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SHORT COMMUNICATION

N-Chlorosuccinimide (NCS)–*N,N*-dimethylformamide (DMF), a reagent for the oxidation of benzylic alcohols to aldehydes and ketones

Mahesh R. Kulkarni[1] · Nitin P. Lad[1] · Nitin D. Gaikwad[1]

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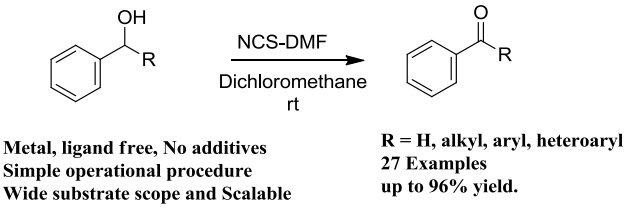
Abstract

The oxidation of benzylic alcohol to corresponding aldehyde and ketone using *N*-chlorosuccinimide (NCS)–*N,N*-dimethylformamide (DMF) has been described. This method gives easy access to the corresponding carbonyl compounds under metal-free conditions, without the use of corrosive reagent at ambient temperature in good yield.

Graphical abstract



Keywords *N*-Chlorosuccinimide (NCS) · *N,N*-Dimethylformamide (DMF) · Benzylic alcohol · Oxidation

Introduction

Aldehydes and ketones are important structural motifs existing in a large number of natural products, pharmaceutical intermediates, key components of biologically active molecules, fragrances, dyes, etc. [1]. Traditional method to synthesize aldehydes and ketones by oxidation of alcohol involves metal based reagents such as Cr(VI) and Mn(VII) [2–5]. Environmental concern prompted chemists to develop new methods; as a result, a variety of reagents and catalysts have been developed. *N*-halo succinimide and other electrophilic halogen sources have been known for a long time for the oxidation of alcohol, and the oxidation using NBS in the absence of any catalyst or additive proceeds in rather harsh reaction conditions [6–9]. Adimurthy et al. reported in their communication about oxidizing benzylic alcohol to aldehyde using NBS; however, they have reported in their communication at low-temperature conversion is low and at the higher-temperature formation of benzyl bromide as an impurity along with a desired product [10]. Somraj Guha et al. reported the synthesis of alpha amino ketone from benzylic alcohol in the presence of NBS at room temperature; however, they have reported in the presence of other halogen sources that NCS reaction is not effective [11]. Chandra Bhushan Tripathi et al. reported Lewis base catalysis by thiourea: *N*-bromosuccinimide-mediated oxidation of alcohols [12]. They have reported that in the absence of thiourea catalyst, reactions are sluggish, and by using NCS, only 5% of alcohol is converted to carbonyl compound. Also, even in the presence of thiourea Lewis base, conversion is only 55%. Jianglong Wu et al. developed a method for the oxidation of benzylic alcohol in aqueous medium in the presence of potassium acetate [13]. *N*-chlorosuccinimide

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✉ Nitin D. Gaikwad
gaikwad.chemistry@gmail.com; gaikwad_nd17@yahoo.co.in

[1] Organic Chemistry Research Centre, Department of Chemistry, K.R.T. Arts, B.H. Commerce and A.M. Science College, Gangapur Road, Nashik, MS 422 002, India

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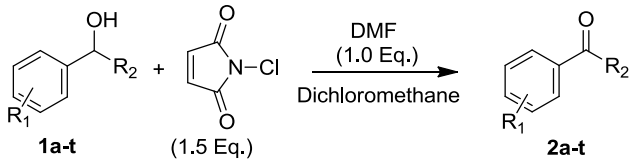
is versatile reagent in synthesis proved to useful for oxidation, chlorination, C–C bond formation, rearrangements and functional group transformation [14]. The oxidation of alcohols to carbonyl compound using NCS always requires appropriate catalyst such as TEMPO, tetrabutylammonium chloride, polymer-supported sulfinimidoyl chloride, *N-tert*-butylbenzenesulfonamide–K_2CO_3 and Corey–Kim reagent (NCS–SMe_2 complex) [15–19]. Due to the odor of the Corey–Kim reagent, it is not user-friendly, and later on, user-friendly alternatives using odorless complex of NCS with dodecyl methyl sulfide are introduced [20] (Scheme 1).

