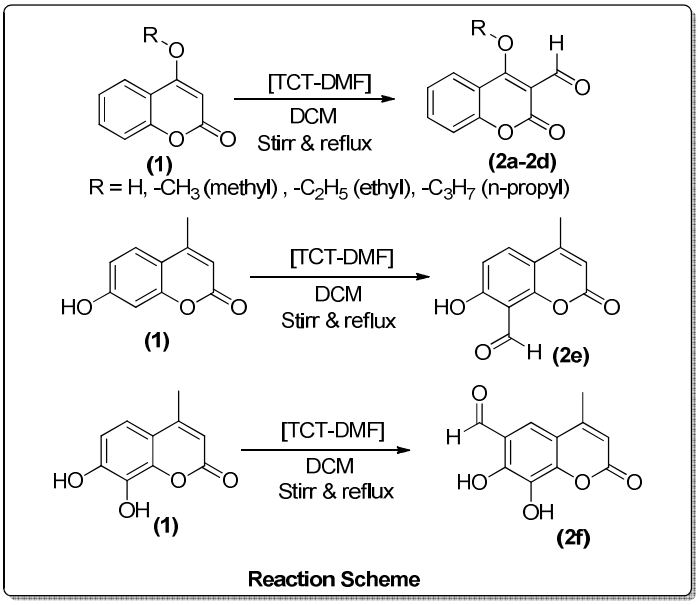
Due to biological importance of Coumarins such as antibacterial[i], anti-cancer[ii], anti-inflammatory[iii], anti-pyretic,anti-biotic[iv], anti-fungal, anti-oxidant[v] and also reported for exhibiting photochemical properties[vi], used as good additives for food and cosmetics[vii]. Various analogues substituted Coumarins such as formyl Coumarins[viii-x]exhibits luminescent properties[xi].

2,4,6-trichloro-1,3,5-triazine (TCT) has been found to be effective reagent for the cyclization reaction and in presence of DMF cyclization followed by formylation.[xii-xvi] Previously reported formylation consist ofhazardous reagent or conditions such as coumarin and otheraromatic compounds[xvii-xx] using hexamethylenetetramine (HMTA) in the presence of Glycero Boric acid[xxi], and in anhydrous acetic acid[xxii]As a part of our interest green approach process[xxiii-xxxi], to overcome these hazardous reagent, catalyst and/or tedious process by using environmentally benign effective V. Haack reagent for the formylation of substituted coumarin. Here we first time report, formylation of hydroxy coumarin and substituted coumarin using [TCT-DMF] as reagent under conventional method.

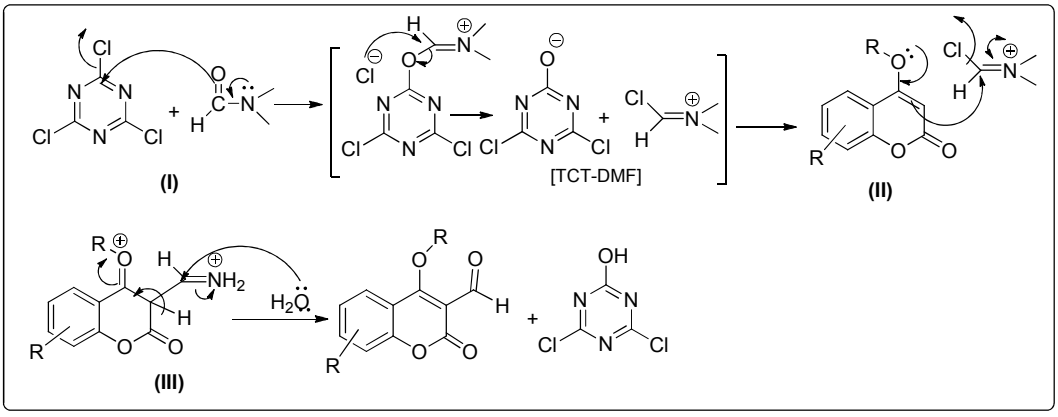


General reaction scheme

Reaction Condition: Cyanuric chloride (0.11 mol) and DMF (0.13 mol), 40ml of DCM stirred for 3h at room temperature, coumarin (**1**) (0.040 mol) was added and stirred under reflux condition.



