



RECENT DEVELOPMENTS ON BISMUTH (III) IN CARBON-CARBON BOND FORMATION CHEMISTRY

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ABSTRACT

The present mini account overview describes briefly prosperous usage of Bismuth (III) as an attractive, green alternative to strong, toxic and hazardous, catalysts in some selected organic named reactions. Scope of this catalyst system is too broad and developments have been too fast only recent account is presented on very important carbon-carbon bond forming named reactions like Knoevenagel, Michael, Doebnor modification of Knoevenagel, Biginelli and Hanstzch wherein both these reactions are also proven combination of Knoevenagel and Michael reactions.

Keywords: bismuth (III) compounds, C-C bond forming name reactions, Bi (OTf)₃.xH₂O

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INTRODUCTION

Over the past decade synthetic organic chemistry have been focusing on increasing the use of environmentally benign/eco-friendly catalysts and reagents for the use of compounds which follow twelve principle of green chemistry.¹⁻³ Bismuth compounds have been employed as green and effective catalysts in many synthetic reactions to replace toxic catalysts e.g. compounds of mercury, lead, thallium, arsenic and antimony etc.

Bismuth: General Information

Now it is relevant to discuss certain general aspects of this element i.e. Bismuth is the 83rd element in the periodic table, which is placed in Group V of the Periodic Table with other members like nitrogen, phosphorus, arsenic and antimony and it is a brittle white metal with a pinkish tinge having an atomic mass of 209.980 amu. Bismuth resembles antimony in its mode of occurrence but relatively it is less common.⁴ Abundance of bismuth in the earth's crust has been estimated (229) to be 0.00002 weight %, i.e. approximately same as silver and is produced as a by-product of copper and tin refining. Bismuth being a radioactive element, it is stable because of it's an extremely long half life ($t_{1/2} \sim 2 \times 10^{18}$ years) makes it practically stable.⁵⁻⁷ Despite its heavy metal status, bismuth and its compounds are relatively non-toxic and can be utilized for a variety of different medicinal as well as catalysts purposes.⁸⁻¹⁴

Lewis Acid and Eco-friendly Nature

Several of the heavy metals have a relatively high toxicity and if used in reactions can be present in by-products. One of the principal factors contributing to the low toxicity of bismuth is the poor solubility of it in aqueous solutions or in bio-fluids at moderate pH values which is found in plasma/fluids of living system.¹⁵ From table 1, it is clear that many bismuth compounds are less toxic than common salt (NaCl) and many other metallic salts.¹⁶

Since Bi-compounds are comparatively non-toxic and have been employed as eco-friendly mild Lewis acid catalysts system in synthetic green chemistry.¹⁷⁻²⁷ Lewis acidity of bismuth (III) compounds are a result of poor shielding of the *f*-orbital electrons (electronic configuration of Bi: [Xe]4*f*¹⁴5*d*¹⁰6*s*²6*p*³) allowing bismuth to accept an electron pair readily as well as availability of unoccupied orbital's elevate its affinity to extend coordination. Electron pair demand of Bi further augmented by strong electron withdrawing groups (EWGs) such as halides, triflate etc. Bismuth exists in two oxidation states, +3