Unfortunately, the traditional oxidation methods have several drawbacks such as metal catalyst, hazards of peroxides, formations of by-products and toxic wastes, tedious workup procedures. This prompted us to find out the simpler process which is atom economical, does not use metal-based reagent, is ready to address industrial processes for green and sustainable chemistry and minimizes the burden on the environment.

Results and discussion

Our interest is in exploring *NCS* for the oxidation of benzylic alcohols to corresponding carbonyl compounds by simple and convenient method without the use of the noxious reagents such as dimethyl sulfide and metal catalyst. Our efforts have identified *DMF-NCS* as an excellent reagent for the oxidation of primary and secondary benzylic alcohols to corresponding carbonyl compounds (Scheme 2).

Our investigation started with the oxidation of benzyl alcohol in the presence of 1.5 eq. *NCS* in DMF at room temperature produced benzaldehyde in 95% yield. Next we elaborated this method for the synthesis of other aldehydes. Further optimization studies showed that DMF is required

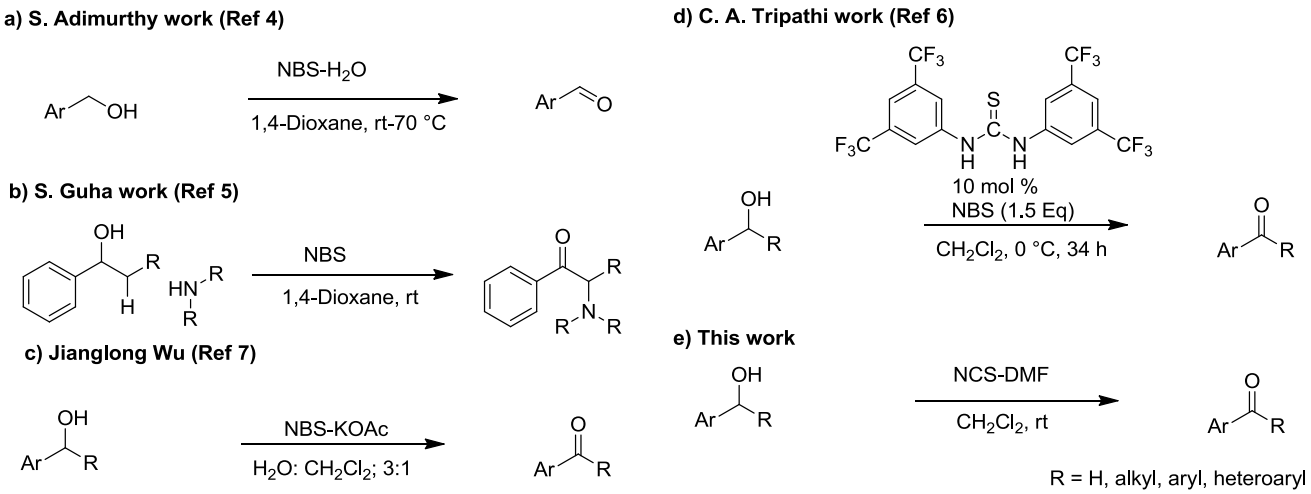


Scheme 2 Oxidation of benzylic alcohol using NCS-DMF

along with NCS for oxidation reactions and it does not work in other solvents. Best results were obtained using 1 equivalent DMF when dichloromethane is solved with 1 equivalent NCS. For complete oxidation, equimolar quantity of NCS is required along with a catalytic amount of DMF in dichloromethane. The rate of reaction is faster when solvent is DMF as compared with reactions in dichloromethane. In other solvents such as water, DMSO and acetonitrile, reactions does not initiate using NCS-DMF. The oxidation of benzyl alcohol using NBS-DMF proceeds with the same efficiency as compared with NCS-DMF; however, reaction is sluggish when NIS-DMF is used. One can use either NCS or NBS as oxidant (Table 1); herein, we used NCS as oxidant in optimized conditions to check substrate scope (Table 2).

