Heterocyclic Letters
Vol. 14| No.4|777-785|Aug-Oct|2024
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

COBALT (II) NITRATE HEXAHYDRATE AS AN EFFICIENT CATALYST FOR THE SYNTHESIS OF β-AMINO KETONES DERIVATIVES

Jitendra R. Deshmukh[a], Uddhav N. Chaudhar[b], Ajay M. Patil[c] and Shivanand G. Sonkamble[c]*

[a]Department of Chemistry, Late Kisandas Gulabchand Kataria College, Daund, Dist.- Pune [M.S.]-413801 India.
[b]Department of Chemistry, Kalikadevi Arts, Commerce and Science College, Shirur Kasar Dist-Beed [M.S.]-413249 India
[c]Department of Chemistry, Pratisthan Mahavidyalaya, Paithan Tal-Paithan Dist-Aurangabad [M.S.]-India
**e-mail: djitu87@gmail.com/ sg_sonkamble@yahoo.co.in Mobile: 9850634673*

ABSTRACT: Eco-friendly protocol was developed for the synthesis of β-amino ketones derivatives using the one pot multi-component reaction of aromatic aldehydes, ketones and aromatic amines in presence of cobalt (II) nitrate hexahydrate in ethanol at room temperature via mannich reaction. The advantages of this eco-friendly protocol are numerous, and include the use of an inexpensive catalyst, high to excellent yield, short reaction time and high catalytic activity that can make this method an interesting alternative to multi-step approaches.

KEYWORDS: Mannich reaction; multi-component reactions, cobalt nitrate; β-Amino carbonyl compounds.

INTRODUCTION:

Multi-component reactions represent a very curious organic synthetic methodology due to their various advantages, such as one-pot and easy operating conditions, atom economy, high chemical yields and cheap substrates[i] Mannich reaction is one of the most unique C–C bond forming reactions in organic transformation for the synthesis of secondary and tertiary amine derivatives. Mannich reaction has been predicted as one of the most prominent multi-component reactions (MCRs) has been utilized for the synthesis of β-amino ketones (Mannich bases) via one-pot condensation of ketone, aldehyde, and amine since its discovery in 1917[ii]. Mannich base are useful synthetic intermediates[iii-vi] and widely applied in the synthesis of natural products[vii] and pharmaceutical chemistry[viii-xi]. Moreover, β-amino ketones and its derivatives are important compounds exhibiting various and useful bioactivities such as anti-inflammatory, analgesic, antidiabetic, antibacterial, and antitumor activities and so on[x]. Marketed, β-amino ketones drugs are widely applied in clinics, for example Ondansetron is a medication used to prevent nausea and vomiting caused by cancer

chemotherapy and radiation therapy and the drug bupropion exhibits anti-depressant properties. The drug benazepril shows anti-hypertension agents are widely used in clinical practices[xi].

For the preparation of the mannich product, the researcher used several reagents, since for the last decade The reagents such as Lewis acids have been reported in the literature and few catalyst includes $Yb(OPf)_3$[xii], $ZrOCl_2$ $8H_2O$[xiii], $Zn(OTf)_2$[xiv], $NbCl_5$[xv], $SnCl_2/SnCl_4$ [xvi-xvii], $BiCl_3$[xviii], $CeCl_3$-$7H_2O$/CAN[xix-xx], $FeCp_2PF_6$ [xxi], $Bi(NO_3)_3$[xxii], $Bi(OTf)_3$[xxiii], and $Ga(OTf)_3$ [xxiv] have been employed for the synthesis of Mannich bases under either solution-phase or solvent-free conditions. Brønsted acid-based catalysts as conc. HCl[xxv], camphor sulfonic acid[xxvi], $HClO_4$-SiO_2[xxvii], polymer-supported sulfonic acid[xxviii], $H_3PW_{12}O_{40}$[xxix], acidic surfactants[xxx], and acidic ionic liquids[xxxi], have been extensively explored for Mannich reaction,which provides a reliable access to Mannich bases. However, these methods are typically limited by large catalyst loading, moderate yield and long reaction time In addition, organometallic complexes of Ti (IV)[xxxii], Bi(III)[xxxiii], Sb(III)[xxxiv], Zr(IV)[xxxv], along with other Lewis acids, such as sulfonium[xxxvi]/iodonium salts[xxxvii] and $SiCl_4$ [xxxviii], also have been used catalysts for this purpose. However, most of the methods have certain drawbacks such as more amounts of catalyst, longer reaction times, low potent, high-cost, high temperature, low yields, tedious work-up procedures, toxic solvents, etc.

