Asian Pub. Corp.

www.asianpubs.org

ARTICLE

Study of CuSCN Catalyzed Conjugate Addition Reactions of Grignard Reagents to Substituted Chalcones with Dilithium Tetrachloromanganate and their Biological Activities

Mohan B. Kale, Shrikant B. Jagtap✉ and Santosh S. Devkate

Asian Journal of Organic & Medicinal Chemistry

Volume: 6 Year: 2021
Issue: 2 Month: April–June
pp: 141–147
DOI: https://doi.org/10.14233/ajomc.2021.AJOMC-P327

Received: 3 June 2021
Accepted: 26 June 2021
Published: 24 July 2021

ABSTRACT

The regioselective 1,4-addition reactions of copper thiocyanate catalyzed Grignard reagents to the substituted chalcones are reported. The homogeneous solution of dilithium tetrachloromanganate is used to transmetallate magnesium by using manganese. It adds regioselectively to substituted chalcone derivatives and forms 1,4-addition products with higher yield under nitrogen atmosphere and at a lower temperature. It have been observed that manganese from dilithium tetrachloromanganate reagent replaces magnesium from Grignard reagent and adds regioselectively by 1,4-addition manner utilizing copper thiocyanate as a catalyst. The course of the reaction in the absence of dilithium tetrachloromanganate reagent was also studied and obtained a mixture of 1,2-addition and 1,4-addition products. In presence of dilithium tetrachloromanganate reagent, a good regioselectivity and higher yield of desired 1,4-addition product were obtained. All the synthesized compounds were also evaluated for their antibacterial activity against *Staphylococcus aureus* (Gram-positive), *Escherichia coli* (Gram-negative) and antifungal activity against *Aspergillus niger*.

KEYWORDS

Dilithium tetrachloromanganate, Copper thiocyanate, Chalcones, Grignard reagent, 1,4-Addition, Antimicrobial activities.

INTRODUCTION

Enantioselective copper-catalyzed 1,4-addition reactions with Grignard reagents or organozinc to enones are the important resources in organic synthesis [1]. Substrate similar to chalcone [2], cyclohexenone [3] and chromone [4] are of particular importance, medical applications arise for enantiopure 1,4-addition products [5]. A wide range of fenchol-based ligands [6] has established applications in enantiopure, chiral organolithium aggregates [7] in addition to enantioselective organozinc catalysts [8]. Step-by-step procedures in which each reaction step is accompanied by a purification process, are slow and tedious work. Therefore, stereoselective domino reactions or *in situ* provisions of reactions represent a significant development because of the step economy [9]. Implementing such conversions in a catalytic approach adding to that benefits. Domino reaction needs a suitable initiator reaction, which establishes reactive compounds for the successive step.

Author affiliations:

Department of Chemistry, Annasaheb Magar Mahavidyalaya, Hadapsar, Pune-411028, India

✉To whom correspondence to be addressed:

E-mail: drshrikantjagtap@yahoo.com

Available online at: http://ajomc.asianpubs.org

An advantageous beginning reaction is a metal-catalyzed 1,4-addition of organometallic reagents to α,β-unsaturated carbonyl compounds [10-18]. The 1,4-addition of organometallic nucleophiles provides reactive metal enolates, which can be beneficially reacted with a wide variety of electrophilic compounds [19,20]. Such enolate-based organic reactions work properly with aldehydes [21-25], alkyl halides [26,27], allylic bromides, acetates [28-31] and nitroso compounds [32]. Metal enolates also react with epoxides [33] participate in cyclopropanation or cross-coupling [34] reactions [35]. The hypothesis was also applicable in an intramolecular manner with additional unsaturated carbonyl compounds [36-38]. Organocopper reagent has been determined as a superior reagent for conjugate addition reaction and is easily accessible by reaction of copper(I) salt with organometallics like organolithium, Grignard reagent or organozinc [39]. Organomagnesium halides and organolithium reagents are similarly applicable for the manufacture of the required alkyl rhodium(I) complexes. These complexes react without difficulty with benzoyl, alkoyl and cinnamoyl chlorides in addition to those of increased complexity to synthesize unsymmetrical ketones in higher yields. Additionally, alkylrhodium(I) complexes do not react with esters, aldehydes or nitriles as acknowledged by the quantitative recovery of ethyl benzoate, benzaldehyde and benzonitrile added simultaneously with the acid chloride and carried out through the normal reaction and isolation processes. Thus, this process allows the ready transformation of acid chlorides to ketones in higher yield under mild reaction conditions (-78 ºC, THF), in the presence of other highly reactive functional groups [40]. An additional advantage is that the starting compound halogenorhodium complex is converted in the recyclable form in the last step, eliminating the requirement for constant resynthesis and resulting in no net intake of the rhodium complex.

Carbonyl alkylation for a long time acknowledged being one of the greatest C-C bond formation reactions in organic chemistry [41]. Specifically, interest has been concentrated on the diastereoselective addition of carbon nucleophiles. Grignard reagents and organolithium to a carbonyl compound having at a minimum one chiral center, resulting in what has been called "1,4-asymmetric induction". Among them, the addition of carbon-based nucleophiles to chiral centers or *p*-alkoxy ketones or aldehydes has been broadly investigated in the last few years [42]. Consequently, two approaches (non-chelation and chelation control) have been developed which permitted the achievement of opposite perception of diastereoselectivity by adequately selecting organometallic reagents. These methodologies have been effectively applied in a variety of natural product syntheses including pheromones, ionophores and carbohydrates [43]. In contrast, the alkylation reaction of ordinary chiral ketones and aldehydes having no capacity to be chelated is constrained by the steric and electronic factors (non-chelation control) and the diastereochemical results would be anticipated by the Cram rule [44]. Here, the several investigations so far have been reported for obtaining only one side of selectivity, that is axial selectivity for cyclic ketones and Cram selectivity for acyclic carbonyl compounds and the respective equatorial and anti-Cram selectivity have not been accomplished in absence of suitable methodologies. The main aim of the study is the development of a reasonable methods to this problem, which provides a high level of diastereo facial selectivity earlier to quite complicated by the recent methodologies [45].

