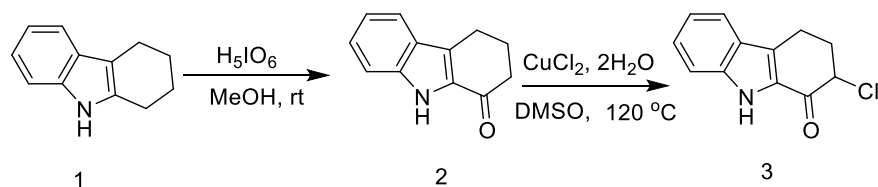


Introduction

α -Chlorination of carbonyl compounds is ubiquitous process used in the synthesis of Plethora of natural and bioactive compounds.¹⁻³ Halo substituted Carbazole has been used in the synthesis of various natural product and semiconducting organic material.⁴⁻⁵ Tipinazole-D is a bioactive natural product of Carbazole derivatives contains chloro substituent.⁶ Some halo substituted 1-oxo tetrahydrocarbazole is used for derivatisation of carbazole.⁷⁻⁸ Earlier we synthesize 2-bromo1-oxotetrahydrocarbazole by bromination of 1-oxo tetrahydrocarbazole by using CuBr_2 in chloroform:ethyl acetate solvent.⁹⁻¹⁰ It has been used in the synthesis of plenty of carbazoloquinone and Carbazole moieties including several natural products.¹¹ While the yield of the bromination reaction is relatively low which affect the total yields of the reactions. We were in search of another method for halogenations for better yield. In literature survey reveals that copper chloride in DMSO applied chlorination of ketones.¹² So, we utilizes this opportunity to explore chlorination of 1-oxo tetrahydrocarbazole, and earlier used this reagent for oxidation of 2- hydroxy acetophenone to glyxol.¹³ This reagent has been applied for the synthesis of 3-chloroflavones from 2-hydroxychalcones.¹⁴ Also used in the dehydrogenation of pyrazoline to pyrazole, isoxazoline to isoxazole,¹⁵ and tetrahydro benzoindazole to dihydro benzoindazole,¹⁶ 3-methylflavanone to 3-methylflavone, tetrahydrocarbazole to carbazole¹⁷⁻¹⁸ and in coupling reactions.¹⁹⁻²¹ For the preparation of α -chloro ketones some of the reagent was used such as trichloroisocyanuric acid ²² and *N*-chlorosuccinimide,²³ Sulfuryl chloride, polymer-supported chlorine.²⁴ A number of these methods are practically inconvenient to use or employ rather harsh reaction conditions. Additionally, synthesis of α -halo carbonyl compound utilizing these schemes have some more downsides like stoichiometryof the catalyst, need of additional oxidant, longer reaction time, tedious procedure by organocatalyst and often generate undesirable α -dihalocarbonyl byproducts. There is no literature available for the synthesis of 2- chloro-1-oxo tetrahydrocarbazole. Therefore, the development of an efficient, simple, atom economic and selective product for α - chlorination is in need. However $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ is inexpensive, mild, easily available, easy to handle, relatively stable and can be easily removed by the water after completion of the reaction.

Results and Discussion

Herein, we explored the regioselective and chemoselective chlorination of 1- oxo tetrahydrocarbazole to 2-chloro-1-oxo tetrahydrocarbezole. We started our experimental strategy with the condensation of commercially available phenyl hydrazine hydrochloride and cyclohexanone, which were readily converted to tetrahydrocarbazole by Fischer-Borsche synthesis. When tetrahydrocarbazole is treated with 1 equivalent of periodic acid in methanol, the 1-oxo-tetrahydro carbazole **1** is afforded an excellent yield. The optimized reaction conditions are listed in Table 1, as no changes observed after 24 h. when the model substrate at room temperature reacted with 10 to 50 mole percent of copper chloride in dimethyl sulfoxide.



Scheme 1. Typical chlorination of 1-oxo-tetrahydrocarbazole.

The formation of desired product is observed in 55% of yield, when temperature is increased to 60 °C and with equimolar quantity of copper chloride and recovery of starting material take place. Accordingly we performed a series of experiments to scrutinize the reagent loading, temperature and time parameters for the best possible yield. The best result was obtained with the use of 2-equivalent copper chloride at 120 °C with 89% yield formed in 20 minutes. Further increase in reagent loading as well as temperature does not improve the yield of the reaction.