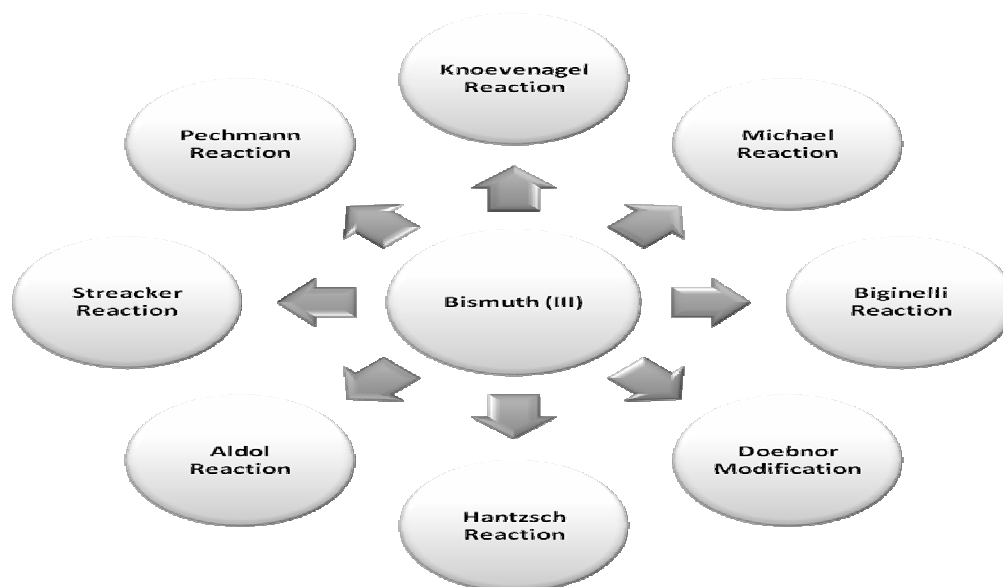
[bismuth (III) halides, bismuth (III) subsalicylate etc.] and +5 [bismuth (V) fluoride, $\text{Ph}_3\text{Bi}(\text{OAc})_2$, Ph_3BiCO_3 etc.]. They are suitable as mild Lewis acid catalysts for organic transformation and synthetic reactions due to their ease of handling and non-corrosive nature. As a result numerous studies have been carried out to establish the effectiveness of Lewis acidity of bismuth compounds and their effects on different synthetic reactions.²⁸⁻³³ Bi (III) catalysts are generally crystalline solids and are commercially available at low cost.³⁴ Because of amplified awareness to green chemistry, bismuth compounds become attractive as green catalysts in place of other, more toxic, metal catalysts derived from elements like indium, nickel, mercury, lead, tin etc.

Table-1: LD₅₀ Values of Common Metal Salts from MSDS Data.¹⁶ (Species-Rat, Route-oral)

HgCl ₂	0.001	SmCl ₃	2.9	YbCl ₃	4.8
NiCl ₂	0.105	BiCl ₃	3.3	Bi ₂ O ₃	5.0
SnCl ₂ ·2H ₂ O	0.7	NaCl	3.8	BiOCl	22
InCl ₃	1.1	ScCl ₃	3.9		
CeCl ₃	2.1	Bi(NO ₃) ₃ ·5H ₂ O	4.4		

Bi³⁺ in C-C Bond Formation Named Reaction

Synthetic organic chemistry have witnessed extensive use of Lewis acids and there are several reviews and now this scattered information is collected and published in book shape too each chapter in this book is written by prominent workers in the area and there are two chapters on bismuth applications in organic synthesis.^{23,24} Recent advances in Bismuth (III) chemistry have expanded the versatility and flexibility of modern green/eco-friendly catalysts for carbon-carbon bond formation reaction and functional group transformations.¹⁹ This mini-review highlights the considerable progress, which has been made in the last decade to tame the reactivity of Bi³⁺ salts.¹⁷⁻¹⁸



This review focuses on recent advances of bismuth in common useful named reactions leading to the formation of C-C bonds these reactions are tools for production of many pharmacological/biological significant compounds. Named reactions showed in Table 2. are almost discovered a century ago or more by inventors as these are popularly called after their names, the classical version of these reactions have undergone a sea change but still do require further refinements and renovations according to present day needs like environment etc Evidently old versions had many problems so developments/productive

investigations were needed to accommodate modern trends and needs. MSDS data (Table 1) shows that Bi (III) are almost neutral and in recent researches these salts are widely accepted by different areas of modern green chemistry.

Efforts made by authors and other research groups in contributing to develop Bi (III) salts as environment friendly green catalysts in popular C-C bond formation major named reactions of organic chemistry are delineated in following Table 2-9.