EXPERIMENTAL

The chemicals for the reaction were purchased from Merck and used after purification. These chemicals were purified by distillation technique. The solvents used for the reaction were dried by different techniques like the Na-benzophenone method for THF drying. IR spectra were determined on a Shimadzu Miracle 10 ATR instrument. ^{1}H NMR spectra were recorded on a bruker 500 MHz spectrometer with $CDCl_3$ as a solvent and TMS as the internal standard. ^{13}C NMR spectra were recorded on Bruker 125 MHz spectrometer with $CDCl_3$ as the solvent. Column chromatography was conducted on silica gel 60 (70-230) mesh. Thin-layer chromatography (TLC) was carried out on aluminum sheets precoated with silica gel.

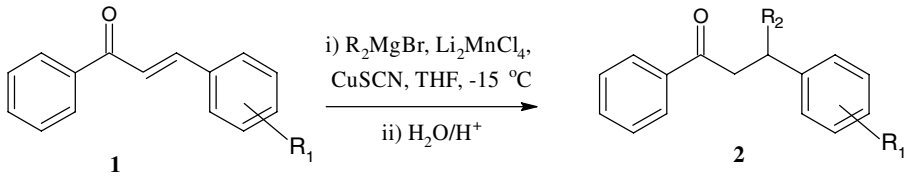
Preparation of Li_2MnCl_4 solution: In a 250 mL single necked round bottom flask were added LiCl (1 M, 10.598 g) and $MnCl_2$ (1 M, 15.730 g) and dried under vacuum at 250 ºC for about 3 h and the solution was allowed to cool at room temperature followed by the addition of 125 mL dry THF. The prepared solution was kept under stirring overnight at room temperature, which is a homogeneous brown coloured 1 M solution of Li_2MnCl_4 and stable at room temperature for several days.

Preparation of Grignard reagent: In a 100 mL three-necked round bottom flask formerly dried using a heating gun and flushed with purified nitrogen gas were added magnesium turnings (0.243 g) and diethyl ether (50 mL), to which added iodine to start the reaction followed by added alkyl/aryl bromide (1.57 g) dropwise by syringe through the septum. After the complete addition of alkyl/aryl halide, the mixture was stirred at room temperature for about 1 h to get a homogenous 1 M solution of Grignard reagent.

Addition of Grignard reagent to chalcone: In a 100 mL three-necked round bottom flask was added dry THF (10 mL), followed by the addition of Grignard reagent (10 mmol) and Li_2MnCl_4 solution (10 mmol) to which added CuSCN (10 mol %) and dropwise addition of chalcone (10 mmol) in THF at -15 ºC, after complete addition of chalcone derivative the conversion of reactant to the product was studied by thin-layer chromatography and reaction were worked up with dil. HCl and stirred for 15 min. The product was extracted with diethyl ether (10 mL × 3) and dried over anhydrous Na_2SO_4 (**Scheme-I**).

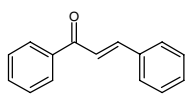
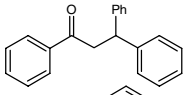
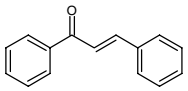
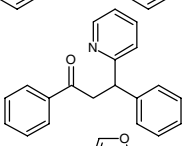
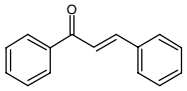
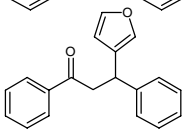
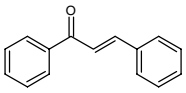
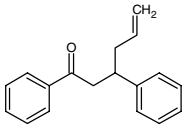
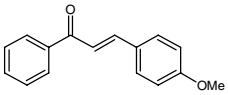
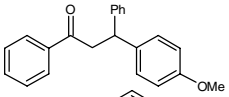
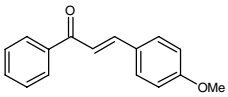
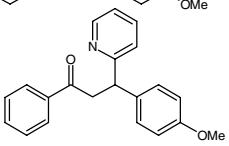
Spectral data of compounds

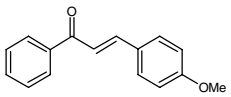
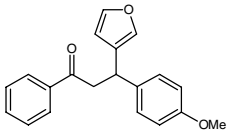
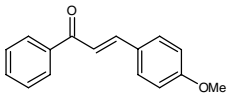
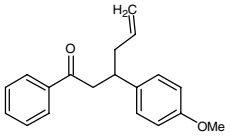
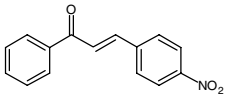
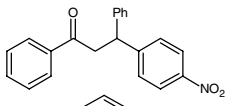
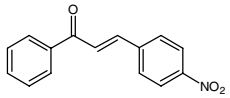
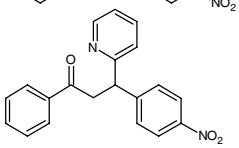
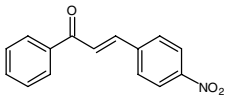
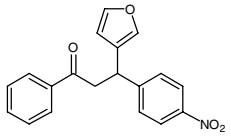
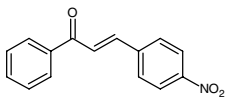
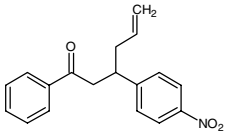
1,3,3-Triphenylpropan-1-one (2a): Colourless liquid, m.f.: $C_{21}H_{18}O$, IR (KBr, ν_{max}, cm^{-1}): 695, 1710, 1600, 2900, 3000. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 7.82 (m, *J* = 8, 2.5 & 0.2 Hz, 2H), 7.35 (m, *J* = 8.1, 2.4 & 0.2 Hz, 2H), 7.42 (dd, *J* = 8 & 2.5 Hz, 1H), 3.43 (d, *J* = 7 Hz, 2H), 4.76 (t, *J* = 7.0 Hz, 1H), 7.25 (m, *J* = 8, 2.5 & 0.1 Hz, 4H), 7.27 (m, 8.1, 2.4 & 0.3 Hz, 4H), 7.19 (dd, 8 & 2.5 Hz, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 136.88, 128.40, 128.64, 132.69, 197.36, 45.84, 48.67, 143.62, 129.49, 128.92, 126.77, Anal. calcd.