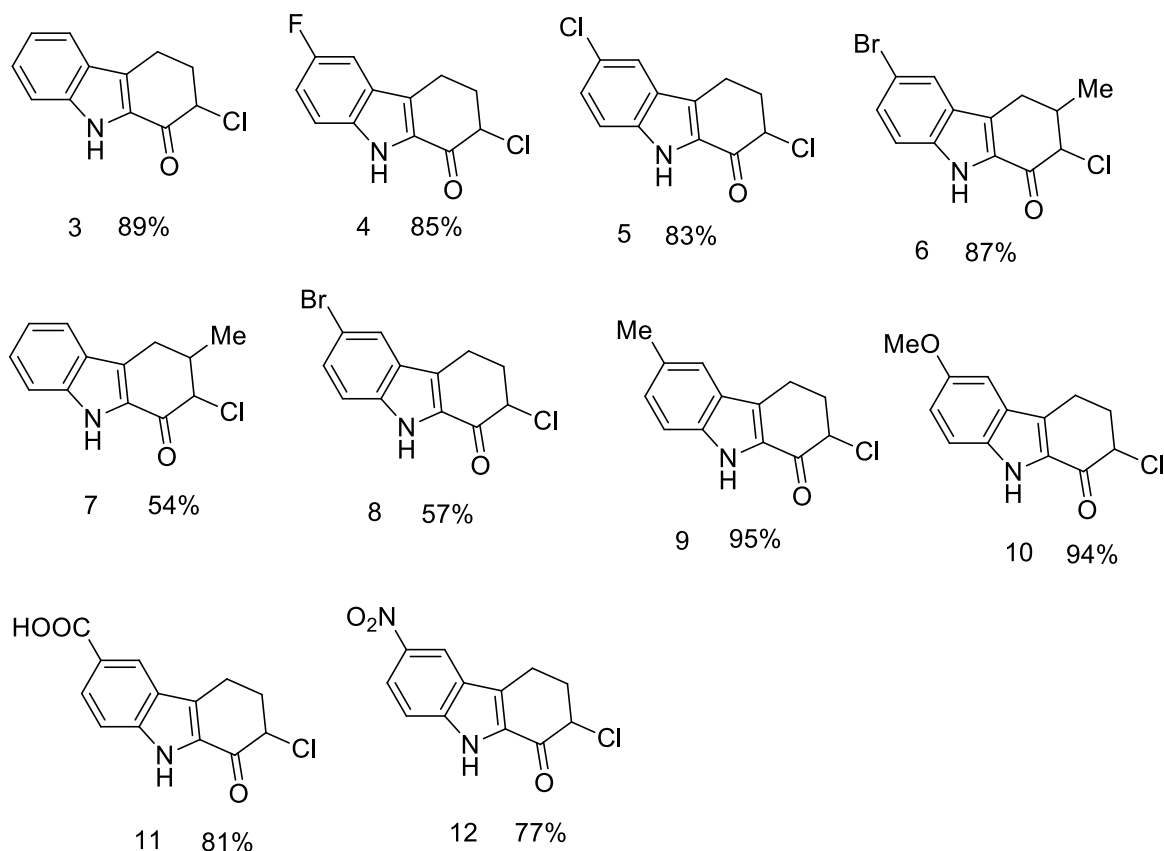
Table 1. Optimization of reaction conditions^{a,b}

Entry	CuCl ₂ ·2H ₂ O (%)	Temp (°C)	Time (h)	Yield (%)
1	10-50	rt	24	NR
2	1eq.	60	8	55
3	2 eq.	120	0.20	89

^aAll the réaction performed in DMSO solvent and different mol %. of the Catalysts.

^bAll the reaction was carried out by using copper chloride (4.2 mmol) and 1-oxo-Tetrahydrocarbazole 2 (2.1 mmol), in 50 mL of DMSO at 120 °C with stirring.