Aldol Condensation

In 1872, C-A. Wurtz and A.P. Borodin discovered most popular carbon-carbon bond forming this condensation reaction in organic synthetic chemistry.⁴⁵⁻⁴⁷ Aldol when dehydrates yields $\alpha\beta$ -unsaturated ketones called chalcones and reaction is named as Claisen-Schmidt reaction. Lewis acids play key role in promoting Aldol and Aldol type condensation,^{48,49} from table 2. it is clear that for this investigation various Bismuth (III) Lewis acids have been extensively used preferentially over the existing one due to their eco-friendly nature, availability and low cost (table 2.).⁵⁰⁻⁶²

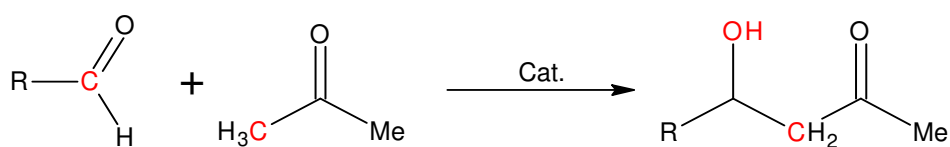


Table-2: Bi³⁺ Catalysed Aldol and Aldol Type Condensation

Bismuth (III) Used	Reactants	Reaction Condition	References
BiCl ₃	Silyl enol ethers & Aldehydes	CH ₂ Cl ₂ , rt	[50-51]
BiCl ₃ -Metal Iodides (1:3)	Silyl enol ethers & Aldehydes	CH ₂ Cl ₂ , -30°C, Ultrasound	[52]
BiCl ₃ -NaI (1:3)	Silyl enol ethers derived from furfural & Aldehydes	CH ₂ Cl ₂ , rt	[53-54]
Bi (OTf) ₃ .4H ₂ O	Silyl enol ethers & Aldehydes/Acetals	CH ₂ Cl ₂ , rt to -70°C	[55]
Bi (OTf) ₃ .4H ₂ O	2- (trimethylsilyloxy) furan & Aldehydes	Diethyl ether, -78°C	[56]
MC (microencapsulated)Bi (OTf) ₃	4-nitro benzaldehyde & acetone	Solvent free, rt	[57]
Bi-ZnF ₂	α -bromocarbonyl compounds and aldehydes	H ₂ O, rt	[58]
Bi (OTf) ₃ .nH ₂ O	silyl enolate and aldehyde	[Bmim]BF ₄ , rt	[59]
Bi (OTf) ₃ .4H ₂ O	dioxinone-derived silyl dienol ethers	Diethyl ether, -78°C	[60]
Bi (OTf) ₃ - Chiral Bipyridine Complexes	Silyl enol ethers & Aldehydes	DME/H ₂ O (9:1), 0 °C	[61]
BiCl ₃ - ZnI	Ketene Silyl Acetal & Chiral $\alpha\beta$ -Epoxyaldehydes	CH ₂ Cl ₂ , rt	[62]

Knoevenagel Reaction

Emil Knoevenagel^{63,64} in 1894 invented this reaction as a proficient way of producing carbon-carbon double bonds and it is also a modified version of Aldol condensation.⁶⁵⁻⁶⁶ The conventional Knoevenagel (Scheme 2.) have been reported in several reviews and monographs the use of ecofriendly and green catalysts system in this reaction is a matter of current interest. In the pursuit of developing green chemistry we did make considerable efforts for solvent free green Knoevenagel condensation utilizing 10mol% BiCl₃ (table 3.).⁶⁷⁻⁶⁸

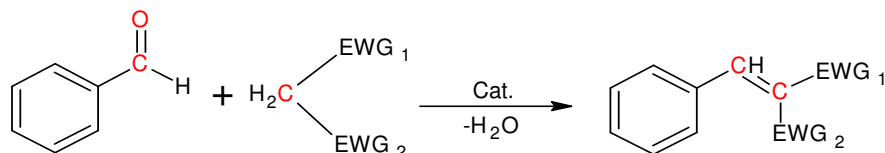


Table-3: Bi⁺³ Catalysed Knoevenagel Condensation

Bismuth (III) Used	Reactants	Reaction Condition	References
10mol% BiCl ₃	Active methylene compds & Aldehydes	Solvent free, 80°C	[67-68]