1 **2**

R_1= H, *p*-OMe, *p*-NO_2 R_2= Ph, 2-Pyridyl, 3-Furyl, Allyl

Entry	Reactant	Product	Time (min)	Yield (%)
2a			40	82
2b			50	76
2c			55	71
2d			45	80
2e			60	68
2f			70	65

Entry	Reactant	Product	Time (min)	Yield (%)
2g			65	63
2h			60	70
2i			35	86
2j			45	76
2k			50	72
2l			45	82

Scheme-I: Addition of Grignard reagents to substituted chalcones

(found) % for $C_{21}H_{18}O$: C, 88.08 (88.09), H, 6.34 (6.33), O, 5.59 (5.59).

1,3-Diphenyl-3-(pyridin-2-yl)propan-1-one (2b): Pale yellow liquid, m.f.: $C_{20}H_{17}NO$, IR (KBr, ν_{max}, cm^{-1}): 1710, 1600, 1650, 2926, 3000, 710. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.83 (m, *J* = 8, 2.4 & 0.1 Hz, 2H), 7.35 (m, *J* = 8, 2.5 & 0.1 Hz, 2H), 7.42 (dd, *J* = 8 & 2.5 Hz, 1H), 3.32 (d, *J* = 7 Hz, 2H), 4.75 (t, *J* = 7 Hz, 1H), 7.24 (m, *J* = 8, 2.3 & 0.3 Hz, 2H), 7.26 (m, *J* = 8, 2.4 & 0.2 Hz, 2H), 7.19 (dd, *J* = 8.1 & 2.5 Hz, 1H), 7.47 (ddd, *J* = 7.68, 1.20 & 0.50 Hz, 1H),7.67 (ddd, *J* = 7.69, 7.33 & 1.81 Hz, 1H), 7.22 (ddd, *J* = 7.36, 4.55 & 1.22 Hz, 1H), 8.59 (ddd, *J* = 4.58, 1.88 & 0.54 Hz, 1H). ^{13}C NMR, (125 MHz, $CDCl_3$) δ ppm: 136.88, 128.40, 128.64, 132.69, 197.36, 44.40, 51.75, 143.21, 129.69, 128.93, 126.72, 165.50, 127.76, 140.43, 120.90, 146.60, Anal. calcd. (found) % for $C_{20}H_{17}NO$: C, 83.59 (83.58), H, 5.96 (5.97), N, 4.87 (4.88), O, 5.57 (5.56).

3-(Furan-3-yl)-1,3-diphenylpropan-1-one (2c): Pale yellow liquid, m.f.: $C_{19}H_{16}O_2$, IR (KBr, ν_{max}, cm^{-1}): 1715, 1600, 1100, 2920, 3010, 690. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.79 (m, *J* = 8.1, 2.4 & 0.3 Hz, 2H), 7.33 (m, *J* = 8.2, 2.5 & 0.3 Hz, 2H), 7.40 (dd, *J* = 8.2, 2. 5 & 0.3 Hz, 1H), 3.29 (d, *J* = 7 Hz, 1H), 4.80 (t, *J* = 7 Hz, 1H), 7.23 (m, *J* = 8.1, 2.4 & 0.2 Hz, 2H), 7.25 (m, *J* = 8.2, 2.4 & 0.2 Hz, 2H), 7.17 (dd, *J* = 8.3 & 2.5 Hz 1H), 6.38 (dd, *J* = 1.74 & 0.91 Hz 1H), 7.33 (dd, *J* = 1.75 & 1.05 Hz 1H), 7.39 (dd, *J* = 1.06 & 0.91 Hz 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 136.88, 128.40, 128.4, 132.69, 198.58, 48.59, 40.45, 141.41, 129.90, 128.11, 128.18, 128.22, 112.46, 146.19, 140.30, Anal. calcd. (found) % for $C_{19}H_{16}O_2$: C, 82.58 (82.56), H, 5.84 (5.85), O, 11.58 (11.59).

1,3-Diphenylhex-5-en-1-one (2d): Colourless liquid, m.f.: $C_{18}H_{18}O$, IR (KBr, ν_{max}, cm^{-1}): 2970, 1600, 1710, 3000, 940, 695. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.80 (m, *J* = 8, 2.5 & 0.3 Hz, 2H), 7.35 (m, *J* = 8, 2.4 & 0.1 Hz, 2H), 7.42 (dd, *J* = 8 & 2.5 Hz, 1H), 3.21 (d, *J* = 7 Hz, 2H), 3.12 (t, *J* = 7 Hz, 1H), 7.29 (m, *J* = 8.1, 2.6 & 0.2 Hz, 2H), 7.26 (m, *J* = 8.1, 2.5 & 0.2 Hz, 2H), 7.15 (dd, *J* = 8 & 2.5 Hz, 1H), 2.17 (d, *J* = 7.7 Hz, 2H), 5.69 (m, *J* = 12, 17 & 7.6 Hz, 1H), 5.04 (dd, *J* = 10, 17 & 2.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 136.88, 128.40, 128.64, 132.69, 198.81, 43.09, 42.72, 144.49, 127.84, 128.50, 127.16, 36.45, 134.31, 117.63. Anal. calcd. (found) % for $C_{18}H_{18}O$: C, 86.36 (86.35), H, 7.25 (7.27), O, 6.39 (6.38).

