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Hydroxylamine Hydrochloride as an effective Catalyst for Form amide derivative Synthesis and their DPPH scavenging activity

Agarwal Deepali *, Agrwal Akansha, Bairagi Anamika and Kasana Virendra Kumar
Organic Synthesis Laboratory, Department of Chemistry, CBSH, G.B. Pant University of Agriculture and Technology, Pantnagar U.S. Nagar 263 145, INDIA

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Abstract

Hydroxylamine hydrochloride offers simple, efficient, economical and environmentally benign method for amidation at room temperature. The reaction was carried out under neat condition affording most of the products in excellent yield. Plausible mechanism to explain the ability of hydroxylamine hydrochloride to enhance the rate of reaction is described. The method is superior as in this method less amount of formic acid is required and reaction proceeds at room temperature. Synthesized formamides were found to have significant radical scavenging effect on 2,2-diphenyl-1-picryl-hydrazyl radicals

Keywords: Hydroxylamine hydrochloride, amidation, environmentally benign, room temperature, radical scavenging.

Introduction

Formylation of amines is required during the synthesis of a number of compounds used in medicinal and industrial fields. In the synthesis of medicinally important compounds such as 1,2 dihydroquinolines, substituted aryl imidazoles, cancer chemo-therapeutic compounds and oxazolidinones the application of N-formylation is well documented[1-4]. Formamides are used as catalyst in the process such as allylation and hydrosilylation of carbonyls compounds[5-6]. They are important precursor in the synthesis of fungicides and herbicides[2]. They are used as reagents for Vilsmeir formylation[7]. Formamides are also used in the synthesis of formamidiens[8] and isocyanide[9-11].

A number of catalysts such as $ZnCl_2$, iridium, ammonium formate, thiamine hydrochloride, guanidine derived ionic liquids, sulfated titanium oxide, sodium formate, sulfated tungstate, amberlite IR 120, melamine trisulfonic acid have been reported to catalyse N- formylation of amines[12-21]. Most of the reported methods of N-formylation methods have one or more disadvantages such as harsh reaction conditions and long reaction time, thermally unstable and toxic catalyst and tedious workup. So, it is desirable to develop mild, convenient and high yielding procedure using non toxic and inexpensive catalyst[22-25].

The present work is in continuation to our earlier work to develop new synthetic methods using environmentally benign and inexpensive catalysts[26-27]. We herein report a convenient and green approach for N-formylation of amines using hydroxylamine hydrochloride as a catalyst under neat condition. Synthesized N-formylated derivatives have been studied for their antioxidant activity viz., radical scavenging effect on DPPH[28].

Material and Methods

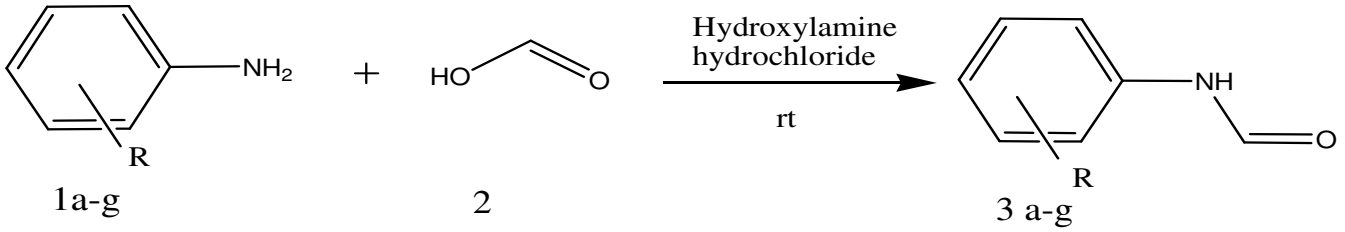
Synthesis: A mixture of aniline (1mmol), hydroxylamine hydrochloride (0.1 mmol) and formic acid (2 mmol) was taken in 100 ml round bottom flask and stirred at room temperature for 70 minutes. After completion of the reaction as indicated by TLC, 20 ml of EtOAc was added to the reaction mixture. The reaction mixture was then transferred to the separating funnel and washed with aq HCl (conc 5%), aq Na_2CO_3 (conc 5%). Organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated to afford the compound without further purification (table-1, entry 4).

DPPH radical scavenging activity: The DPPH free radical scavenging activity was determined according to the method described by Chen and Ho (1995).[29] To the 5 ml 0.004% ethanolic solution of DPPH, varying amount (5, 10, 15, 20 and 25 µl) of ethanolic solutions of formamide derivatives was added. The test solution was prepared in triplicate and placed in dark for 2 h. The absorbance at 517 was recorded at room temperature. The percent DPPH radical scavenging activity of compound was calculated using following equation:

% DPPH radical scavenging activity = [1-(Absorbance of sample/ Absorbance of control)] × 100

BHT (butylated hydroxytoluene), ascorbic acid and gallic acid were used as a reference compounds. IC_{50} value (µg of compound per ml) was calculated by interpolation from linear regression analysis.