In present study was to develop a new method for the synthesis of β-amino ketones derivatives using inexpensive, eco-friendly and non-hazardous homogeneous cobalt (II) nitrate (15 mol%) as catalyst in ethanol at room temperature via mannich reaction.

EXPERIMENITAL:

All reactions were performed at room temperature. High speed stirring was carried out with magnetic force. All the starting materials were got from commercially accessible sources and used without further purification. Melting points were measured by open capillary technique and are uncorrected. FTIR spectra were noted on alpha T BRUKER model. ^{1}HNMR and ^{13}CNMR spectra were recorded at ambient temperature on a BRUKER AVANCE DRX-500 MHz spectrophotometer using $CDCl_3$ as the solvent and TMS as an internal standard. The purity of newly synthesized compounds and the changes of reaction were observed by thin layer chromatography (TLC) on Merck pre-coated silica gel 60 F254 aluminium sheets, visualized by UV light.

GENERAL PROCEDURE: A mixture of ketone (1.0 mmol), substituted aromatic aldehyde (1.0 mmol), substituted aromatic amines (1.0 mmol) and Cobalt nitrate hexahydrate (15 mol %) in 3.0 mL ethanol was stirred at room temperature for the respective time specified in Tables 3. The progress of reaction was determined by TLC. Subsequent completion of the reaction, the reaction mass is poured on crushed ice. The precipitate was filtered off, and washed with cold water and dried in air to get pure product. The solid product was purified by ethanol.

1, 3-Diphenyl-3- (phenyl amino) propan-1-one (4a):

White solid, MP: 169-170 ºC; FTIR (KBr, cm^{-1}): 3384, 3023,2877,1669, 1597,1510,743,685, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 7 Hz, 2H), 7.55 (t, J = 7 Hz, 1H), 7.43 (m, 4H), 7.31 (t, J = 7 Hz, 2H), 7.22 (t, J = 7 Hz, 1H), 7.08 (t, J = 7.5 Hz, 2H), 6.65 (t, J = 7 Hz, 1H), 6.55(d, J = 8 Hz, 2H), 5.00 (s 1H), 4.54(s 1H),3.51 (dd, J = 16, 5 Hz, 1H), 3.41 (dd, J = 16, 7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 146.9, 142.9, 136.7, 133.4, 129.0, 128.9, 128.8, 128.6, 128.2, 127.3, 126.3, 117.7, 113.8, 54.7, 46.2. HRMS (EI): m/z calculated for $[M+H]^+$ [C21H20NO]? 302.1533,

1,3-Diphenyl-3-(p-tolylamino) propan-1-one (4b):

White solid MP: 138–139 °C. FTIR (KBr, cm^{-1}): 3400, 3019, 2914, 1678, 1619, 1523,744,683. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s,2H), 7.2-7.5 (m, 8H), 6.89 (s,2H), 6.47(s,2H), 4.96(s,1H), 4.41(s,1H), 3.47(d,1H), 3.41(d,1H), 2.17(s,3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 144.6, 143.1, 136.7, 133.3, 129.5, 128.7, 128.6, 128.1, 127.2, 126.9, 126.3, 113.9, 55.0, 46.3, 20.3; HRMS (EI): m/z calculated for [M+H$^+$ [$C_{22}H_{22}NO$] 316.1700.