Further, we checked the scope of the optimized method on other substrates, and to our privilege, this method works on a variety of benzylic alcohols (Table 2). The corresponding carbonyl compounds were isolated in good yield (Table 2, up to 96%).

On electron-rich benzyl alcohol, the reaction is faster as compared to benzylic alcohols with deactivating groups. With electron-rich benzylic alcohol, reactions are too fast and led to the formation of by-products; hence, moderate yield is obtained. In case of benzylic alcohol **1h**, **1i**, the yield is low due to the formation of impurities along with unreacted starting material, and in case of the oxidation



Scheme 1 Approaches for the oxidation of benzylic alcohol by *N*-halo succinimide

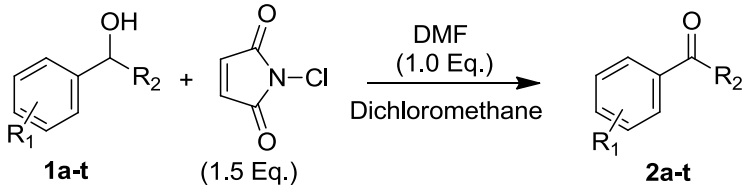
Table 1 Solvent and catalyst optimization studies

Entry[a]	Oxidant	Solvent	Time	Yield
1	0.5 Eq. NCS	DMF	16 h	50%
2	**1.0 Eq. NCS**	**DMF**	**1 h**	**95%**
3	1.0 Eq. NCS	Dichloromethane	16 h	No reaction
4	1.0 Eq. NCS	DMSO	16 h	No reaction
5	1.0 Eq. NCS	Water	16 h	No reaction
6	1.0 Eq. NCS	Acetonitrile	16 h	No reaction
7	DMF	DMF	16 h	No reaction
8	1.0 Eq. NCS + 5.0 Eq. DMF	Dichloromethane	3 h	96%
9	1.0 Eq. NCS + 5.0 Eq. DMF	DMSO	16 h	No reaction
10	1.0 Eq. NCS + 0.1 Eq. DMF	Dichloromethane	16 h	89%
11	1.0 Eq. NCS + 0.25 Eq. DMF	Dichloromethane	3 h	93%
12	**1.0 Eq. NCS + 1.0 Eq. DMF**	**Dichloromethane**	**3 h**	**95%**
13	**1.5 Eq. NCS + 1.0 Eq. DMF**	**Dichloromethane**	**3 h**	**95%**
14	1.0 Eq. NBS + 1.0 Eq. DMF	Dichloromethane	3 h	95%
15	1.0 Eq. NIS + 1.0 Eq. DMF	Dichloromethane	3 h	31%

Bold indicates the optimized condition

[a]All reactions carried out at room temperature; optimization studies carried out on benzyl alcohol **1a** as a model substrate

Table 2 Substrate scope for alcohol oxidation



Product	R1	R2	Time	Yield (%)[a]
2a	H	H	1 h	95
2b	4-Me	H	0.25 h	93
2c	3-OMe	H	0.25 h	69
2d	2-NO_2	H	16.0 h	61
2e	2-Br	H	2.0 h	88
2f	2-Br,3,4-OMe	H	16.0 h	49
2 g	2-Br, 4,6-F	H	8.0 h	81
2 h	2-Br,3-OH,4-OMe	H	4.0 h	41
2i	3-F, 4-CF_3	H	8.0 h	29
2j	H	Me	0.25 h	96
2 k	H	Ph	1.0 h	95
2 l	4-Cl	Et	2.0 h	87
2 m	3-Br, 6-Me	Me	4.0 h	79
2n	4-Br	Me	1.45 h	93
2o	4-OMe	Me	1.0 h	45

[a]Yield are of isolated products

of **1d**, **1j**, the yield is moderate due to incomplete reaction. The optimized reaction conditions on secondary benzylic alcohols are also consistent to afford corresponding ketone.