3-(4-Methoxyphenyl)-1,3-diphenylpropan-1-one (2e): Colourless liquid, m.f.: $C_{22}H_{20}O_2$, IR (KBr, ν_{max}, cm^{-1}): 2971, 1600, 1120, 3000, 790, 695, 1715. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.84 (m, *J* = 8, 2.6 & 0.3 Hz, 2H), 7.38 (m, *J* = 8, 2.5 & 0.2 Hz, 2H), 7.45 (dd, *J* = 8 & 2.4 Hz, 1H), 3.17 (d, *J* = 7.5 Hz, 2H), 4.74 (t, *J* = 7 Hz, 1H), 7.21 (m, *J* = 8, 2.4 & 0.2 Hz, 2H), 6.99 (m, *J* = 8.1, 2.4 & 0.3 Hz, 2H), 3.80 (S, 3H), 7.09 (m, *J* = 8.1, 2.4 & 0.2 Hz, 2H) 7.13 (m, *J* = 8.0, 2.4 & 0.3 Hz, 2H), 7.21 (dd, *J* = 8 & 2.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 136.88, 128.40, 128.64, 132.69, 197.36, 45.84, 48.67, 135.79, 129.52, 114.16, 157.96, 143.62, 129.49, 128.92, 126.77. Anal. calcd. (found) % for $C_{22}H_{20}O_2$: C, 83.51 (83.52), H, 6.37 (6.38), O, 10.11 (10.13).

3-(4-Methoxyphenyl)-1-phenyl-3-(pyridin-2-yl)propan-1-one (2f): Pale yellow Liquid, m.f.: $C_{21}H_{19}NO_2$, IR (KBr, ν_{max}, cm^{-1}): 2930, 1640, 1150, 3000, 1645, 1600, 695, 820. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.85 (m, *J* = 8, 2.5 & 1.5 Hz, 2H), 7.38 (m, *J* = 8, 2.5 & 1.5 Hz, 2H), 7.45 (dd, *J* = 8 & 2.5 Hz, 1H), 3.20 (d, *J* = 7 Hz, 2H), 4.74 (t, *J* = 7 Hz, 1H), 7.19 (m, *J* = 8, 2.4 & 0.6 Hz, 2H), 6.98. (m, *J* = 8.2, 2.4 & 0.5 Hz, 2H), 3.81 (S, 3H), 7.31 (ddd, *J* = 7.66, 1.20 & 0.40 Hz, 1H), 7.52 (ddd, *J* = 7.68, 7.32 & 1.81 Hz, 1H), 7.22 (ddd, *J* = 7.35, 4.61 & 1.28 Hz, 1H), 8.46 (ddd, *J* = 4.60, 1.89 & 0.55 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 136.88, 128.40, 128.64, 132.69, 197.36, 44.40, 51.75, 135.78, 130.35, 113.56, 158.17, 56.04, 165.50, 127.76, 140.43, 120.90, 146.60. Anal. calcd. (found) % for $C_{21}H_{19}NO_2$: C, 79.47 (79.48), H, 6.03 (6.02), N, 4.41 (4.42), O, 10.08 (10.09).

3-(Furan-3-yl)-3-(4-methoxyphenyl)-1-phenylpropan-1-one (2g): Liquid, m.f.: $C_{20}H_{18}O_3$, IR (KBr, ν_{max}, cm^{-1}): 2930, 1600, 1220, 3000, 1715, 810, 695. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.79 (m, *J* = 8, 2.4 & 0.6 Hz, 2H), 7.33 (m, *J* = 8, 1.0 & 0.4 Hz, 2H), 7.40 (dd, *J* = 8 & 2.5 Hz, 1H), 3.56 (d, *J* = 7 Hz, 2H), 4.78 (t, *J* = 7 Hz, 1H), 7.20 (m, *J* = 8, 2.4 & 1.5 Hz, 2H), 6.85 (m, *J* = 8, 2.5 & 1.5 Hz, 2H), 3.80 (S, *J* = 6 Hz, 3H), 6.36 (dd, 1.70 & 0.90 Hz, 1H), 7.28 (dd, *J* = 1.70 & 1.02 Hz, 1H), 7.32 (dd, *J* = 1.06 & 0.90 Hz 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 136.88, 128.40, 128.64, 132.69, 198.58, 48.59, 40.45, 133.71, 129.89, 113.75, 159.49, 56.04, 128.22, 140.30, 146.19, 112.46. Anal. calcd. (found) % for $C_{20}H_{18}O_3$: C, 78.41 (78.42), H, 5.92 (5.90), O, 15.67 (15.68).

3-(4-Methoxyphenyl)-1-phenylhex-5-en-1-one (2h): Liquid, m.f.: $C_{19}H_{20}O_2$, IR (KBr, ν_{max}, cm^{-1}): 2940, 1600, 1100, 3000, 1640, 695, 810, 1715. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 779 (m, *J* = 8, 2.5 & 1.5 Hz, 2H), 7.35 (m, *J* = 8, 2.6 & 0.4 Hz, 2H), 7.42 (dd, *J* = 8 & 2.5, 1H), 3.21 (d, *J* = 7.0 Hz, 2H), 3.12 (t, *J* = 7 Hz, 1H), 7.27 (m, *J* = 8, 2.5 & 1.2 Hz, 2H), 6.86 (m, *J* = 8, 1.4 & 0.5 Hz, 2H), 3.80 (S, 3H), 2.51 (d, *J* = 7.5 Hz, 2H), 5.69 (m, *J* = 10 & 16 Hz, 1H), 5.04 (dd, *J* = 10, 17 &2.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 136.88, 128.40, 128.64, 132.69, 198.8, 43.09, 42.72, 137.35 127.47, 114.58, 158.02, 56.04, 36.45, 134.31, 117.63. Anal. calcd. (found) % for $C_{19}H_{20}O_2$: C, 81.40 (81.41), H, 7.19 (7.20), O, 11.41 (11.43).