Reaction scheme 1. Synthesis of formyl coumarins by using [TCT-DMF] reagent under Conventional method.



Plausible mechanism for the synthesis of formyl coumarins by using [TCT-DMF] Complex.

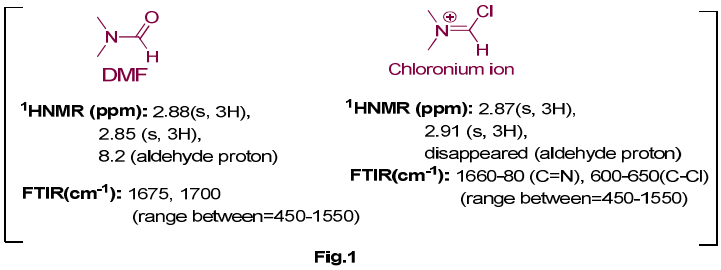
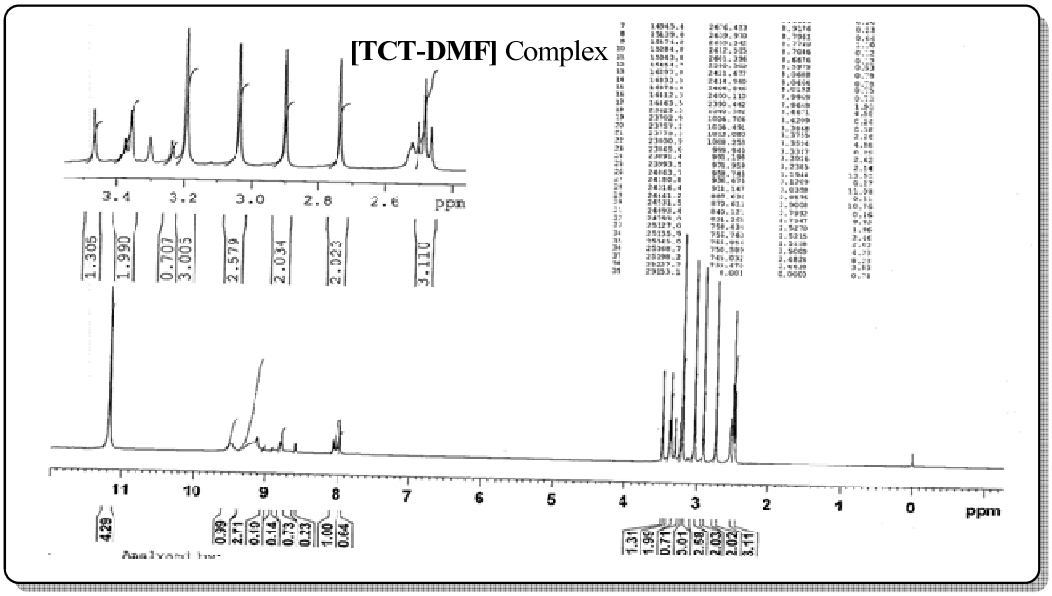


Figure 1a. Compared spectral characterization of DMF and [TCT-DMF] reagent.

[1]HNMR Spectra of [TCT-DMF] Complex/ Reagent:



[TCT-DMF] Complex

Experimental section

All the compounds used in synthesis were of analytical grade; the melting points of the compounds were determined in open head capillary and are uncorrected. The IR spectra of the compounds were recorded in the region of 4000-400 $^{cm-1}$ by using KBr pallet on FT-IR Perkin spectrophotometer. H[1]NMR spectra were recorded on a DRX-300 Bruker FT-NMR spectrophotometer in $CDCl_3$. The values of chemical shift are expressed in δ ppm as an unit. All the compounds were checked for purity by thin layer chromatography.