3- (4-Chlorophenyl) -1-phenyl-3- (phenyl amino) propan-1-one (4c):

Crisme white solid, MP 106–107 °C, FTIR (KBr, cm^{-1}): 3389, 3027, 2920, 1665, 1507, 1367, 747,682. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J=7.5 Hz, 2H), 7.56 (t, J=7.5 Hz, 1H), 7.44 (t, J= 8 Hz, 2H), 7.37 (d, J=8 Hz, 2H), 7.26 (t, J= 8 Hz,2H), 7.0 (t, J= 8 Hz, 2H), 6.67 (t, J=7.5 Hz, 1H), 6.52 (d, J= 8, 2H), 4.97 (dd, J= 6.5, 6 Hz, 1H), 4.55 (s,1H), 3.45 (dd, J=16, 7.5 Hz, 1H), 3.41 (dd, J= 16.5, 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 146.6, 141.5, 136.5, 133.5, 132.9, 129.2, 129.1, 128.9, 128.7, 128.5, 128.1, 127.8, 118.0, 113.8, 54.1, 46.0. HRMS (EI): m/z calculated for [M+H] $^+$ [$C_{21}H_{19}ClNO$] 336.1154.

3-(4-Chlorophenylamino)-1,3-diphenylpropan-1-one (4d):

White solid; M.P: 171-172ºC; FTIR (KBr, νmax, cm^{-1}): 3369, 3024,2932,1663, 1598, 1496, 1283, 809, 680; ; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.90 (d, J=8 Hz,2H), 7.56 (t, J = 4 Hz, 1H), 7.39-7.45 (m, 4H), 7.25-7.33 (m, 2H), 7.01 (d, J = 8 Hz, 2H), 6.46 (d, J = 8 Hz, 2H), 4.94 (t, J = 8 Hz, 1H), 4.60 (s, 1H,-NH), 3.48 (dd, J = 16 and 8 Hz, 1H), 3.48 (dd, J = 16 and 8 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 145.6, 142.5, 136.6, 133.5, 128.9, 128.7, 128.2, 127.5, 126.3, 122.4, 114.9, 54.9, 46.2. HRMS (EI): m/z calculated for [M+H]$^+$ [$C_{21}H_{19}ClNO$] 336.1154.

3- ((4-Chlorophenyl) amino) -3-phenyl-1- (p-tolyl) propan-1-one (4j):

White solid, M.P.: 110–111 °C. FTIR (KBr, cm^{-1}): 3385, 3025, 2918, 1662, 1598, 1288, 807,698.

^{1} H NMR (500 MHz, CDCl3) δ 7.79 (d, J=8.0 Hz, 2H), 7.40 (d, J=7.5 Hz, 2H), 7.31 (t, J=7.5Hz ,8 Hz, 2H), 7.24 (dd, J=8, 5.5 Hz, 3H), 7.0 (d, J=8.5 Hz, 2H), 6.45 (d, J=8.5 Hz, 2H), 4.91 (s, 1H), 4.66(s,1H), 3.45 (dd, J=16, 5 Hz, 1H), 3.36 (dd, J=16, 8 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 197.8, 145.6, 144.4, 142.6, 134.1, 130.4, 129.4, 129.3, 129.1, 128.9, 128.6, 128.4, 128.3, 127.6, 127.4, 126.3, 122.3, 122.1, 114.9, 55.0, 46.1, 21.6.; HRMS (ESI+): m/z calcd for C22H21ClNO [M + H] $^+$ 350.1306; found 350.1307.

3-Phenyl-3-(phenyl amino)-1-(p-tolyl)propan-1-one (4k) :

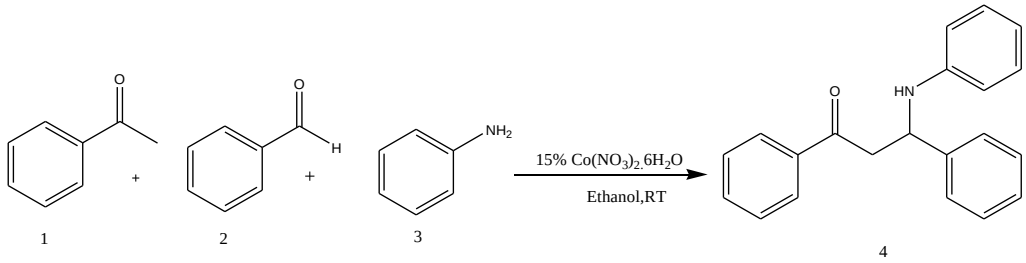
Gray solid, M.P.: 120–122 °C. FTIR (KBr, cm^{-1}): 3379, 3023, 1661, 1598, 1286, 747,693. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J=8.0 Hz, 2H), 7.43 (d, J=7 Hz, 2H), 7.21-7.32 (m, 5H), 7.27 (d, J=7.6 Hz, 3H), 7.05-7.09 (m, 2H), 6.64 (t, J=14.5, 7.5 Hz, 1H), 6.55 (d, J=8.5 Hz, 2H), 4.98 (t, J=7.5, 5 Hz, 1H), 4.56 (s,1H), 3.49 (dd, J=16.0, 5 Hz, 1H), 3.37 (dd, J=16.0, 7.5 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 147.0, 144.3, 143.1, 134.2, 129.4, 129.1, 128.8, 128.3, 127.3, 126.3, 117.7, 113.8, 54.9, 46.2, 21.6.; HRMS (ESI+): m/z calcd for C22H22NO [M + H$^+$ 316.1306;