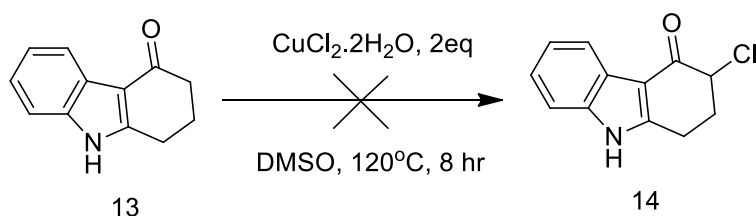
Several solvents, such as dimethyl sulphoxide, acetonitrile, PEG, dichloroethane, dimethylformamide and diphenyl ether were examined as the reaction medium, while DMSO was found to be a suitable solvent for the direct synthesis of 1-oxo-2-chloro-tetrahydrocarbazoles. It may be due to the stabilizing ability of DMSO with copper enolates species. With the optimized condition in hand, we decided to explore the scope of this established methodology for the direct synthesis of the series of substituted 1-oxo-2-chloro-tetrahydrocarbazoles. The starting substituted 1-oxotetrahydrocarbazoles were prepared with 1 equiv. of periodic acid in methanol solvent from -10 °C to room temperature and tetrahydrocarbazole were prepared via Fischer-Borsche synthesis, which involves the treatment of substituted phenyl hydrazines with cyclohexanone or 4-methylcyclohexanone in acetic acid under the reflux condition for 8 h as per literature procedure. Accordingly, when the range of substituted 1-oxo tetrahydrocarbazoles were treated with CuCl₂·2H₂O (2 equivalent) in DMSO at 120 °C a series of substituted 2-chloro-1-oxo tetrahydrocarbazoles were generated in good to excellent yield and the results are summarized in Scheme 2.



Scheme 2. Substituted 2-chloro-1-oxo tetrahydrocarbazoles.

We expected the dehydrogenation reaction as per our earlier research work by using the same catalytic process but no other byproducts are formed.¹⁰ The reaction is compatible with electron withdrawing and electron donating groups. It is important to note that electrons donating Cl, CH₃ etc.

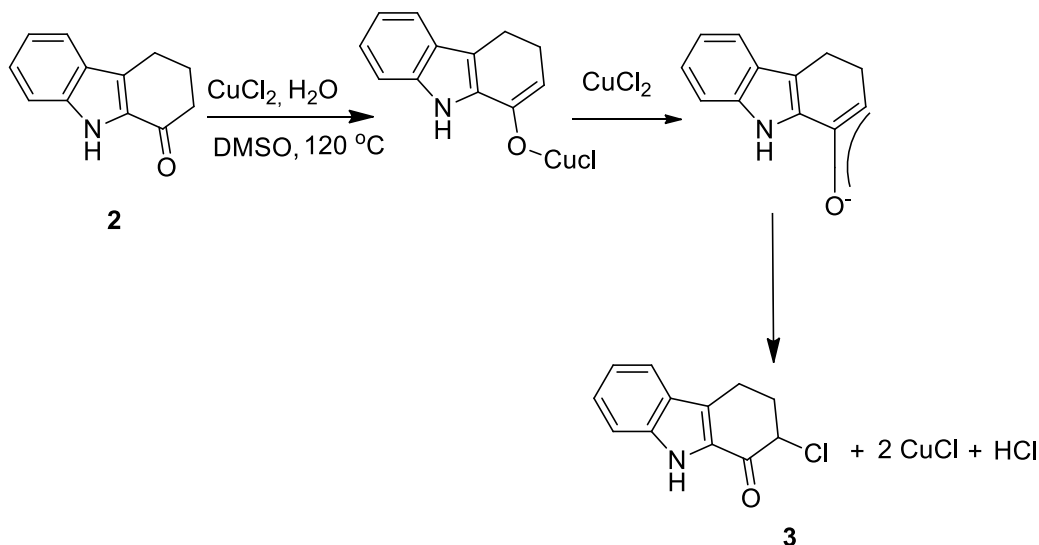
Substitutions do not affect the yield of the products of chlorination on the indole ring. However, we have not tested the reaction with higher molar ratio and higher temperature as we required only chlorination products. Methyl group at 3- position may have steric influence for the entry of chloro group, which resulted comparatively in lower yield. Therefore, approximately all electron neutral, rich and deficient substituents in the benzene ring of tetrahydrocarbazole were well acceptable in the α -chlorination reaction. The ¹H NMR spectrum of **3** showed a typical signal doublet of doublet at δ 4.97 for the methane proton (-CHCl). Its ¹³C NMR spectrum showed one typical signal at δ 61.29 due to the methane carbon (-CHCl) of α -carbonyl, thus confirming the formation of **3**. In the same way when 4-oxo tetrahydrocarbazole **13** was treated with 2 equiv. of CuCl₂·2H₂O in DMSO solvent at 120 °C for 8h in Scheme 3.