Result and Discussion

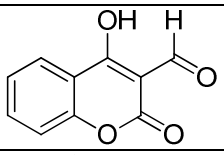
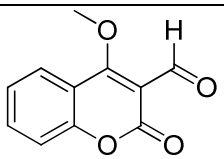
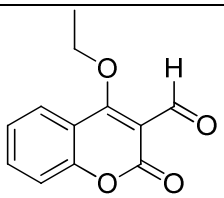
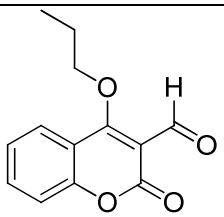
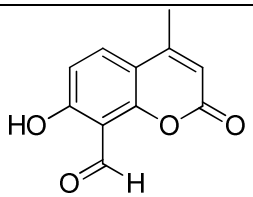
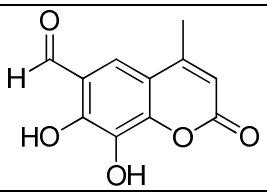
On our literature survey, there is no any report by green approach for the formylation of heterocyclic compound. Initially, we prepared [TCT-DMF] as a formylative complex or reagent by optimized various solvents in different time of reaction (Table **1.,** entry 1-7) among these DCM was the best solvent not only for the preparation of reagent but also formylation of coumarinwith a good yield (Table **1.,** entry 2). For the first 1-2 h there was no yield of product obtained, if we increase the time of reaction more than 3h there is no any significant effect on the yield of product. Thus we select DCM as solvent for the synthesis of formylation coumarin, all example were tested reasonably good yield (Table **2**.) could be achieved in a conventional method in particular4-alkoxy coumarin gave better yield (Table **2**, entry 2) than hydroxy and other substituent of coumarin (Table **2**.). The structures of compound were substantiated by FTIR, [1]HNMR, [13]CNMR and Mass Spectrometry, prepared reagent [TCT-DMF] were confirmed by [1]H NMR and IR Spectroscopy (fig.**1**).

Table 1 Optimization of solvent for the synthesis of formyl coumarins:

Sr. no.	Solvent	Time (h)/Yield[a] (%)	Time(h)/Yield[a] (%)	Time(h)/Yield[a] (%)
1	DMF	2/00	3/68	4/68
2	DCM	2/00	**3/86**	4/85
3	$CHCl_3$	2/00	3/65	4/66
4	Toluene	2/00	3/62	4/64
5	CH_3CN	2/00	3/68	4/70
6	Nitrobenzene	2/00	3/65	4/66
7	THF	2/00	3/60	4/62

[a]Isolated yield:

Table 2 Synthesis of coumarin carbaldehyde derivatives under conventional method:

Sr. no.	Compound	Molecular structure	Molecular formula	Yield(%)/Time(h)	Melting Point (^{0}C)
1	2a		$C_{10}H_6O_4$	70/5	160-162
2	2b		$C_{11}H_8O_4$	**86/3**	120-122
3	2c		$C_{12}H_{10}O_4$	82/3	148-150
4	2d		$C_{13}H_{12}O_4$	78/4	159-161
5	2e		$C_{11}H_8O_4$	74/5	140-142
6	2f		$C_{11}H_8O_5$	72/5	180-182

Reaction condition: Cyanuric chloride (0.11 mol) and DMF (0.13 mol) and DCM (45ml) in a round bottom flask and stirred for 3h at room temperature, white colored precipitate formed [TCT-DMF] to this reagent, coumarin (**1**) (0.098 mol) in reflux condition.
[a]Isolated yield

General procedure for the synthesis of formyl coumarin derivatives (2a-2f):

Conventional method:

Cyanuric chloride (0.11 mol) and DMF (0.13 mol), were added to 45ml of DCM as solvent in a round bottom flask and stirred for 3h at room temperature, white colored precipitate formed [TCT-DMF] to this reagent, coumarin (**1**) (0.040 mol) was added and stirred under reflux condition. Progress of the reaction was monitored by TLC. The reaction mixture was then cooled to room temperaturewater was added, stirred for few minutes then organic layer was extracted with water. The precipitateswere filtered, dried and crystallized from ethanolyield 70-86%. (The last two 2e, 2f products were purified by column chromatography)

Spectral Characterization data:

4-hydroxy-2-oxo-2H-chromene-3-carbaldehyde (2a):

IR (cm^{-1}): 3325, 1730.