Doebner condensation/ modification

It is a customized account of Knoevenagel reaction which was given by O. Doebner in 1900.⁶⁹⁻⁷⁰ Always pyridine or piperidine type catalyst systems have been used for this decarboxylative Knoevenagel to obtain unsaturated acids from a range of aldehydes and malonic acids.⁷¹⁻⁷⁷ In this reaction also our group⁷⁸ have significant contribution for the production highly commercially and otherwise significant (E)-cinnamic acids.⁷⁹⁻⁸⁶ In this pursuit cinnamic acids were obtained in good to very good yields employing 5-10mol% BiCl₃ (table 5.).⁷⁸ In another simplification we were tempted to employ another variant to examine efficiency of bismuth salts in this important reaction of organic chemistry. In this protocol we used bismuth triflate and other bismuth salts in this reaction. We observed bismuth triflates in less catalytic amount gives excellent results as shown in table 4. demonstrating Bi (OTf)₃.xH₂O proven more economic and efficient catalyst.⁸⁷

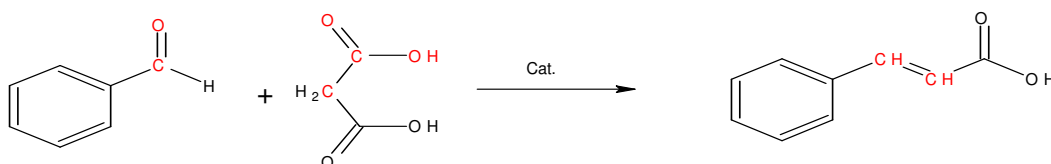


Table 4. Comparison of Bismuth (III) catalysed for synthesis of (2E)-3- (4-methoxyphenyl)prop-2-enoic acid.⁸⁷

Entry	Bismuth (III) Salts	Amount (mol %)	Time (min)	Yield (%) ^a
1	-----	-----	3.5	<10
2	Bi (OTf) ₃ .xH ₂ O, PEG	5 mol % 1ml	3.5	95
3	BiCl ₃ , Sol.free	5 mol % Sol.free	3.5	78
4	Bi (NO ₃) ₃ .5H ₂ O	5 mol % Sol.free	3.5	82
5	BiCl ₃ , KI, PEG	5 mol % (1:3) 1ml	3.5	88

^a Isolated yields after recrystallization

Table-5: Bi⁺³ Catalysed Doebnor Modification

Bismuth (III) Used	Reactants	Reaction Condition	References
BiCl ₃	Malonic acid & Aldehydes	Solvent free, MWI	[78]
Bi (OTf) ₃ .xH ₂ O	--do--	PEG, MWI	[87]

Michael Reaction

Arthur Michael discovered⁸⁸⁻⁹⁰ this reaction which is very similar to Knoevenagel reaction and in conventional chemistry in both the reactions similar solvents and catalysts has been employed and volumous research work is reported and both seem complimentary to each other. Precisely, Knoevenagel is 1-2 and Michael is 1-4 conjugate addition on to carbonyl and electron deficient alkenes respectively. In pursuit of green chemistry here also authors and others did make considerable contribution in developing some environment benign protocols using non-polluting catalysts i.e. bismuth (III) salts and replacing volatile organic solvents (VOCs) under solvent free conditions.⁹¹⁻¹⁰⁸