Scheme 3. Synthesis of 3-chloro-4-oxo tetrahydro carbazole.

Under this condition no reaction was observed. It is confirmed that the carbonyl group at 4-position in tetrahydrocarbazole is not reactive as the carbonyl group at 2- position.

As per literature, the mechanism in Scheme 4 was explained to ketones by reaction of silyl enol ethers with CuCl_2 to form α -chloro ketones. The coordination of the carbonyl group **2** to copper chloride followed by alpha C-H activation which gives intermediate and involving a radical or ionic species generated from the collapse of the copper (II) converted to 2-chloro 1-oxo tetrahydrocarbazole in some literature.²⁵ However we can neither nor ruled out any other possibility in the Mechanism.



Scheme 4. Plausible Mechnism.

Conclusions

We have successfully synthesized the substituted 2-chloro-1-oxo-tetrahydrocarbazole with 50-97% yield by using 2.0 equivalent copper (II) chloride dihydrate in DMSO. The scope of this method is successfully checked by using a range of electron donating to electron withdrawing substituents in the aromatic ring of 1-oxo-tetrahydrocarbazole. This method is regioselective, chemoselective, and oxidant free, acid free, simple to perform and easy to handle.

Experimental Section

General. All solvents were pre-distilled before use. All liquid reagents and solvents were used distilled and stored in anhydrous condition. Dry THF was prepared by freshly distillation from blue solution of THF containing wired sodium and benzophenone under nitrogen atmosphere. Dry DCM was obtained from pre distillation followed by redistilling over calcium hydride and stored over molecular sieves (4 Å). Dry DMF, chloroform, methanol were prepared by distillation under nitrogen atmosphere and stored over 4 Å molecular sieves. Purification of intermediate compounds was done by crystallization or column chromatography by using petroleum ether (60–80 °C) and ethyl acetate over Silica gel (100–200 mesh). All anhydrous reactions were carried out under a nitrogen atmosphere. ^1H NMR spectrum was recorded on

VARIAN Mercury 300 and 500 MHz instrument and unit ppm by using TMS-internal standard in CDCl_3 and DMSO solvent. ^{13}C -NMR spectra were recorded on 75 MHz instrument using Varian Mercury lamp. All HRESIMS were recorded on Bruker Impact HD ESI source.

General Procedure for compounds 3-12 (Scheme 2). In a 50 mL round bottom flask, copper (II) chloride dihydrate (4.2 mmol) was stirred in DMSO (5 mL) for 5 min at room temperature. Tetrahydrocarbazole substrates (2.1mmol) were slowly added to reaction mixture at room temperature. Allow the reaction mixture to stir at 120 °C for 20 mins. The reaction progress was monitored by thin layer chromatography and poured into crushed ice. The reaction mass kept for overnight, filtered and dried. The product was purified by column chromatography (hexane: ethyl acetate).

2-Chloro-2,3,4,9-tetrahydro-1H-carbazol-1-one (3). Orange solid, Yield: 89% (410.4mg); mp 144-146 °C; IR(vcm^{-1}): 3285,2936,1649,1458,811,728,670; ^1H NMR (400 MHz, DMSO- d_6): δ 11.82 (s, 1H), 7.71 (d, J 8.2 Hz, 1H), 7.44–7.34 (m, 2H), 7.14–7.10 (m, 1H), 4.97 (dd, J 7.3, 3.8 Hz, 1H), 3.12–3.06 (m, 2H), 2.69–2.63 (m, 1H), 2.48–2.42 (m, 1H). ^{13}C NMR (101 MHz, DMSO- d_6): δ 183.66, 139.33, 129.41, 128.57, 127.48, 125.36, 121.94, 120.57, 113.36, 61.29, 34.43, 18.85.; (DEPT) ^{13}C NMR (101 MHz, DMSO- d_6): δ 127.49, 121.95, 120.57, 113.36, 61.29, 34.43, 18.85.