3-(4-Nitrophenyl)-1,3-diphenylpropan-1-one (2i): Liquid, m.f.: $C_{21}H_{17}NO_3$, IR (KBr, ν_{max}, cm^{-1}): 2930, 1600, 3000, 1540, 850, 710, 1715. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.83 (m, *J* = 8, 2.5 & 0.4 Hz, 2H), 7.36 (m, *J* = 8.1, 2.4 & 0.5 Hz, 2H), 7.43 (dd, *J* = 8.2 & 2.3 Hz, 1H), 3.26 (d, *J* = 7 Hz, 2H), 4.77 (t, *J* = 7 Hz, 1H), 7.51 (m, *J* = 8.0, 2.3 & 1.5 Hz, 2H), 8.17 (m, *J* = 8.0, 2.4 & 0.5 Hz, 2H), 7.20 (m, *J* = 8.0, 2.5 & 0.5 Hz, 2H), 7.26 (m, *J* = 8.1, 2.4 & 0.6 Hz, 2H), 7.18 (dd, *J* = 8.0 & 2.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm, 136.88, 128.40, 128.64, 132.69, 197.30, 45.84, 48.67, 150.96, 129.65, 124.09, 147.44, 143.67, 129.49, 128.92, 126.77. Anal. calcd. (found) % for $C_{21}H_{17}NO_3$: C, 76.12 (76.13), H, 5.17 (5.18), N, 4.23 (4.24), O, 14.49 (14.46).

3-(4-Nitrophenyl)-1-phenyl-3-(pyridin-2-yl)propan-1-one (2j): Liquid, m.f.: $C_{20}H_{16}N_2O_3$, IR (KBr, ν_{max}, cm^{-1}): 2940, 1600, 695, 3000, 1540, 850, 1350, 1715. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.84 (m, *J* = 8.0, 2.5, 1.5 Hz, 2H), 7.36 (m, *J* = 7.9, 2.5 & 0.7 Hz, 2H), 7.43 (dd, *J* = 7.8 & 2.5 Hz, 1H), 3.76 (d, *J* = 7.0 Hz, 2H), 4.75 (t, *J* = 7 Hz, 1H), 7.47 (m, *J* = 8.0, 2.4 & 1.5 Hz, 2H), 8.17 (m, *J* = 8.0, 2.3 & 0.6 Hz, 2H), 746 (ddd, *J* = 7.65, 1.19 & 0.42 Hz, 1H), 7.68 (ddd, *J* = 7.67, 7.33 & 1.82 Hz, 1H), 7.22 (ddd, *J* = 7.34, 4.55 & 1.29 Hz, 1H), 8.58 (ddd, *J* = 4.62 & 0.51 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 136.88, 128.4., 128.64, 132.69, 197.36, 44.40, 51.75, 149.88, 129.91, 124.42, 147.13, 165.50, 12.76, 140.43, 120.90, 146.60. Anal. calcd. (found) % for $C_{20}H_{16}N_2O_3$: C, 72.28 (72.27), H, 4.85 (4.86), N, 8.43 (8.42), O, 14.44 (14.45).

3-(Furan-3-yl)-3-(4-nitrophenyl)-1-phenylpropan-1-one (2k): Liquid, m.f.: $C_{19}H_{15}NO_4$, IR (KBr, ν_{max}, cm^{-1}): 2940, 1600, 695, 3000, 1540, 850, 1350, 1715, ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.82 (m, *J* = 8.0, 2.5, 1.5 Hz, 2H), 7.34 (m, *J* = 7.9, 2.5 & 0.7 Hz, 2H), 7.41 (dd, *J* = 7.8 & 2.5 Hz, 1H), 3.28 (d, *J* = 7.0 Hz, 2H), 4.81 (t, *J* = 7 Hz, 1H), 7.49 (m, *J* = 8.0, 2.4 & 1.5 Hz, 2H), 8.16 (m, *J* = 8.0, 2.3 & 0.6 Hz, 2H), 6.25 (dd, *J* = 1.72, 0.90 Hz, 1H), 7.28 (dd, *J* = 1.75 & 1.05 Hz, 1H), 7.40 (dd, *J* = 1.06 & 0.92). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 136.88, 128.4., 128.64, 132.69, 198.58, 48.59, 40.45, 150.53, 129.54, 123.14, 148.23, 128.22, 112.46, 146.19, 140.30. Anal. calcd. (found) % for $C_{19}H_{15}NO_4$: C, 71.02 (71.01), H, 4.71 (4.70), N, 4.36 (4.35), O, 19.19 (19.21).

3-(4-Nitrophenyl)-1-phenylhex-5-en-1-one (2l): Liquid, m.f.: $C_{18}H_{17}NO_3$, IR (KBr, ν_{max}, cm^{-1}): 2940, 1600, 1540, 3000, 1640, 695, 810, 1715, 990,1660. ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 7.80 (m, *J* = 8, 2.5 & 1.5 Hz, 2H), 7.34 (m, *J* = 8, 2.6 & 0.4 Hz, 2H), 7.42 (dd, *J* = 8 & 2.5, 1H), 2.80 (d, *J* = 7.0 Hz, 2H), 3.12 (t, *J* = 7 Hz, 1H), 7.56 (m, *J* = 8, 2.5 & 1.2 Hz, 2H), 8.15 (m, *J* = 8, 1.4 & 0.5 Hz, 2H), 2.49 (d, *J* = 7.5 Hz, 2H), 5.69 (m, *J* = 10 & 16 Hz, 1H), 5.04 (dd, *J* = 10, 17 & 2.1 Hz, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 136.88, 128.40, 128.64, 132.69, 198.81, 43.09, 42.72, 152.02, 127.99, 124.27, 147.40, 36.45, 134.31, 117.63. Anal. calcd. (found) % for $C_{18}H_{17}NO_3$: C, 73.20 (73.21), H, 5.80 (5.81), N, 4.74 (4.75), O, 16.25 (16.24).

Antimicrobial activity: All the sythesized compounds were tested for their antibacterial activity against *Staphylococcus aureus* (Gram-positive), *Escherichia coli* (Gram-negative) and antifungal activity against *Aspergillus niger* (fungus).

Agar well diffusion method: The agar plate area was inoculated by distributing a volume of the microbial inoculum over the whole agar surface. Then, a small aperture with a diameter of 6 to 8 mm was punched aseptically with a sterilized cork borer or a tip and a volume (20-100 mL) of the antimicrobial agent or extract solution at desirable concentration is passed into the well. Then, agar plates are incubated at 37 ºC.