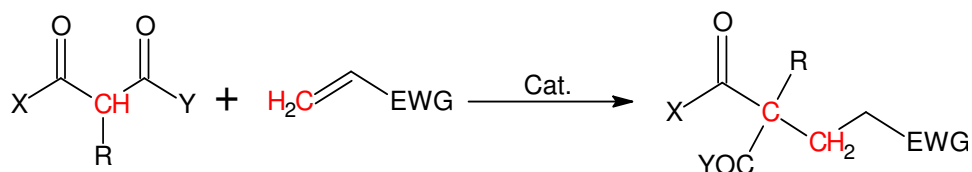


Table-6: Bi⁺³ Catalysed Michael and Michael Type Reaction

Bismuth (III) Used	Reactants	Reaction Condition	References
BiCl ₃	1,3-dicarbonyl compds & α,β -unsaturated carbonyl compds	Solvent free, MWI	[91]
Bi (NO ₃) ₃ .5H ₂ O	Indoles & 1,2-unsaturated ketones	H ₂ O, 25 °C	[92]
Bi (NO ₃) ₃ .5H ₂ O	<i>trans</i> -1-phenylbut-2-en-1-one or 4-methylpent-3-en-2-one & 1,3-oxazolidin-2-one	CH ₂ Cl ₂ , rt	[93]
BiOCIO ₄ .xH ₂ O	Indoles & 1,2-unsaturated ketones	CH ₃ CN, r.t., sonication	[94]
Bi (OTf) ₃ .xH ₂ O	indole or thiol & $\alpha\beta$ -unsaturated carbonyl compds	CH ₃ CN, r.t.	[95]
Bi (OTf) ₃ .xH ₂ O	Indoles & p-quinones	CH ₃ CN, r.t.	[96]
Bi (OTf) ₃	$\alpha\beta$ -ethylenic compds & Aliphatic amines	CH ₃ CN, r.t.	[97]
Bi (OTf) ₃	$\alpha\beta$ -enones & Indoles	CH ₃ CN, r.t.	[98]
Bi (OTf) ₃	1,2-bis (trimethylsilyloxy)cyclo butene & 1,2-diaza-1,3-butadines	One-pot, r.t.	[99]
Bi (OTf) ₃	$\alpha\beta$ -unsatd.esters & conjugated amines	Solvent free, MWI	[100]
BiCl ₃	Pyrroles & Electron-deficient olefines	Silica gel, Solveni free, MWI	[101-102]

Microencapsulated Bi (OTf) ₃	Aliph. Amines & αβ-unsatd. Esters and nitriles	Solvent free, rt	[103]
BiCl ₃	Aryltin compds. & Nitroalkenes	Palladium (II) salt in acetic acid	[104-105]
BiCl ₃	Furan derivatives	Metal iodide systems, mild condition	[106]
BiCl ₃	α-(trimethylsiloxy)styrene / 1-(trimethylsiloxy)cyclohexene & aldehydes/ Ketones/ acetals/ enones	Metalic iodide systems, -30 and -70°	[107]
BiCl ₃	Silyl enol ethers & αβ-unsatd. ketones	CH ₂ Cl ₂ , r.t.	[108]

Hantzsch Reaction

More than a century ago, in 1881, 1,4-dihydropyridine synthesis was described by Arthur Hantzsch and now produced pyridine is popular as Hantzsch 1,4-dihydropyridine.^{109,110} Exploration of these pyridines in the beginning were quite slow, later it picked up very fast because of their structural resemblance to reduced nicotinamide adenine dinucleotide (NADH), which is an established hydrogen transferring agent in biological processes.¹¹¹ Since these molecules had great significance to biologists as they are taken to be privileged molecule of chemistry (possessing more than one activity such as Nifedipine, Nicardipine, Amlodipine, Nitrendipine, Nimodipine and others have been used as calcium channel blockers, and are used most frequently as cardiovascular agents for the treatment of hypertension) and their use in clinical practice attracted much attention of chemists to develop greener production process. Though, large number of other catalysis in this reaction are also reported¹¹² even then reports are there of uncatalysed reaction¹¹³ Present authors also made effective contribution in this direction using bismuth (III) salt mainly for synthesis of Hantzsch pyridines.¹¹⁴ Oxidation of Hantzsch 1,4-dihydropyridine also reported by using bismuth salts which produce oxidized products in excellent yields (table 6.).¹¹⁴⁻¹²²