Furthermore, we have tested the scope of this method on heterocyclic substrate (Fig. 1), the di-pyridylmethanol oxidized under optimized conditions and isolated product in 91% yield (compound **2u**) also **2t** is isolated in 61% as per

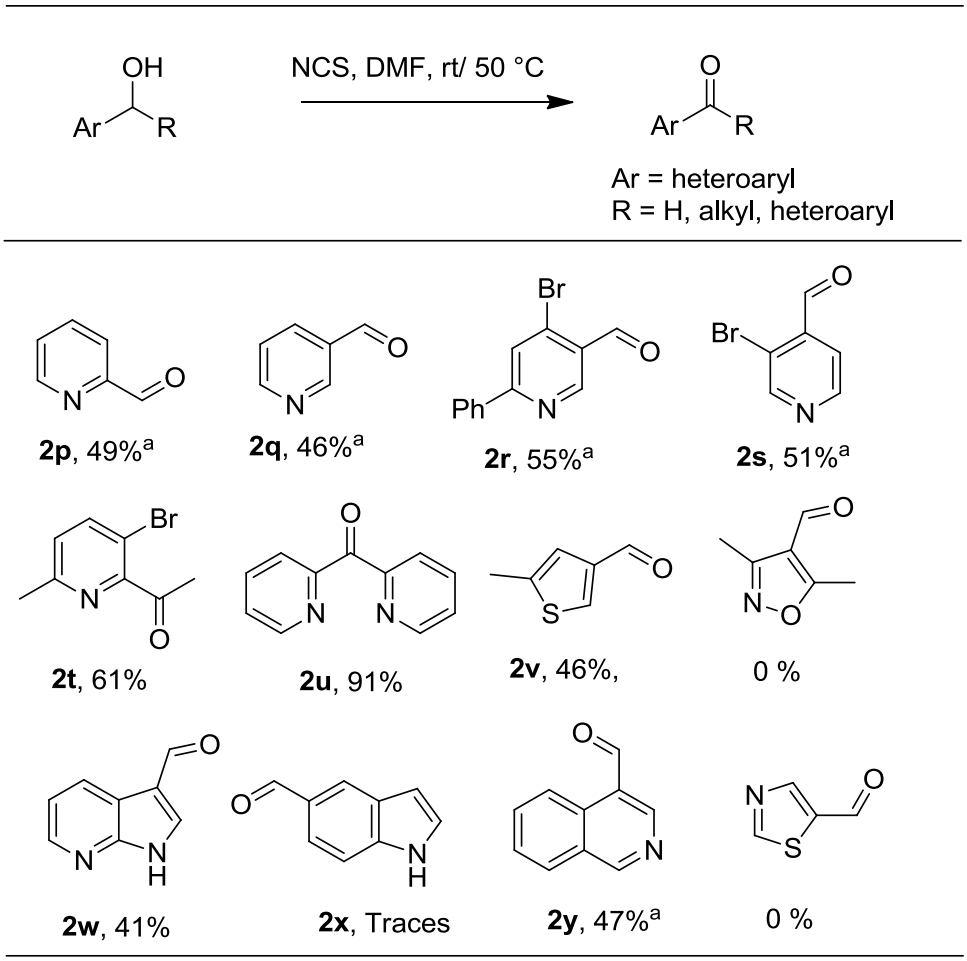


Fig. 1 Substrate scope for alcohol oxidation on heterocyclic substrates. [a]At room temperature, the oxidation is not initiated; however, on heating to 50 °C for 16 h, 60–70% conversion was observed by TLC; the yield 0% no reaction initiation even on heating at 50 °C for 16 h (isolated back starting materials). In case of **2x**, traces of product was confirmed by LC–MS, and the starting material was degraded under reaction conditions