2-Chloro-6-fluoro-2,3,4,9-tetrahydro-1H-carbazol-1-one (4). Orange solid, Yield: 85% (424.1mg); mp 138-140 °C; IR (vcm^{-1}): 3275, 2926, 1646, 1450, 811, 730, 668; ^1H NMR (400 MHz,DMSO- d_6) δ 11.93 (s, 1H), 7.49 (dd, J 9.4, 2.5Hz, 1H), 7.43 (dd, J 9.0, 4.5Hz, 1H), 7.22(td, J 9.2, 2.5 Hz, 1H), 4.97(dd, J 7.4, 3.8 Hz, 1H), 3.08–3.00 (m, 2H), 2.69–2.60 (m, 1H), 2.44 (td, J 13.4, 5.6Hz, 1H). ^{13}C NMR (101 MHz, DMSO- d_6): δ 183.84, 158.70-156.37, 136.01, 130.85, 128.25-128.19, 125.36-125.26, 116.52-116.25, 114.83-114.73,106.17-105.94, 61.18, 34.32,18.84. DEPT ^{13}C NMR (101 MHz, DMSO- d_6): δ 116.52-116.25, 114.83-114.73, 106.18-105.95, 61.18, 34.32, 18.85. HRMS $\text{C}_{12}\text{H}_9\text{ClFNO}$ [$\text{M} + \text{H}$] $^+$ Calc: 238.0390; Found: 238.0376.

2,6-Dichloro-2,3,4,9-tetrahydro-1H-carbazol-1-one (5). Orange solid. Yield: 83% (442.89 mg); mp 164-166 °C; IR(vcm^{-1}): 3267, 2833, 1647, 1533, 809, 723, 667; ^1H NMR (400 MHz, DMSO- d_6): δ 11.98 (s, 1H), 7.75 (s, 1H), 7.43 (d, J 8.8Hz, 1H), 7.33 (dd, J 8.8, 2.0 Hz, 1H), 4.98–4.91 (m, 1H), 3.04 (dd, J 10.8, 5.4 Hz, 2H), 2.68–2.58 (m, 1H), 2.44 (dt, J 13.6, 6.6 Hz,1H). ^{13}C NMR (101 MHz, DMSO- d_6): δ 183.87, 137.60, 130.53, 127.86, 127.43, 126.27, 125.13, 121.02 115.04, 61.10, 34.27, 18.73. HRMS $\text{C}_{12}\text{H}_9\text{Cl}_2\text{NO}$ [$\text{M}+\text{H}$] $^+$ Calc :254.009 ; Found: 254.0095.

1-Oxo-2-chloro-3-methyl-tetrahydrocarbazole (8). Orange solid, Yield: 57% (279.6 mg); IR (v cm^{-1}): 3235, 2435, 1728, 1458, 1128, 740, 670; ^1H NMR (400 MHz, DMSO- d_6): δ 11.78 (s, D_2O exchange, 1H), 7.71(d, J 8.0Hz, 1H), 7.42 (d, J 8.0 Hz, 1H), 7.32 (t, J 7.5 Hz, 8.0 Hz, 1H), 7.12 (t, J 7.0 Hz, 7.5 Hz, 1H),4.98 (d, J 3.9Hz,1H), 2.91 (dd, 4.5Hz,4.8Hz, 2H), 2.16-2.08 (m, 1H), 1.14 (d, J 1.5 Hz, 3H); ^{13}C NMR (101MHz, DMSO- d_6): δ 185.72, 139.18, 134.93, 130.37, 127.18, 125.23, 121.84, 120.53, 113.32, 59.80, 37.04, 28.45, 22.18.