RESULTS AND DISCUSSION

All the starting compound chalcones were synthesized by Aldol condensation reactions of aldehydes and ketones. The Grignard reagents were prepared by using the inert atmosphere of nitrogen gas. To account for the importance of Li_2MnCl_4 in this method, the reactions were performed in the absence and presence of Li_2MnCl_4 reagent. It has been observed that reaction requires a longer time in absence of dilithium tetrachloromanganate and gives lower yields and poor regioselectivity offering 1,2-addition product. However, the reaction was carried out in the presence of Li_2MnCl_4 in different solvents like THF, diethyl ether and 1,4-dioxane wherein the reaction gives different yields and high regioselectivity (Table-1).

TABLE-1
EFFECT OF CATALYST AND SOLVENT FOR THE SYNTHESIS OF **2a**

Entry	Reagent	Solvent	Time (min)	Yield (%)
1	Li_2MnCl_4	THF	40	82
2	Li_2MnCl_4	Diethyl ether	50	75
3	Li_2MnCl_4	1,4-Dioxane	70	62
4	–	THF	60	70
5	–	Diethyl ether	65	62
6	–	1,4-Dioxane	90	58

Table-2 shows the results obtained from using the molar ratio of Grignard reagent for the synthesis of compound **2a**. It has also been observed that substituted chalcones give higher results and good regioselectivity with Grignard reagents in the presence of a homogeneous solution of Li_2MnCl_4 with copper thiocyanate. The ratio of the reactants to the Grignard reagents used was 1:1 and also studied in using different equivalents for example 1:1.1 and 1:1.2. The nucleophilic attack of the Grignard reagent was occurred at 1,4-position of substituted chalcones to yield desired products. It has also been found that the poor regioselectivity obtained in absence of Li_2MnCl_4 reagent and mixture of products were formed with 1,2-addition and 1,4-addition.

TABLE-2
EFFECT OF MOLAR RATIO OF GRIGNARD REAGENT AND SOLVENT FOR THE SYNTHESIS OF **2a**

Entry	Grignard (molar ratio)	Solvent	Time (min)	Yield (%)
1	1:1	THF	40	82
2	1:1	Diethyl ether	50	75
3	1:1	1,4-Dioxane	70	62
4	1:1.1	THF	40	84
5	1:1.1	Diethyl ether	50	78
6	1:1.1	1,4-Dioxane	70	64
7	1:1.2	THF	40	86
8	1:1.2	Diethyl ether	50	80
9	1:1.2	1,4-Dioxane	70	67

Antimicrobial activity: Compound **2g** exhibits zone of inhibition of 2 mm for antibacterial activity, it is less than compound **2h**, **2i** and compound **2l**. Inhibition zone of 4 mm was observed in compound **2g** for antifungal activity which is far lower in comparision to all other synthesized compounds. Compound **2h** displays 15 mm of inhibition zone for *S. aureus* which is greater than inhibition zone of compound **2l** (14 mm) and compound **2i** (12 mm). Compounds **2j** and **2k** show zero activity against *S. aureus* for *E. coli*, compound **2h** shows better activity with inhibition zone of 9 mm which is higher than compound **2j** (5 mm), compound **2k** (4 mm), compound **2i** (3 mm) and compound **2g** (2 mm). Compound **2l** shows zero activity for *E. coli*. With the zone of inhibition of 13 mm compound **2l** shows the higher antifungal activity than all the synthesized compounds (Table-3).

TABLE-3
ANTIMICROBIAL ACTIVITIES OF SUBSTITUTED CHALCONES AGAINST BACTERIAL TEST ORGANISM

Compound	Inhibition zone (mm)		
	Staphylococcus aureus	*Escherichia coli*	*Aspergillus niger*
2g	2	2	4
2h	15	9	12
2i	12	3	5
2j	–	5	9
2k	–	4	10
2l	14	–	13
Control	6	7	–

Conclusion

In conclusion, 1,4-addition of Grignard reagents to the various substituted derivatives of chalcones in the presence of dilithium tetrachloromanganate reagent under nitrogen atmosphere resulted in the higher yields. The simple workup of reaction, higher yields and good regioselectivity of the reaction make this Li_2MnCl_4 reagent the most appropriate option to the reported literature. The fewer reaction times, easy workup of reaction and higher yield make copper thiocyanate catalyst a more convenient alternative to the reported methods. The synthesized compound **2g**, **2h**, **2i**, **2j**, **2k** and **2l** were also tested for their antibacterial activity against *Staphylococcus aureus* (Gram-positive), *Escherichia coli* (Gram-negative) and antifungal activity against *Aspergillus niger* (fungus). The findings of activity of these compounds show the moderate to good antibacterial and antifungal activities.

ACKNOWLEDGEMENTS

The authors thank the Central Instrumentation Facility, Savitribai Phule Pune University, Pune, India and Department of Chemistry Annasaheb Magar Mahavidyalaya, Pune, India for the spectral analysis.

REFERENCES

1. C. Zhuang, W. Zhang, C. Sheng, W. Zhang, C. Xing and Z. Miao, Chalcone: A Privileged Structure in Medicinal Chemistry, *Chem. Rev.*, **117**, 7762 (2017); https://doi.org/10.1021/acs.chemrev.7b00020
2. A. Alexakis, J. Vastra, J. Burton, C. Benhaim and P. Mangeney, Asymmetric Conjugate Addition of Diethyl Zinc to Enones with Chiral Phosphorus Ligands derived from TADDOL, *Tetrahedron Lett.*, **39**, 7869 (1998); https://doi.org/10.1016/S0040-4039(98)01761-4
3. A. Alexakis, J. Frutos and P. Mangeney, Chiral Phosphorus Ligands for the Asymmetric Conjugate Addition of Organocopper Reagents, *Tetrahedron Asymm.*, **4**, 2427 (1993); https://doi.org/10.1016/S0957-4166(00)82216-8
4. S.T. Saengchantara and T.W. Wallace, Conjugate Addition to 3-(p-Tolylsulphinyl)chromone: A Route to 2-Substituted Chromones and