RESULTS AND DISCUSSION:

Cobalt nitrate reagent was explored for the synthesis of β-amino ketones derivatives as an efficient catalyst. The reaction of aromatic aldehydes, acetophenone and aniline in ethanol was carried out at room temperature. Initially, for reaction conditions optimization, the condensation reaction of benzaldehyde, acetophenone and aniline in ethanol at room temperature was used as a model reaction (Scheme 1). When the reaction of benzaldehyde (1.0 mmol) was carried out with acetophenone (1.0 mmol) and aniline (1.0 mmol) in ethanol (5.0 mL) at room temperature for 24 hours in absence of cobalt nitrate catalyst, no significant yield is obtained (Table 1, entry 1). This means that the involvement of catalyst is necessary for the initiation of the reaction. By increasing the amount of catalyst used from 2 to 15

mol%, the yield gradually increased from 42 to 94% (Table 1, entries 2-7). The obtained results show that the best yield for the synthesis of compound **4** were observed when using 15 mol% of the catalyst, the reaction completes in 11 hours with a yield of 94% at room temperature (Table 1, entry 6). Increasing the concentration from 15 to 20 mol% of cobalt nitrate, at room temperature, does not result in any noticeable changes in the reaction time or yields (Table 1, entries 6-7).

With these optimized reaction conditions, effect of different solvents such as THF, DMF, $CHCl_3$, CH_2Cl_2, acetonitrile and ethanol were investigated (Table 2). Among the tested solvents, ethanol was found to be better over the other tested solvents in terms of both yield of the product and reaction time (Table 2 Entry 6) for this transformation.



Scheme 1 synthesis of β-amino carbonyl compounds via Mannich-reaction.

Table 1 The direct Mannich reaction: effect of catalysis [a]

Entry	Amount of catalyst (mol %)	Time (h)	Yield (%) [b]
1	-	24	Trace
2	2	18	42
3	5	15	65
4	7	14	76
5	10	12	82
6	15	11	94
7	20	11	94

[a] **Reaction conditions**: acetophenone (1.0 mmol); benzaldehyde (1.0 mmol); aniline (1.0 mmol) and ethanol (5.0 ml) at room temperature. [b] Isolated yields.

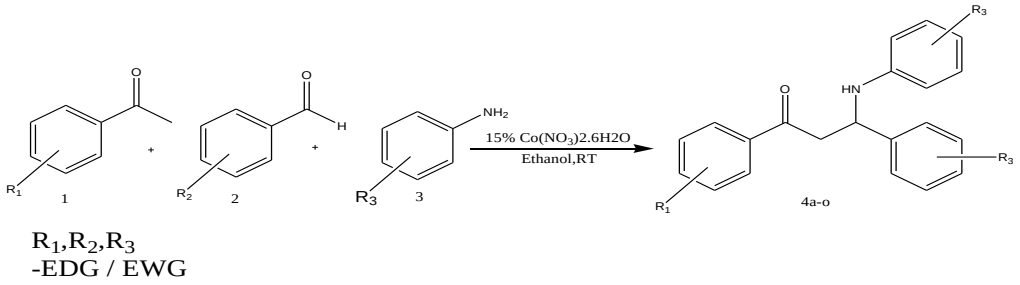
Table 2 The direct Mannich reaction catalyzed by 15 mol% cobalt nitrate hexahydrate in different solvents: effect of solvents[a]

Entry	Solvent	Reaction Time (h)	Yield (%)[b]
1	THF	36	20
2	DMF	36	25
3	$CHCl_3$	24	28
4	CH_2Cl_2	24	30
5	CH_3CN	20	60
6	EtOH	11	94

[a]**Reaction conditions:** acetophenone (5 mmol); benzaldehyde (5 mmol); aniline (5 mmol) at room temperature [b]Isolated yields.