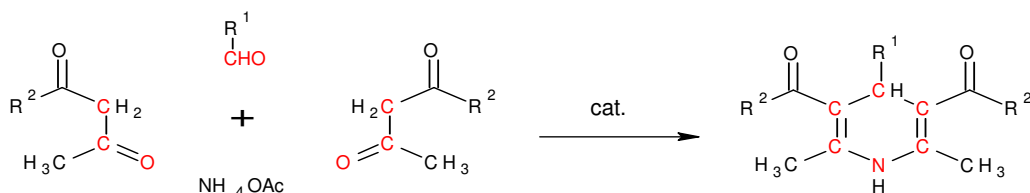
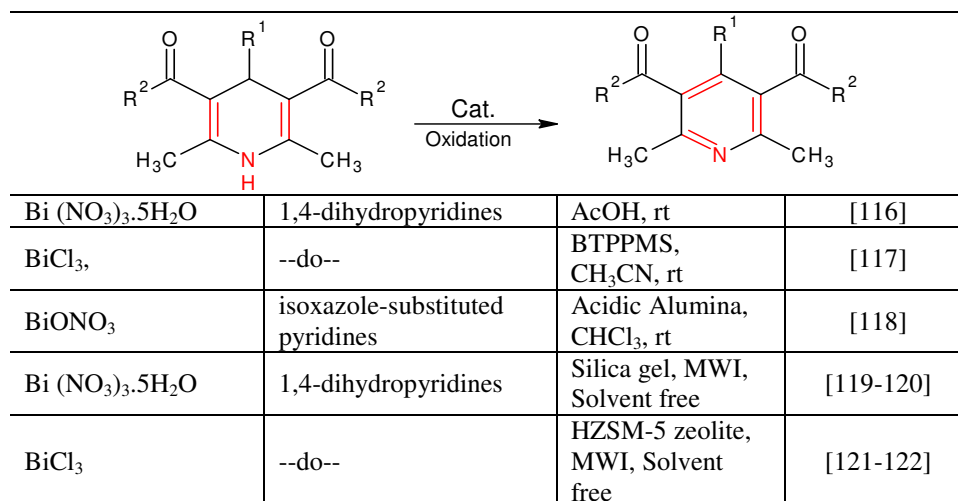


Table-7: Bi³⁺ Catalysed Hantzsch Reaction

Bismuth (III) Used	Reactants	Reaction Condition	References
BiCl ₃	Active methylene compds, Ammonium acetate & Aldehydes	Solvent free, rt	[114]
BiBr ₃	Subs. Anilines & Enol ethers	Anhydrous CH ₃ CN, 50°C	[115]

Hantzsch Oxidation



Biginelli Reaction

Italian chemist, Pietro Biginelli about a decade later (after synthesis of Hantzsch 1,4-dihydropyridine) heated same three components acetoacetic ester, benzaldehyde in equimolar ratio, urea (slightly in excess) in alcohol and few drops of conc. hydrochloric acid.^{112,123-126} He isolated a new compound (now called Biginelli compound^{127,128} and is undoubtedly aza analogue of Hantzsch pyridine) along with small amount of Hantzsch pyridine. Biginelli compounds showed promising antibacterial activity¹²⁹ and other promising activity is anti-HIV i.e. antiviral activity¹³⁰ because of the skeletal resemblance with natural batzelladine alkaloids, viz. batzelladine B. These compounds are also important as analgesic,¹³¹ anti-inflammatory,¹³² antihypertensive^{133,134} and specially worth mentioning here is monastrol which has excellent anticancer activity.¹³⁵ These two reactions Hantzsch and Biginelli are selected since they are now well developed three component reactions and also they are combination of previously discussed two reactions viz. Knoevenagel followed by Michael so both are tandem/cascade reactions.

Before presenting work on Bismuth catalysis in this reaction one puzzle is also worth mentioning here i.e. a catalysis is needed or not since detail is irrelevant here only a question is recorded.¹³⁶ But if one goes by this statement other question arises is it all Knoevenagel reactions and Michael reactions can proceed uncatalyzed obviously it is not possible. For efficient synthesis of Biginelli compounds almost all bismuth salts are reported to enhance reaction rate and yields summary of these are given in table 7.¹³⁷⁻¹⁴⁹