Chiral Substituted Chroman-4-ones, *Tetrahedron*, **46**, 6553 (1990); https://doi.org/10.1016/S0040-4020(01)96020-X
5. G.P. Ellis, Chromenes, Chromanones and Chromones, John Wiley & Sons: New York (1977).
6. B. Goldfuss, T. Löschmann and F. Rominger, Phosphinofenchol or Metastable Phosphorane? Phosphorus Derivatives of Fenchol, *Chem. Eur. J.*, **7**, 2028 (2001); https://doi.org/10.1002/1521-3765(20010504)7:9<2028::AID-CHEM2028>3.0.CO;2-Y
7. B. Goldfuss, M. Steigelmann, *J. Mol. Model.*, **6**, 166 (2000); https://doi.org/10.1007/s0089400060166
8. B. Goldfuss, M. Steigelmann, F. Rominger and H. Urtel, Chiral Modular n-Butyllithium Aggregates: *n*BuLi Complexes with Anisyl Fencholates, *Chem. Eur. J.*, **7**, 4456 (2001); https://doi.org/10.1002/1521-3765(20011015)7:20<4456::AID-CHEM4456>3.0.CO;2-S
9. P.A. Wender, V.A. Verma, T.J. Paxton and T.H. Pillow, Function-Oriented Synthesis, Step Economy and Drug Design, *Acc. Chem. Res.*, **41**, 40 (2008); https://doi.org/10.1021/ar700155p
10. S.R. Harutyunyan, T. den Hartog, K. Geurts, A.J. Minnaard and B.L. Feringa, Catalytic Asymmetric Conjugate Addition and Allylic Alkylation with Grignard Reagents, *Chem. Rev.*, **108**, 2824 (2008); https://doi.org/10.1021/cr068424k
11. F. Lopez, A.J. Minnaard and B.L. Feringa, Catalytic Enantioselective Conjugate Addition with Grignard Reagents, *Acc. Chem. Res.*, **40**, 179 (2007); https://doi.org/10.1021/ar0501976
12. A. Alexakis, J.E. Bäckvall, N. Krause, O. Pàmies and M. Diéguez, Enantioselective Copper-Catalyzed Conjugate Addition and Allylic Substitution Reactions, *Chem. Rev.*, **108**, 2796 (2008); https://doi.org/10.1021/cr0683515
13. S.-Y. Wang and T.-P. Loh, Highly Enantioselective Cu(I)–Tol-BINAP-Catalyzed Asymmetric Conjugate Addition of Grignard Reagents to α,β-Unsaturated Esters, *Chem. Commun.*, **46**, 8694 (2010); https://doi.org/10.1039/c0cc03211e
14. J. Christoffers, G. Koripelly, A. Rosiak and M. Rössle, Recent Advances in Metal-Catalyzed Asymmetric Conjugate Additions, *Synthesis*, 1279 (2007); https://doi.org/10.1055/s-2007-966005
15. A. Gutnov, Palladium-Catalyzed Asymmetric Conjugate Addition of Aryl–Metal Species, *Eur. J. Org. Chem.*, **2008**, 4547 (2008); https://doi.org/10.1002/ejoc.200800541
16. T. Hayashi and K. Yamasaki, Rhodium-Catalyzed Asymmetric 1,4-Addition and Its Related Asymmetric Reactions, *Chem. Rev.*, **103**, 2829 (2003); https://doi.org/10.1021/cr020022z
17. H.J. Edwards, J.D. Hargrave, S.D. Penrose and C.G. Frost, Synthetic Applications of Rhodium Catalyzed Conjugate Addition, *Chem. Soc. Rev.*, **39**, 2093 (2010); https://doi.org/10.1039/b919762c
18. T. Hayashi, Rhodium-Catalyzed Asymmetric Addition of Organo-Boron and -Titanium Reagents to Electron-Deficient Olefins, *Bull. Chem. Soc. Jpn.*, **77**, 13 (2004); https://doi.org/10.1246/bcsj.77.13
19. H.-C. Guo and J.-A. Ma, Catalytic Asymmetric Tandem Transformations Triggered by Conjugate Additions, *Angew. Chem. Int. Ed.*, **45**, 354 (2006); https://doi.org/10.1002/anie.200500195
20. T. Jerphagnon, M.G. Pizzuti, A.J. Minnaard and B.L. Feringa, Recent Advances in Enantioselective Copper-Catalyzed 1,4-Addition, *Chem. Soc. Rev.*, **38**, 1039 (2009); https://doi.org/10.1039/b816853a
21. L.A. Arnold, R. Naasz, A.J. Minnaard and B.L. Feringa, Catalytic Enantio-selective Synthesis of Prostaglandin E_1 Methyl Ester using a Tandem 1,4-Addition-Aldol Reaction to a Cyclopenten-3,5-dione Monoacetal, *J. Am. Chem. Soc.*, **123**, 5841 (2001); https://doi.org/10.1021/ja015900+
22. L.A. Arnold, R. Naasz, A.J. Minnaard and B.L. Feringa, Catalytic Enantioselective Synthesis of (-)-Prostaglandin E_1 Methyl Ester Based on a Tandem 1,4-Addition-Aldol Reaction, *J. Org. Chem.*, **67**, 7244 (2002); https://doi.org/10.1021/jo025987x
23. M.K. Brown, S.J. Degrado and A.H. Hoveyda, Highly Enantioselective Cu-Catalyzed Conjugate Additions of Dialkylzinc Reagents to Unsaturated Furanones and Pyranones: Preparation of Air-Stable and Catalytically Active Cu-Peptide Complexes, *Angew. Chem. Int. Ed.*, **44**, 5306 (2005); https://doi.org/10.1002/anie.200501251
24. G.P. Howell, S.P. Fletcher, K. Geurts, B. ter Horst and B.L. Feringa, Catalytic Asymmetric Synthesis of Acyclic Arrays by Tandem 1,4-Addition-Aldol Reactions, *J. Am. Chem. Soc.*, **128**, 14977 (2006); https://doi.org/10.1021/ja0651862