As a results, further set of experiments, in order to make the generality of the reaction, various aromatic aldehydes having both electron-donating as well as electron-withdrawing substituents were transformed into β-amino carbonyl compounds via Mannich-reaction in

high to excellent yields. Aromatic amine substrates (m-and p-substituted) with electron donating group-substituted amines afforded the corresponding products in better yields than electron-withdrawing group substituted amines (Table 1, b,d,f,g entries). Strongly electron withdrawing substituents like 4-NO_2 and o-substituted amines failed to yield any desired product due to steric hindrance of ortho-substituents. The entire results are summarized in Table 3.



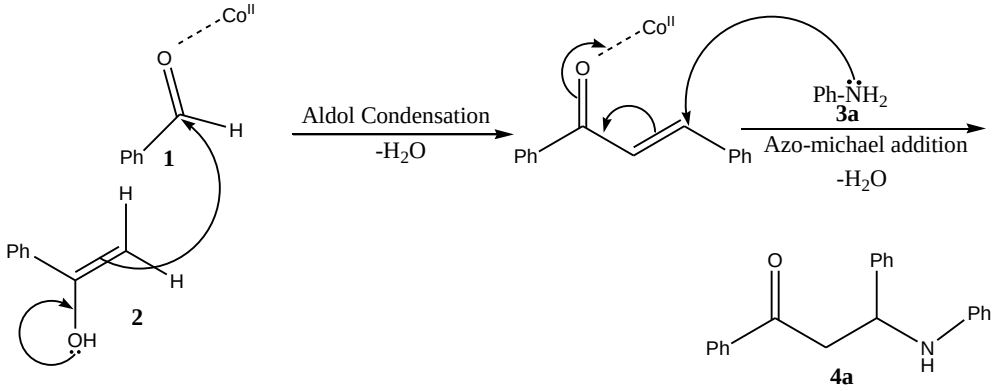
Scheme 2 Mannich reaction between substituted aromatic aldehydes, ketones and anilines

Table 3 synthesis of β-amino carbonyl compounds via Mannich-reaction[a].

Entry	Ketones ($-R_1$)	Aldehydes (R_2)	Amines (R_3)	Time (hr)	Yield (%)[b]	Melting Point ^oC
4a	-H	-H	-H	11	93	**169-170**
4b	-H	-H	*p*-CH_3	12	91	138–139
4c	-H	*p*-Cl	-H	10	92	**106-107**
4d	-H	-H	*p*-Cl	13	84	**171-172**
4e	-H	*p*-OCH_3	-H	12.5	82	**149-150**
4f	-H	*p*-Cl	*p*-Cl	11.5	90	**119-121**
4g	-H	*p*-CH_3	*H*	10.5	93	**133-134**
4h	-H	*p*-NO_2	-H	14	68	**108-110**
4i	-H	-H	*p*-NO_2	15	Trace	-
4j	*p*-CH_3	-H	*p*-Cl	10	90	**110-111**
4k	*p*-CH_3	-H	-H	11	89	**120-122**
4l	*p*-OCH_3	-H	-H	13	85	**136-138**
4m	-H	*p*-F	-H	11	91	**102-104**
4n	-H	*H*	m-Cl	11	89	**130-131**
4o	-H	*p*-Br	-H	13	86	**138-139**

[a] **Reaction conditions**: acetophenone (1.0 mmol); benzaldehyde (1.0 mmol); aniline (1.0 mmol) and 15 mol% Cobalt nitrate in ethanol (5.0 ml) at room temperature.
[b] Isolated yields.