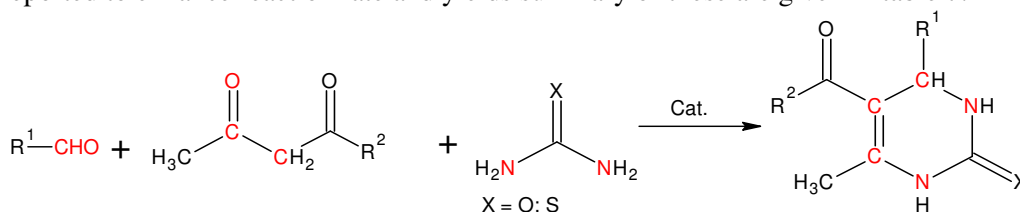


Table-8: Bi⁺³ Catalysed Biginelli Reaction

Bismuth (III) Used	Reactants	Reaction Condition	References
BiCl ₃	Active methylene compds, Urea/Thiourea & Aldehydes	CH ₃ CN, reflux	[137]
Bi (OTf) ₃	--do--	CH ₃ CN, rt	[138]
BiONO ₃	--do--	Anhydrous CH ₃ CN, 40°C- 50°C	[139]
Bi (NO ₃) ₃ .5H ₂ O	--do--	CH ₃ CN, reflux	[140-142]

Bi(OClO ₄) _x .xH ₂ O	--do--	CH ₃ CN, 40°C-50°C	[143]
Polyaniline-bismoclite complex (PANI-BC)	--do--	EtOH, Heating	[144]
Bi(NO ₃) ₃ .5H ₂ O	--do--	MWI	[145-146]
Bi(NO ₃) ₃ .5H ₂ O	Primary Alcohols were used instead of Aldehydes	CH ₃ CN /TBAB,	[147]
Bi(NO ₃) ₃ .5H ₂ O	Benzyl halides were used instead of Aldehydes	TBAF, 120°C	[148]
Bi(TFA)	Ketones were used instead of Active methylene compds	[nbpy]FeCl ₄ , TMSCl, 70°C	[149]

Strecker Reaction

Historically, α -amino nitriles is an oldest multi-component reaction reported by Strecker in 1850 and is named after his name which employs aldehydes, amines and sodium cyanide/potassium cyanide to afford α -amino nitriles.¹⁵⁰ This involves addition of cyanide to C=N bond is common strategy to obtain α -amino nitriles, which serve as important synthons in organic chemistry for the synthesis of a variety of heterocycles. These nitriles can be conveniently converted into a variety of amino acids¹⁵¹⁻¹⁵² and several nitrogen heterocycles like thiadiazoles,¹⁵³ imidazoles¹⁵⁴ and other biologically significant compounds such as saframycin A.¹⁵⁵ In this reaction only BiCl₃ was employed by S. K. De *et al.*¹⁵⁶ (table 8.) and use of other salts of bismuth is still remain unexplored.

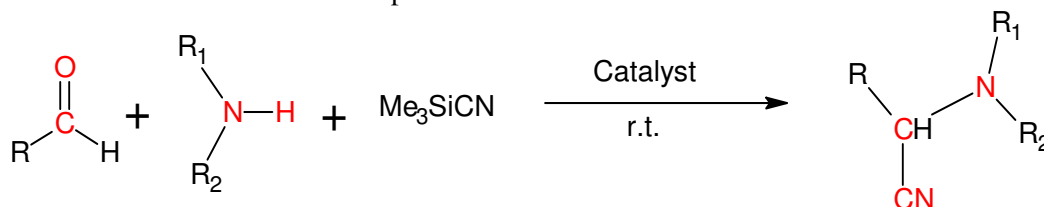


Table-9: Bi⁺³ Catalysed Strecker Reaction

Bismuth (III) Used	Reactants	Reaction Condition	References
BiCl ₃	aldehydes, amines and trimethylsilyl cyanide	CH ₃ CN, rt	[156]

Pechmann Reaction

Classically, the Pechmann reaction¹⁵⁷ refers to the condensation of β -ketoesters with phenols in the presence of excess of acid catalysts to produce 4-substituted heterocyclic compounds i.e. coumarins, involving tandem hydroxyalkylation, transesterification and dehydration. Esterification/transesterification followed by attack of the activated carbonyl ortho to the oxygen to generate the new ring via dehydration, as in case of aldol condensation.¹⁵⁸⁻¹⁵⁹ Under solvent free condition utilizing Bi(NO₃)₃.5H₂O and BiCl₃ catalyzed Pechmann reaction came in light during extensive literature survey and both salts provide products in high yields without any side products formation.¹⁶⁰⁻¹⁶²