25. K. Yoshida, M. Ogasawara and T. Hayashi, A New Type of Catalytic Tandem 1,4-Addition-Aldol Reaction Which Proceeds through an (Oxa-π-allyl)rhodium Intermediate, *J. Am. Chem. Soc.*, **124**, 10984 (2002); https://doi.org/10.1021/ja0271025
26. S.J. Degrado, H. Mizutani and A.H. Hoveyda, Modular Peptide-Based Phosphine Ligands in Asymmetric Catalysis: Efficient and Enantioselective Cu-Catalyzed Conjugate Additions to Five-, Six-, and Seven-Membered Cyclic Enones, *J. Am. Chem. Soc.*, **123**, 755 (2001); https://doi.org/10.1021/ja003698p
27. H. Mizutani, S.J. Degrado and A.H. Hoveyda, Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzinc Reagents to Acyclic Aliphatic Enones, *J. Am. Chem. Soc.*, **124**, 779 (2002); https://doi.org/10.1021/ja0122849
28. E.W. Dijk, L. Panella, P. Pinho, R. Naasz, A. Meetsma, A.J. Minnaard and B.L. Feringa, The Asymmetric Synthesis of (-)-Pumiliotoxin C using Tandem Catalysis, *Tetrahedron*, **60**, 9687 (2004); https://doi.org/10.1016/j.tet.2004.06.148
29. R. Naasz, L.A. Arnold, A.J. Minnaard and B.L. Feringa, Enantioselective Synthesis of Bicyclic Compounds *via* Catalytic 1,4-Addition-Ring Closing Metathesis, *Chem. Commun.*, 735 (2001); https://doi.org/10.1039/b100283j
30. X. Rathgeb, S. March and A. Alexakis, One-Pot Asymmetric Conjugate Addition-Trapping of Zinc Enolates by Activated Electrophiles, *J. Org. Chem.*, **71**, 5737 (2006); https://doi.org/10.1021/jo060814j
31. R. Šebesta, M.G. Pizzuti, A.J. Minnaard and B.L. Feringa, Copper-Catalyzed Enantioselective Conjugate Addition of Organometallic Reagents to Acyclic Dienones, *Adv. Synth. Catal.*, **349**, 1931 (2007); https://doi.org/10.1002/adsc.200600272
32. Y.-J. Xu, Q.-Z. Liu and L. Dong, Copper-Catalyzed Enantioselective Tandem Conjugate Addition/N-Nitroso Aldol Reaction, *Synlett*, 273 (2007); https://doi.org/10.1055/s-2007-968012
33. M. Welker, S. Woodward and A. Alexakis, Tandem Reactions with Chiral Enolates: Preparation of Allylic Alcohols *via* Trapping with Vinyl Oxiranes, *Org. Lett.*, **12**, 576 (2010); https://doi.org/10.1021/ol9027682
34. R.M. Suárez, D. Peña, A.J. Minnaard and B.L. Feringa, Tandem One Pot Asymmetric Conjugate Addition-Vinyl Triflate Formation-Cross Coupling Methodology, *Org. Biomol. Chem.*, **3**, 729 (2005); https://doi.org/10.1039/B418028C
35. T. den Hartog, A. Rudolph, B. Maciá, A.J. Minnaard and B.L. Feringa, Copper-Catalyzed Enantioselective Synthesis of *trans*-1-Alkyl-2-substituted Cyclopropanes *via* Tandem Conjugate Addition-Intramolecular Enolate Trapping, *J. Am. Chem. Soc.*, **132**, 14349 (2010); https://doi.org/10.1021/ja105704m
36. K. Li and A. Alexakis, Copper Catalyzed Tandem Asymmetric Conjugate Addition-Cyclization Reaction in the Presence of Chiral Phosphoramidite Ligands, *Tetrahedron Lett.*, **46**, 8019 (2005); https://doi.org/10.1016/j.tetlet.2005.09.065
37. K. Li and A. Alexakis, Copper-Catalyzed Enantioselective Intramolecular Conjugate Addition/Trapping Reactions: Synthesis of Cyclic Compounds with Multichiral Centers, *Chem. Eur. J.*, **13**, 3765 (2007); https://doi.org/10.1002/chem.200601327
38. K. Agapiou, D.F. Cauble and M.J.J. Krische, Copper-Catalyzed Tandem Conjugate Addition-Electrophilic Trapping: Ketones, Esters and Nitriles as Terminal Electrophiles, *J. Am. Chem. Soc.*, **126**, 4528 (2004); https://doi.org/10.1021/ja0306031
39. P. Perlmutter, Conjugate Addition Reactions in Organic Synthesis, Tetrahedron Organic Chemistry Series, Pergamon Press: Oxford, vol. 9 (1992).
40. J.P. Collman, S.R. Winter and D.R. Clark, Selective Syntheses of Aliphatic Ketones using Sodium Tetracarbonylferrate(II), *J. Am. Chem. Soc.*, **94**, 1788 (1972); https://doi.org/10.1021/ja00760a084

41. E.C. Ashby and J.T. Laemmle, Stereochemistry of Organometallic Compound Addition to Ketones, *Chem. Rev.*, **75**, 521 (1975); https://doi.org/10.1021/cr60296a005
42. B. Weidmann and D. Seebach, Organometallic Compounds of Titanium and Zirconium as Selective Nucleophilic Reagents in Organic Synthesis, *Angew. Chem. Int. Ed. Engl.*, **22**, 31 (1983); https://doi.org/10.1002/anie.198300311
43. J.A. Simon, The Total Synthesis of Natural Products, Wiley: New York, vol. 1-5 (1973-1983).
44. J.D. Morrison and H.S. Mosher, Asymmetric Organic Reactions; Prentice Hall: New York (1971).
45. K. Maruoka, T. Itoh and H. Yamamoto, Methylaluminum *bis*(2,6-Di-*tert*-butyl-4-alkylphenoxide). A New Reagent for Obtaining Unusual Equatorial and Anti-cram Selectivity in Carbonyl Alkylation, *J. Am. Chem. Soc.*, **107**, 4573 (1985); https://doi.org/10.1021/ja00301a048