2-Chloro-6-methoxy-2,3,4,9-tetrahydro-1H-carbazol-1-one (10). Orange solid, Yield: 94%; mp 178-180 °C; ^1H NMR (400 MHz,DMSO- d_6): δ 11.67 (s, 1H), 7.33 (d, J 9.0 Hz, 1H), 7.13 (d, J 2.4 Hz, 1H), 7.02 (dd, J 9.0, 2.5 Hz, 1H), 4.95–4.91 (m, 1H), 3.79 (s, 3H), 3.07–3.3 (m, 2H), 2.66–2.60 (m, 1H), 2.43 (dd, J 13.8, 7.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO- d_6): δ 183.44, 154.35, 134.80, 129.73, 127.96, 125.51, 119.33, 114.37, 101.56, 61.29, 55.83, 34.41, 18.83.

2-Chloro-1-oxo-2,3,4,9-tetrahydro-1H-carbazole-6-carboxylicacid (11). Orange solid, Yield: 81%; mp 290 °C; IR(vcm^{-1}): 3400-3520, 3265, 2936, 1728, 1648, 1510, 1450, 1293, 1020, 801, 732, 672; ^1H NMR (400 MHz, DMSO- d_6): δ 12.13 (s, 1H), 8.37 (s, 1H), 7.92 (d, J 8.8 Hz, 1H), 7.48 (d, J 8.8 Hz, 1H), 4.99–4.94 (m, 1H), 3.12 (d, J 4.1Hz, 2H), 2.66 (dd, J 13.5, 4.5Hz, 1H), 2.43 (d, J 7.3Hz, 1H); ^{13}C NMR(101 MHz,DMSO- d_6): δ 183.85, 168.21, 141.36, 130.69, 129.95, 127.93, 124.96, 124.80, 123.21, 113.21, 61.05, 34.23,18.72. HRMS $\text{C}_{13}\text{H}_{10}\text{ClNO}_3$ [$\text{M} + \text{H}$] $^+$ Calc : 264.0383 ; Found 264.0383.

2-Chloro-6-nitro-2,3,4,9-tetrahydro-1H-carbazol-1-one (12). Orange solid, Yield: 77%; mp 154-158 °C (decompose); IR(vcm^{-1}): 3278, 2927, 1647, 1538, 1452, 1358, 812, 734, 669; ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 12.52 (s, 1H), 8.70 (s, 1H), 8.15 (dd, J 9.2, 1.8 Hz, 1H), 7.54 (d, J 9.2 Hz, 1H), 5.02 (dd, J 6.9, 3.1 Hz, 1H), 3.15 (t, J 5.6 Hz, 2H), 2.72–2.64 (m, 1H), 2.45 (m, J 13.6, 5.9 Hz, 1H). ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$): δ 184.08, 141.72, 141.66, 132.20, 130.81, 124.53, 121.77, 119.62, 113.96, 60.92, 34.09, 18.82. HRMS $\text{C}_{12}\text{H}_9\text{ClN}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ Calc: 265.033; Found: 265.0379.

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Supplementary Material

Supplementary material containing the ^1H and ^{13}C NMR spectra is available.

References

1. Yu J.; Zang C. *Synthesis* **2009**, 14, 2324-2328.
<https://doi.org/10.1055/s-0029-1216856>
2. Shibata N.; Kohno J.; Takai K.; Ishimaru T.; Nakamura S.; Tonu T.; Kanemasa S. *Angew. Chem. Int. Ed.* **2005**, 44, 4204-4207.
<https://doi.org/10.1002/anie.200501041>
3. Chong S.; Su Y.; Wu L.; Zang W.; Ma J.; Chen X.; Huang D.; Wang K. H.; Hu Y.; *Synthesis* **2016**, 48, 1359-1370. Akula R.; Galligan M.S.; Ibrahim H. *Synthesis*, **2011**, 2, 347-351.
<https://doi.org/10.1055/s-0035-1561572>
4. Qian X.; Zhu Y.; Chang W. Y.; Song J.; Pan B.; Lu L.; Gao H. H.; Zhnag J.Y.; *ACS Applied material interfaces*, **2015**, 7, 9015.
<https://doi.org/10.1021/am508400a>
5. Paramasivam M.; Chitumalla R. K.; Singh S. P.; Isham A.; Han L.; Rao V.J.; Bhanuprakash K. *J. Phys. chem.* **2015**, 119, 17053-17064.
<https://doi.org/10.1021/acs.jpcc.5b04629>
6. Takano S.; Moria M.; Ugasawara K. *J. Org. Chem.* **1991**, 56, 5982-5984.
<https://doi.org/10.1021/jo00021a006>
7. Chakraborti D. P.; Islam A.; Bhattacharya P. *J. Org. Chem.* **1973**, 38, 2728-2729.
<https://doi.org/10.1021/jo00955a038>
8. Saha C.; Choudhary B. K. *Phytochemistry* **1998**, 48, 363-366.
[https://doi.org/10.1016/S0031-9422\(97\)01135-7](https://doi.org/10.1016/S0031-9422(97)01135-7)
9. Lokhande P. D.; Humane V. T.; Naykode M.; Ghom M. H. *Tetrahedron Lett.* **2016**, 57, 688-699.
<https://doi.org/10.1016/j.tetlet.2016.01.002>
10. Ghom M. H.; Naykode M.; Humane V. T.; Lokhande P. D. *Tetrahedron Lett.* **2019**, 60, 1029-1031.