Mechanism: The mechanism of the reaction first carried out by aldol condensation and then followed by the azo michael addition reaction to produce desired Mannish base product (Scheme 3), involving $Co(NO_3)_2.6H2O$ as catalyzed three-component Mannish reaction afford the desired Mannish base (Scheme 3). The Mechanism involves the $Co(NO_3)_2.6H2O$. to strongly activate the carbonyl compounds, hence, the reaction goes via aldol condensation to produce intermediates 3a, then the compound 3a reacts with 3b via Azo-Michael addition type reaction and gives desire product 4a.



Scheme 3 Proposed mechanism for Mannish reaction 4a

CONCLUSION:

In summary, we have developed a novel and efficient method for the synthesis of functionalized β-amino ketones derivatives through the one-pot multi-components via mannich reaction in presence of cobalt nitrate hexahydrate (Co $(NO_3)_2.6H_2O$ as a catalyst. This protocol exhibits a wide range of applications for various easily accessible mannich bases under mild reaction conditions, and the corresponding products were obtained in good to excellent yields. These results will offer considerable applications to complex targets in organic and medicinal chemistry.

ACKNOWLEDGEMENT:

Authors are thankful to Chairman Bhimthadi Education Society's and Principal, Late Kisandas Gulabchand Kataria College, Daund,.Dist-Pune Maharashtra (India) for providing necessary laboratory facilities to carry out this work.

REFERENCES:

i. Filho J.F.A.; Lemos B. C.; De Souza A.S.; Pinheiro S.; and Greco S.J.; Multicomponent Mannich reactions:General aspects, methodologies and applications; Tetrahedron; 2017, **73**(50), 6977-7004.

ii. Mannich C.; Eine Synthese von β-ketonbasen; Arch. Pharm.; 1917, **255**(2-4),261–276.

iii. Arend M.; Westermann B.; Risch N.; Modern variants of the Mannich reaction; Angew. Chem.Int. Ed.;1998,**37**(8),1044-1070.

iv. Kobayash S.; Ishitani H.; Catalytic enantioselective addition to imines; Chem Rev.; 1999, **99**(5), 1069–1094.

v. Filho J.F.A.; Lemos B. C.; De Souza A.S.; Pinheiro S.; and Greco S.J.; Multicomponent Mannich reactions: General aspects, methodologies and applications;Tetrahedron; 2017, **73**(50), 6977-7004.

vi. Paul J.; Presset M.; Le Gall E.; Multicomponent Mannich-like reactions of organometallic species.*;* Eur.J.Org.Chem.;2017,**2017**(17),2386–2406.

vii. Toure B.B.; Hall D.G.; Natural product synthesis using multicomponent reaction strategies; Chem.Rev.;2009, **109**(9),4439–4486.

viii. Roman G.; Mannich bases in medicinal chemistry and drug design: Euro.J.Med Chem.; 2015,89,743–816.

ix. Subramaniapillai S.G.; Mannich reaction: A versatile and convenient approach to bioactive skeletons; J. Chem. Sci.; 2013, **125**(3),467–482.

x. a) Tucker, M.L; Jackson, M.R; Scales, M.D; Spurling, N.W; Tweats, D.J; Capel-

Edwards,K; Ondansetron: pre-clinical safety evaluation. European journal of cancer & clinical oncology, **1989,** 989, 25, pp. S79-93. PMID: **2533905** b) Dicato, M.A; Oral treatment with ondansetron in an outpatient setting . European journal of cancer. 27 (1991) S18 PMID: **1831630** c) Patel, K; Allen, S; Haque, M. N; Angelescu, I; Baumeister, D; Tracy, D.K; Bupropion: a systematic review and meta-analysis of effectiveness as an antidepressant. Ther Adv. Psychopharmacol, 2016,6, 99–144. d) O'Byrne, P.M; Williams, R; Walsh, J.J. J.F; Synthesis, Screening and Pharmacokinetic Evaluation of Potential Prodrugs of Bupropion. Part One: *In Vitro* Development. Pharmaceuticals, 2014,7, 595–620.

xi. a) Hashmi H.R.T.; Jabbour R.; Schreiber Z.; Khaja, M.; Benazepril-Induced Agranulocytosis: A Case Report and Review of the Literature Am J Case Rep.;2016, 17,425-428. b) Rezka M.R.; Badr K.A.; Application to a bioequivalence study; J. Pharm. Biomed. Anal.; 2014, 98,1-8.