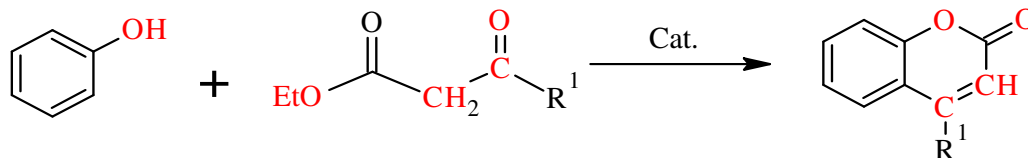


Table-10: Bi⁺³ Catalysed Pechmann Reaction

Bismuth (III) Used	Reactants	Reaction Condition	References
Bi (NO ₃) ₃ .5H ₂ O	phenol & β-ketoesters	Solvent free, 80°C	[160]
BiCl ₃	--do--	Solvent free, 75°C or 125°C	[161]
BiCl ₃	--do--	Ultrasound, rt	[162]

Earliest C-C bond forming reaction seems to be Aldol reaction and others like Knoevenagel and Michael also are old reaction of the past century. Next is discussed Biginelli and Hantzsch dihydropyridine which both have similarity as they involve Knoevenagel and Michael reaction both or involve these reactions concurrently. So they are a mix of both, so here this account primarily is around Aldol, Knoevenagel, Michael and some other reactions are also touched. This selection seemed desirable since we were to punctuate this account with our own work also. From above table it is understandable that various Bismuth salts are employed for same reaction by even same workers or different group of chemists in these reactions. As we know from MSDS data these catalysts are less toxic than common edible salt used by human and every salt of Bismuth (III) gave good results either yields or reaction rate in efficient way in each above discussed reactions. Other metal halide in combination of Bismuth salts further enhanced its catalytic activity to speed-up the reaction but as promoter used metal halide can effect greener nature and other features of these novel Bismuth catalysts. After investigating various trivalent bismuth compounds it is seems that mainly triflates are superior in every way like catalytic activity, moisture tolerance, recycling, inexpensive and eco-friendly etc. In case of multicomponent reactions Knoevenagel, Strecker, Hantzsch synthesis and Doebnor there are only few reports especially with BiCl₃ we hope other triflates like bismuth compounds would further accelerate these reactions.

CONCLUSIONS

In the beginning of this article we have presented detailed account of bismuth's properties which have attracted the attention of chemists around the world the result of which very clear from large number of reviews published on this topic not only this fragmented information has come up in chapters written by authorities on this attractive mild Lewis acid Poor solubility of Bismuth salts in bio-fluid indicating that these are green catalysts of present century and widely accepted by research chemists. Other features which make Bi salts popular are their easy availability, inexpensive, non-corrosiveness nature and stability. Role of green and eco-friendly Bi (III) catalysts to speed-up many other C-C bond forming reactions (with various related substrates), asymmetric synthesis and synthetic transformations do still remain unexplored. These Bi catalysts would be a substitute or take position of previously used non-green catalysts systems to protect ecosystem and environment which could be gift to next generation. We do hope this paper would further stimulate researches on bismuth salts.

ACKNOWLEDGEMENTS

The authors are thankful to the Council of Scientific and Industrial Research (CSIR), New Delhi, India for financial assistance and to the Indian National Science Academy (INSA), New Delhi, India for additional financial support for this research project. Also authors thanks Council of Scientific and Industrial Research (CSIR) India for award of fellowship and RSIC (DST) Punjab University Chandigarh for spectral analysis. One of us Jagir S. Sandhu highly appreciates dedicated team of his research associates

which was nearly a dozen or so presently occupying responsible positions in CSIR India and Universities in this country who were contributor in bismuth chemistry and their names are in references.

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