- <https://doi.org/10.1016/j.tetlet.2019.03.022>
11. Naykode M. S.; Tambe S. D.; Lokhande P. D. *Chemistry Select* **2017**, 2, 567-570.
<https://doi.org/10.1002/slct.201601759>
12. Kosower E. M.; Cole W. J.; Wu G. S.; Cordy D. E.; Meisters G. J. *Org. Chem.* **1963**, 28, 630–633.
<https://doi.org/10.1021/jo01038a007>
13. Gaikwad H.; Waghmare S. R.; Hankare P. D.; Lokhande P. D. *Indian J. Chem. Sect. B*, **2013**, 52B, 300-305.
14. Kabalka G.W.; Mereddy A. R. *Tetrahedron Lett.* **2005**, 46, 6315-6317.
<https://doi.org/10.1016/j.tetlet.2005.07.038>
15. Lokhande P. D.; Dalvi B.; Nawaghare B. R.; Humne V.; Kareem A. *Indian J. Chem. Sect. B*, **2014**, 53B, 1091-1097.
16. Lokhande P. D.; Hasanzadeh K.; Khaledi H.; Ali H. M. *J. Heterocycl. Chem.* **2012**, 29, 1398-1406.
<https://doi.org/10.1002/jhet.1049>
17. Yang D.; Yan Y. L.; Lui B. *J. Org. Chem.* **2002**, 67, 7429-7431.
<https://doi.org/10.1021/jo026025t>
18. Zhang Y.; Shibatomi K.; Yamamoto H. *J. Am. Chem. Soc.* **2004**, 126, 15038 -15039.
<https://doi.org/10.1021/ja0454485>
19. Cheng S.-F.; Lin C.-S.; Liu L. K. *J. Chin. Chem. Soc.* **1997**, 44, 309-312.
<https://doi.org/10.1002/jccs.199700046>
20. Meketa M. L.; Mahajan Y. R.; Weinreb S. M. *Tetrahedron Lett.* **2005**, 46, 4749-4751.
<https://doi.org/10.1016/j.tetlet.2005.05.055>
21. Shi X.-X.; Dai L.-X. *J. Org.Chem.* **1993**, 58, 4596-4598.
<https://doi.org/10.1021/jo00069a020>
22. Zhu Y.W.; Shi Y. X. *Catalysis Lett.* **2016**, 146, 570 -574.
<https://doi.org/10.1007/s10562-015-1676-3>
23. Zhou Z. S.; Li L.; He X. H. *Chin. Chem. Lett.* **2012**, 23, 1213-1216.
<https://doi.org/10.1016/j.ccllet.2012.09.014>
24. Swamy P.; Kumar M. A.; Reddy M. M.; Narender N. *Chemistry Lett.* **2012**, 41, 432- 434.
<https://doi.org/10.1246/cl.2012.432>
25. Ito Y.; Nakatsuka M.; Saegusa T. *J. Org. Chem.* **1980**, 45, 2022-2024.
<https://doi.org/10.1021/jo01298a062>

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