

Niobium [V] Chloride Catalysed Efficient One Pot Synthesis of β -Malonophosphonates

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Abstract: An Efficient method is described for the one pot synthesis of β -Malonophosphonates Derivatives employing Niobium [V] Chloride as a catalyst using water ethanol solvent system at Room temperature. Method offers advantages such as, high yield for products with high reaction rates, mild reaction conditions and easy work up procedures.

Key Words: Niobium [V] Chloride, β -Malonophosphonates, organophosphorus compound. Micheal Addition

Introduction

β -Malonophosphonates are an important class of Carbon – Phosphorous bonded molecules. The structural framework of these molecules which is characterized by phosphonate group at β position, play very important role in the field of medicinal chemistry (Cui J and KS Ju 2025). These molecules act as intermediate in the formation of enzyme inhibitors, peptide mimetics, and antimicrobial agents due to their ability to imitate phosphate esters while resisting hydrolysis (Kalla RMN *et al* 2015). Also, the application of nitrile-based chemical structure has unambiguous importance in the number of anti-microbial pharmaceuticals (Fleming FF *et al* 2010; Murphy ST *et al* 2007).

Although numerous reports on the synthesis of β -phosphonomalononitriles are available in the literature but most of the protocols essentially involve the addition of phosphite nucleophiles to benzyldine malononitrile, the reports on the one-pot multicomponent synthesis of β -phosphonomalononitriles are very restricted in numbers. (Sobhani S, Rezazadeh S, 2011; Wadgaonkar PA *et al* 2012; Kalla RMN and Kim I 2017; Sarvari SH and Tavakolian M, 2012). However, these methods have disadvantage such as long reaction time, low yields of desired products or tedious work up procedures etc, (Sobhani S and Jahanshahi R 2013).

Niobium pentachloride has emerged as strong mediator for accelerating rate of reaction hence find many applications in chemical field. It acts as Lewis acid and employed efficiently in many organic transformations and various multicomponent reactions, Such as Biginelli reaction

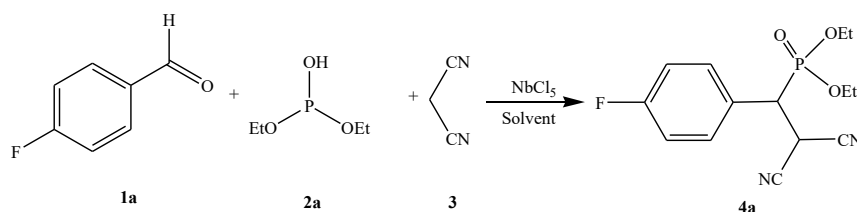
(Camilo FF *et al* 2020), diels-alder reaction (de Castroa VR *et al* 2014)), Quinoxaline Derivatives (Jahan A *et al* 2011), tetrahydropyran derivative (Narsaiah AV *et al* 2005), Quinoxalines (Venkateswarlu Y and Leelavathi P 2010), cycloaddition reactions (Kuhn FE *et al* 2014), alkylation reaction (Butenko TA *et al* 2018) and other transformations (Russo PA *et al* 2019; Naito S *et al* 2013). It is mild, stable and low hygroscopic thus easy to use. Literature survey reveals that the reports on catalytic use of Niobium pentachloride are limited and have scope to explore it.

Thus, impressed with efficacy of the Niobium pentachloride as catalyst and bioactivity of phosphonomalononitriles we explored further the catalytic activity of Niobium pentachloride compound in the one pot synthesis of β -phosphonomalononitriles derivatives.

Result and Discussion

The model reaction between p-fluorobenzaldehyde (**1a**), diethyl phosphite (**2a**) and malononitrile (**3**) in presence of catalysts Niobium pentachloride was chosen for optimisation. The reaction was studied using various solvents at room temperatures as depicted in Table 1.

Table 1: Effect of solvents, catalytic loading and temperature on synthesis of [2,2-Dicyano-1-(4-fluoro-phenyl)-ethyl]-phosphonic acid diethyl ester.