^{1}H NMR: δppm = 13.5 (s, 1H), 10.36 (s, 1H), 7.40-7.90 (m, 4H)

^{13}NMR: δppm = 190.4, 178.2, 160.9, 150.9, 128.1, 125.3, 115.4, 114.2, 95.3

Mass: [M^{+}+1]; 190.026

4-methoxy-2-oxo-2H-chromene-3-carbaldehyde (2b):

IR (cm^{-1}): 1720, 1315

^{1}H NMR: δppm = 3.55–3.60 (s, 3H), 10.30–10.40 (s, 1H), 7.40-7.90 (m, 4H)

^{13}NMR: δ ppm = 190.3, 181.2, 162.4, 153.2, 128.1, 125.2, 123.2, 117.2, 116.3, 92.2, 60.1

Mass: [M^{+}+1]; 204.0422

4-ethoxy-2-oxo-2H-chromene-3-carbaldehyde (2c):

IR (cm^{-1}): 2860, 1720, 1624

^{1}H NMR: δppm = 1.21–1.43 (t, 3H), 4.02–4.12 (q, 2H), 10.40 (s, 1H), 7.40-7.90 (m, 4H)

^{13}NMR: δ ppm = 191.3, 180.2, 162.2, 152.1, 128.3, 125.1, 123. 117.4, 116, 94.2, 60.3, 15.3

Mass: [M^{+}+1]; 218.057

2-oxo-4-propoxy-2H-chromene-3-carbaldehyde (2d):

IR (cm^{-1}): 2860, 1725

^{1}H NMR: δppm = 0.98-1.12 (t, 3H), 1.78-1.82 (m, 2H), 4.02 (t, 2H), 10.40-1.52 (s, 1H), 7.32-7.85 (m, 4H)

^{13}NMR: δ ppm = 191.2, 180.3, 162, 152, 128.2, 126.1, 123.3, 117.2, 90, 68, 23.1, 10.5

Mass: [M^{+}+1]; 232.0735

7-hydroxy-4-methyl-2-oxo-2H-chromene-8-carbaldehyde (2e):

IR (cm^{-1}):3350, 1730, 1615

^{1}H NMR: δppm = 12.20-12.32 (s, 1H), 10.60–10.69 (s, 1H), 7.70-7.80 (d, 1H), 6.90 (d, 1H), 6.14–6.26 (s, 1H),2.32-2.45 (s, 3H)

^{13}NMR: δ ppm = 191.3, 165, 160, 152, 150, 135, 120, 115, 112, 20.2

Mass: [M^{+}+1]; 204.0421

7,8-dihydroxy-4-methyl-2-oxo-2H-chromene-6-carbaldehyde (2f):
IR (cm^{-1}): 3352, 1722
^{1}H NMR: δppm = 2.41–2.52 (s, 3H), 10.30–10.42 (s, 1H), 5.32-5.40 (s, 2H), 6.20-6.32 (s, 1H)
^{13}NMR: δ ppm = 192.3, 161.1, 152.2, 152, 151.2, 140.3, 125.2, 120.3, 115.2, 112.1, 20.3
Mass: [M^{+}+1]; 220.0371

Conclusion

Herein we first time report formylation of hydroxy coumarin and substituted coumarins using an efficient Vilsmeier-Hack reagent [TCT-DMF] in good yield by simple stirr and reflux condition. By using environmentally benign cyanuric chloride-DMFover the hazardous reagent or catalyst such as $POCl_3$, $PCl_5/ZnCl_2$, CO/HCl, HMTA/TFAA, HCN/HCl, Boric acid, $COCl_2$ etc.

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