xii. Yi W.B.; Cai C.; Mannich-type reactions of aromatic aldehydes, anilines, and methyl ketones in fluorous biphase systems created by rare earth (III) perfluorooctane sulfonates catalysts in fluorous media; Journal of Fluorine Chemistry; 2006,**127**(11),1515-1521**.**

xiii. Eftekhari-Sis B.; Abdollahifar A.; Hashemi M.M.; Zirak M.; Stereoselective Synthesis of β-Amino Ketones via Direct Mannich-Type Reactions, Catalyzed with $ZrOCl_2 \cdot 8H_2O$ under Solvent-Free Conditions; Eur. J. Org. Chem.; 2006, **2006**(22), 5152-5157.

xiv. Yang Y.Y.; Shou W.G.; Wang Y.G.; Synthesis of β-amino carbonyl compounds via a $Zn(OTf)_2$-catalyzed cascade reaction of anilines with aromatic aldehydes and carbonyl compounds; Tetrahedron, 2006; **62**(43),10079–10086.

xv. Yang R.W.; Li B.G.; Huang, T.K.; Shi L.; Lu X.X.; $NbCl_5$-Catalyzed one-pot Mannich-type reaction: Three component synthesis of β-amino carbonyl compounds; Tetrahedron Lett.; 2007, **48**(12),2071-2073.

xvi. Wang M.; Song Z.G.; Wan X.; Zhao S.; $SnCl_2$-catalyzed three-component one-pot Mannich-type reaction: Efficient synthesis of β-aminocarbonyl compounds; Monatsh Chem.; 2009,**140**(10),1205–1208.

xvii. Wang M.; Song Z.G.; Liang Y.; $SnCl_4$ $5H_2O$-Catalyzed synthesis of β-amino carbonyl compounds via a direct Mannich-type reaction; Preparative Biochemistry &Biotechnology; 2011,**41**(1),1–6.

xviii. Li H; Zeng H.Y.; Shao H.W.; Bismuth (III) chloride-catalyzed one-pot Mannich reaction: Three-component synthesis of β-amino carbonyl compounds; Tetrahedron Lett.; 2009,**50**(49), 6858–6860.

xix. Dai Y.; Li B.D.; Quan H.D.; Lu C.X.; $CeCl_3$ $7H_2O$ as an efficient catalyst for one-pot synthesis of β-amino ketones by three-component Mannich reaction. Chine. Chem. Lett.; 2010,**21**(1),31–34.

xx. Kidwai M.; Bhatnagar D.; Mishra N K.; Bansal V.; CAN catalyzed synthesis of β-amino carbonyl compounds via Mannich reaction in PEG; Catalysis Commun.; 2008,**9**(15),2547–2549.

xxi. Kureshy R.I.; Agrawal S.; Saravanan S.; Khan N.H.; Shah A.K.; Abdi S.H.R.; Bajaj H.C.; Suresh E.; Direct Mannich reaction mediated by $Fe(Cp)_2PF_6$ under solvent-free conditions; Tetrahedron Lett. 2010,**51**(3),489–494.

xxii. Sheik Mansoor S.; Aswin K.; Logaiya K.; Sudhan S.P.N.; An efficient synthesis of β-amino ketone compounds through one-pot three-component Mannich-type reactions using bismuth nitrate as catalyst; Journal of Saudi Chemical Society;2015,**19**(4),379-386.

xxiii. Udgire S.; Gaikwad M.; Patil P.; Bi(OTf)3 as a Highly Potent Catalyst for the Synthesis of Mannich Bases under Milder Conditions; Journal of Applied Organometallic Chemistry; 2022, **2**(1),31-38.

xxiv. Zhang G.L.; Huang Z.H.; Zou J.P.; $Ga(OTf)_3$-catalyzed Three-component Mannich reaction in water promoted by ultrasound irradiation; Chin. J.Chem.;2009;**27**(10),1967- 1974.