Entry	Solvent	Catalyst mol %	Temperature (°C)	Time (min)	Yield ^a (%)
1	Water	10	RT	240	47
2	Ethanol	10	RT	180	80
3	Ethanol: Water (50:50)	10	RT	90	95
4	Acetonitrile	10	RT	300	41
5	Dichloroethane	10	RT	480	28
6	Chloroform	10	RT	480	34
7	Solvent free	10	RT	600	38
8	Solvent free	10	50	540	42
9	Ethanol: Water (50:50)	10	50	90	91
10	Ethanol: Water (50:50)	10	80	2	95
11	Ethanol: Water (50:50)	5	RT	200	81
12	Ethanol: Water (50:50)	15	RT	90	96

^a: Isolated Yield

Initially the reaction was screened using polar solvents. When protic solvent water was used as reaction media it proceeded in 240 minutes to give 47 % yield for desired product **4a** [Table 1, entry 1]. Moderate 80 % yield was obtained in ethanol solvent and reaction completed in 180

minutes [Table 1, entry 2]. Exciting results were observed in Ethanol: water solvent system as excellent 95 % yield was obtained for **4a** in 90 minutes [Table 1, entry 3]. Nevertheless, in acetonitrile solvent results were deteriorated with increased reaction time and 41 % yield for the product **4a** [Table 1, entry 4]. The performance of reaction was even worse in non-polar solvents dichloromethane and chloroform yielding product as 28 % and 34 % respectively and sluggish reaction rate [Table 1, entry 5 and 6]. Further, the reaction under solvent free condition did not give satisfactory results with long reaction hours and low yield 38 % [Table 1, entry 7]. Solvent free reaction at elevated temperature (50 °C) also shown unaccepted results to yield **4a** only 42 % [Table 1, entry 8]. Thus, the optimum solvent system for the reaction was Ethanol: water system. Which may be attributed to presence of hydroxy molecule from water which form complex with niobium pentachloride catalyst and accelerate reaction (Sobhani S, and Jahanshahi R 2013; Naito S *et al* 2013).

But when temperature was raised to 50° C and 80° C with optimised solvent system no observable changes were noted with almost constant time and yield for product [Table 1, entry 9 and 10]. When reaction was further investigated at 5 mole % catalytic concentration, the product yield was dropped to 74 % although continued for 200 minutes [Table 1, entry 11]. No significant changes were seen at increased concentration of niobium pentachloride (15 mole %) to give 96 % yield [Table 1, entry 12].

Table 2. Synthesis of derivatives of β -malonophosphonates using various aromatic aldehydes **1(a-r)**, dialkyl phosphite ester (**2a / 2b**) and malononitrile (**3**).

Entry	R	R ₁	Product	Yield ^a (%)
1.	4-F	Et	4a	95
2.	4-Cl	Et	4b	91
3.	3-NO ₂	Et	4c	95
4.	4-NO ₂	Et	4d	93
5.	H	Et	4e	95
6.	2-Cl	Et	4f	88
7.	4-OH	Et	4g	89

8.	2-OH	Et	4h	89
9.	4-Me	Et	4i	90
10.	H	Me	4j	91
11.	4-Cl	Me	4k	89
12.	3-NO ₂	Me	4l	93
13.	4-NO ₂	Me	4m	92
14.	4-F	Me	4n	94
15.	2-Cl	Me	4o	86
16.	4-OH	Me	4p	87
17.	2-OH	Me	4q	85
18.	4-Me	Me	4r	88

^a: Isolated Yield. All reactions were performed in Ethanol: water (50:50) system at 10 mole % of catalyst niobium pentachloride and stirred at room temperature for 90 minutes.

Encouraged with the results the above obtained effective reaction protocol was extended to other aromatic aldehydes. The obtained results are summarised in table 2. It can be observed from table 2, that the substituent on the aromatic ring noticeably show effect on the reaction result. Aldehydes with electron-withdrawing groups yielded β -malonophosphonates higher than those containing electron-donating substituents. The electron-withdrawing nature increase the electrophilicity of aromatic aldehyde resulting higher yields. Whereas, electron-donating groups reduce the electrophilicity of the aldehyde giving slightly lower yields. Nonetheless, due to the strong Lewis acidity of NbCl₅, outstanding yields were obtained for a diverse range of substituted aromatic aldehydes, representing the versatility and efficiency of the catalytic system.