Table-1
N-formylation of amines (3a-g) with formic acid (2) using hydroxylamine hydrochloride under solvent free condition



1a-g 2 3 a-g

Entry	Amine	R	Products	Time (min)	%Yield[a]
1	3a	4-CH_3	3a	330	76
2	3b	2-Cl	3b	60	93
3	3c	4-F	3c	90	80
4	3d	H	3d	70	97
5	3e	3-$COCH_3$	3e	230	75
6	3f	2-OH	3f	200	95
7	3g	4-NO_2	3g	20	90

[a] Isolated yield

Table-2
Comparison of hydroxylamine hydrochloride catalyzed N-formylation with other reported methods

Entry	Catalyst	Temperature	Amine: HCOOH	Ref.
1	$ZnCl_2$	70°C	1:3	13
2	Ammonium formate	Reflux	-	15
3	Thiamine hydrochloride	80°C	1:4	16
4	Amberlite IR 320	Microwave	1:3	21
5	Melamine Trisulfonic acid	60°C	1:2	22
6	Hydroxylamine hydrochloride	Rt	1:2	Present work

Results and Discussion

Syhthesis: N-formylation reaction afforded good to excellent (table-1, entry 1-7) involving hydroxylamine hydrochloride as a catalyst under solvent free condition. Superiority of our protocol in comparison to reported methods in literature may be established by comparing the results of our protocol with those of reported methods. The two important features of our method are requirement of fewer amounts of formic acid and low temperature (room temperature). The amine: formic acid ratio and temperature for reported methods using different catalysts are given in table-2. Perusal of table-2 clearly indicates that hydroxylamine hydrochloride as a catalyst is most efficient in terms of temperature, time and mole ratio of amine and formic acid.

DPPH radical scavenging activity: DPPH is a stable free radical with an absorption maximum at 517 nm. When an antioxidant is present in the medium, it donates protons to DPPH radical which lowers the initial absorbance of DPPH solution. Figure-2 showed that with increasing the concentration of formamide derivatives, the DPPH free radical scavenging activity increases and attained constant value. Perusal of table-3 reveals that all the formamide derivatives with –H, CH_3, -Cl, -NO_2, -$COCH_3$, -F, -OH groups exhibit free radical scavenging activity as it is evident from their IC_{50} values. These compounds were found to exhibit activity, comparable with standards i.e. BHT, gallic acid and ascorbic acid.

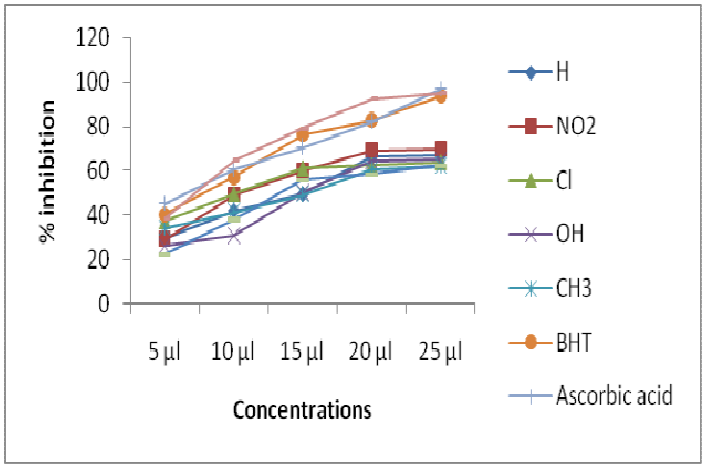


Figure-2
The effect of ethanolic solution of formamide derivatives on DPPH scavenging activity

Table-3
Free radical scavenging activity of formamide derivatives and standards in the antioxidant activity evaluation assays

Compounds	DPPH (IC_{50}) µg/ml
3a	3.05
3b	2.26
3c	2.87
3d	2.91
3e	3.2
3f	3.23
3g	2.4
BHT	1.47
Gallic acid	1.3
Ascorbic acid	1.3

Spectral Characterization data of selected compounds: N-(2-chlorophenyl)-formamide (3b): IR (KBr, cm^{-1}): 3251, 2900, 1939, 1790, 1663, 1540; ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 7.04-7.7 (m, 4H, Ar), 8.38 (1s, 1H, NH), 8.70 (1s, 1H, CHO). **N-(phenyl)-formamide (3d):** IR (KBr, cm^{-1}): 3408, 1586, 1394; ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 7.07-7.55 (m, 5H, Ar),8.39 (s, 1H, NH), 8.71 (s, 1H, CHO) **N-(2-hydroxyphenyl)-formamide (3f):** IR (KBr, cm^{-1}): 3376, 3089, 2877, 1655, 1590, 1376, 1279; NMR ($CDCl_3$, 300 MHz): δ ppm 7.01-7.18 (m, 4H, Ar), 6.87 (s, 1H, OH), 7.26 (s, 1H, NH), 8.27 (s, 1H, CHO). **N-(4-nitrophenyl)-formamide (3g):** IR (KBr, cm^{-1}): 3212, 3082, 1688, 1595; ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 7.2-7.7 (m, 4H, Ar), 8.22 (s, 1H, NH), 8.9 (s, 1H, CHO).

Conclusion

In conclusion, hydroxylamine hydrochloride is an efficient catalyst for N-formylation of amines. Two salient features of our protocol are requirement of fewer amounts of formic acid and low temperature. The protocol provides simple, economical and environment friendly method for formamide synthesis. The results reveal that all the ethanolic solutions of synthesized formamide derivatives showed significant DPPH radical scavenging activity to produce broad spectrum of antioxidant potential to create effective defense system against free radical attack.

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