xxv. Yi L.; Lei H.S.; Zou J.H.; Xu X.J.; The Mannich Reaction of Butanone, Aromatic Aldehydes and Aromatic Amines; Synth.Commun.;1991,**21**(20),2109-2117.

xxvi. Wu Y-S.; Cai J.; Hu Z- Y.; Lin G X.; A new class of metal-free catalysts for direct diastereo- and regioselective Mannich reactions in aqueous media; Tetrahedron Lett.; 2004, **45**(48),8949-8952.

xxvii. Bigdeli M.A.; Nemati F.; Mahdavinia G.H.; HClO4–SiO2 catalyzed stereoselective synthesis of β-amino ketones via a direct Mannich-type reaction; Tetrahedron Lett.; 2007,**48**(38), 6801–6804.

xxviii. Iimura S.; Nobuton D.; Manabe K.; Kobayashi, S; Mannich-type reactions in water using a hydrophobic polymer-supported sulfonic acid catalyst; Chem. commun.; 2003, 14, 1644–1645.

xxix. Azizi, B; Torkiyan, L; Saidi, M.R; Highly efficient one-pot three-component Mannich reaction in water catalyzed by heteropoly acids. Org. Lett.; 2006, **8**(10), 2079–2082.

xxx. Manabe K.; Kobayashi S.; Mannich-type reactions of aldehydes, amines, and ketones in a colloidal dispersion system created by a Brønsted acid-surfactant-combined catalyst in water; Org. Lett.; 1999, **1**(12),1965–1967.

xxxi. Alvim, H.G.O; Bataglion, G.A; Ramos, L.M.; De Oliveira, A.L; De Oliveira, H.C.B; Eberlin, M.N; De Macedo, J.L; Da Silva, W.A; Task-specific ionic liquid incorporating anionic heteropolyacid-catalyzed Hantzsch and Mannich multicomponent reactions. Ionic liquid effect probed by ESI-MS (/MS) Tetrahedron, 2014,**70**(20),3306–3313.

xxxii. Wu Y.; Wang X.; Luo Y.L.; Wang J.; Jian Y.J.; Sun H.M.; Zhang G.F.; Zhang W.Q.; Gao Z.W.; Solvent strategy for unleashing Lewis acidity of titanocene dichloride for rapid Mannich reactions; RSC Adv.; 2016, 6,15298–15303.

xxxiii. Zhang X.W.; Yin S.F.; Qiu R.H.; Xia J.; Dai W.L.; Yu Z.Y.; Au C.T.; Wong W.F.; Synthesis and structure of an air-stable hypervalent organobismuth (III) perfluorooctanesulfonate and its use as high-efficiency catalyst for Mannich-type reactions in water; Journal of Organometallic Chemistry; 2009,**694**(22),3559–3564.

xxxiv. Xia J.; Qiu R.H.; Yin S.F.; Zhang X.W.; Luo S.L.; Au C.T.; Xia K.; Wong W.Y.; Synthesis and structure of an air-stable organoantimony complex and its use as a catalyst for direct diastereoselective Mannich reactions in water; Journal of Organometallic Chemistry, 2010,**695**(10-11),1487–1492.

xxxv. Qiu R.H.; Xu X.H.; Peng L.F.; Zhao Y.L.; Li N.B.; Yin S.F.; Strong Lewis acids of air-stable metallocene bis(perfluorooctanesulfonate)s as high-efficiency catalysts for carbonyl group transformation reactions; Chem.Eur.J.; 2012,**18**(20),6172–6182.

xxxvi. Khan A.T.; Parvin T.; Choudhury L.H.; Bromodimethylsulfonium bromide catalyzed three-component Mannich-type reactions; Eur.J.Org.Chem.;2008,**2008**(5),834–839.

xxxvii. Zhang Y.X.; Han J.W.; Liu Z.J.; Diaryliodonium salts as efficient Lewis acid catalysts for direct three component Mannich reactions; RSC Adv.; 2015,**5**(32), 25485–25488.

xxxviii. Azizi N.; Baghi R.; Batebi E.; Bolourtchian, S.M; Catalytic stereoselective

Mannich reaction under solvent-free conditions; Comptes Rendus Chimie, 2012, **15**(4), 278–282.

Received on July 5, 2024.