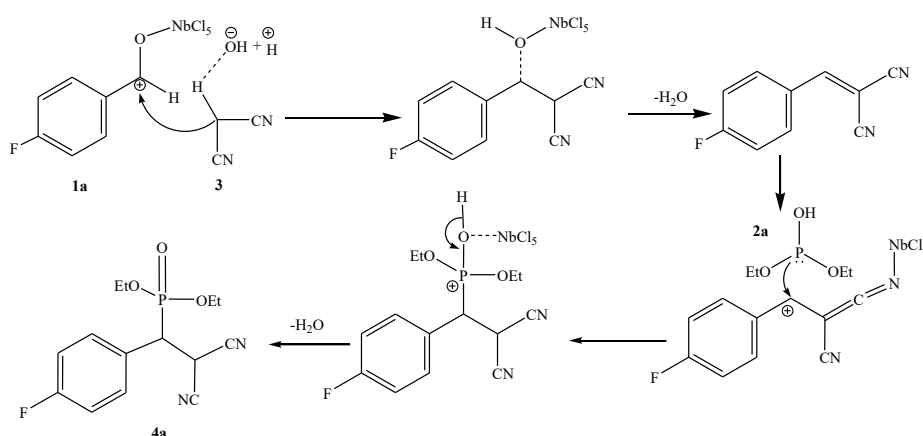


Figure 1: Plausible Mechanism for the synthesis of [2,2-Dicyano-1-(4-fluoro-phenyl)-ethyl]-phosphonic acid diethyl ester

On the basis of literature (Sobhani S, and Jahanshahi R 2013) and obtained results, the plausible mechanism is depicted in figure 1, It can be assumed that Niobium(V) chloride coordinate with the aldehyde oxygen, enhancing electrophilicity of carbonyl carbon. Malononitrile attacks the activated carbon centre, forming an intermediate Knoevenagel adduct which further undergoes nucleophilic addition with phosphite ester, followed by proton transfer, yielding the β -malonophosphonate product while regenerating the catalyst.

Experimental Procedure

General details

All solvents were used as commercial grade without further purification. Aluminium sheets 20 x 20cm, Silica gel 60 F₂₅₄, Merck grade was used for thin layer chromatography to determine progress of reaction. The column chromatography was carried out over silica gel (80–120 mesh). ¹H and ¹³C NMR spectra were recorded on a Bruker 300 MHz spectrometer in CDCl₃ solvent. Mass spectra were taken on Polaris-Q Thermoscientific GC-MS..

General procedure for synthesis of β -Phosphonomalonates.

Aromatic aldehydes (1 mmol) and dialkylphosphite ester (1.2 mmol) , malononitrile and catalyst niobium pentachloride (10 mol %) were stirred for 90 minutes. The progress of reaction was monitored by thin layer chromatography. After completion of the reaction, the product was separated using chloroform in separating funnel. The obtained crude mixture was subjected to column chromatography to afford the pure β -Phosphonomalonates.

Spectral Data for representative compound.

Diethyl 2, 2-dicyano-1-(4-fluorophenyl)ethylphosphonate (**4a**): White solid, M. P. 169–171°C, ¹HNMR (300 MHz, CDCl₃): 7.22–7.40 (m, 2H), 6.81–6.88 (m, 2H), 4.49 (t, 1H), 4.08 (m, 4H), 3.52 (d, 1H), 1.18 (t, 3H), 1.10 (t, 3H); ¹³C-NMR (75 MHz, CDCl₃): δ 159.01, 127.96, 128.04, 115.76, 114.00, 113.20, 65.88, 64.55, 42.10, 26.91, 16.45, 16.02; ³¹P NMR (162 MHz, CDCl₃): δ 21.88; GC-MS: m/z 310 (M⁺). Elemental Analysis: C₁₄H₁₆FN₂O₃P: C, 54.20; H, 5.20; F, 6.12; N, 9.03; P, 9.98; Found C, 54.19; H, 5.18; F, 6.14; N, 9.05; P, 10.00

Diethyl 2, 2-dicyano-1-(3-nitrophenyl) ethylphosphonate (**5c**): Yellowish solid,; M. P. 136–138°C, ¹HNMR (300 MHz, CDCl₃): 7.40–7.60 (m, 2H), 6.70–6.99 (m, 2H), 4.49 (t, 1H), 3.98 (m, 4H), 3.61 (d, 1H), 1.10 (t, 3H), 0.92 (t, 3H); ¹³C-NMR (75 MHz, CDCl₃): δ 149.97, 143.10, 132.93, 123.10, 115.11, 114.02, 66.00, 65.21, 42.96, 29.04, 16.60, 15.98; ³¹P NMR (162 MHz, CDCl₃): δ 22.27; GC-MS: m/z 337 (M⁺); Elemental Analysis: C₁₄H₁₆N₃O₅P: C, 49.86; H, 4.78; N, 12.46; P, 9.18; Found C, 49.83; H, 4.76; N, 12.43; P, 9.15

Conclusion:

In conclusion, the NbCl_5 -catalyst provides a simple, efficient, and high-yielding route for one-pot synthesis of β -malonophosphonates. The methodology shows comprehensive substrate compatibility, affording great yields for wide range of aromatic aldehydes. In addition operational simplicity, short reaction times and high atom economy make this protocol an attractive and sustainable approach for synthesizing valuable β -malonophosphonate derivatives.

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