the optimized reaction conditions. However, for synthesis of **2p**, **2q**, **2s**, **2y** reaction was not initiated under optimized reaction conditions; however, on heating at 50 °C for 4–16 h corresponding aldehyde was obtained, but in some cases reaction was incomplete (Fig. 1). In case of the other heterocyclic compounds, the low yield is due to the formation of by-products and incomplete reactions (Fig. 1, **2v**, **2W**, **2y**). The thiazol-5-yl-methanol was not oxidized under the reaction conditions even after heating at 50 °C for 16 h. The (3,5-dimethylisoxazol-4-yl)methanol was degraded under the reaction conditions at room temperature, and traces of product were observed with 1*H*-indole-5-carbaldehyde with the formations of by-products. This is a very useful oxidation method for the oxidation of primary and secondary benzylic alcohols; in many cases, no chromatographic purifications are also required.

Supplementary data

Scan spectra associated with this article can be found in the online version.

Conclusions

In conclusion, we have developed mild and efficient method for the oxidation of benzylic alcohol to aldehydes and ketones under ambient condition using NCS-DMF. These conditions can be adopted to a wide range of benzylic alcohol under metal-free conditions without the use of any additives.

Experimental section

Generally, all the chemicals and solvents were procured from commercial suppliers such as Sigma-Aldrich Chemical Co. and Fischer Scientific and were used as received unless otherwise indicated. All reactions were performed under an inert atmosphere unless otherwise noted. Analytical silica gel 60 F254-coated TLC plates were purchased from Merck Chemicals and were visualized with UV light or by treatment with TLC reagents such as 2,4-DNP. Flash column chromatography was carried out on CombiFlash R_f using silica gel (230–400 mesh). ^{1}H-NMR spectra were routinely

recorded on Bruker 400 MHz FT NMR, with tetramethylsilane (TMS) as an internal standard. Mass spectral (MS) data were obtained on a Bruker Daltonics spectrometer using an electrospray ionization quadrupole time of flight (ESI-QTOF) analyzer.

Procedure for the oxidation of benzylic alcohols to aldehydes and ketones

Method A 1.00 mmol of benzyl alcohol in 10 mL of dichloromethane was taken in a 25-mL, round-bottomed flask. DMF (1.0 mmol) and *N*-chlorosuccinimide (1.5 mmol) were added. The reaction mixture was stirred at room temperature, and progress of reaction was monitored by TLC. The reaction mixture was diluted with dichloromethane (10 mL) and washed with 10 mL of saturated sodium bicarbonate solution, water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate is evaporated to get crude product, which was purified by flash column chromatography over silica gel (*n*-hexane–ethyl acetate) to get the pure benzaldehyde.

Method B 1.00 mmol of benzyl alcohol in 5 mL of DMF was taken in a 25-mL, round-bottomed flask, and *N*-chlorosuccinimide (1.5 mmol) was added. The reaction mixture was stirred at room temperature for appropriate time. The progress of reaction was monitored by TLC. The reaction mixture was poured over water (25 mL) and extracted with ethyl acetate (3 × 10 mL). Combined organic layers were washed with saturated sodium bicarbonate solution (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate is evaporated to get crude product, which was purified by flash column chromatography over silica gel (*n*-hexane–ethyl acetate) to get the pure benzaldehyde.

2a. Benzaldehyde

Yield: 95.0%; Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.07 (s, 1H), 8.16 (d, J = 7.2 Hz, 2H), 7.68 (t, J = 7.2 Hz, 1H), 7.58 (t, J = 7.2 Hz, 2H).

2d. 2-nitrobenzaldehyde

Yield: 61.10%; Colorless liquid; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.48 (s, 1H), 8.17 (d, J = 7.6 Hz, 1H), 8.01 (dd, J = 7.2 Hz, 1.6 Hz, 1H), 7.87–7.79 (m, 2H).

2e. 2-bromobenzaldehyde

Yield: 88.21%; Colorless liquid; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.41 (s, 1H), 7.97–7.95 (m, 1H), 7.71–7.68 (m, 1H), 7.52–7.46 (m, 2H).

2f. 2-bromo-3,4-dimethoxybenzaldehyde

Yield: 49.42%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.28 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 3.98 (s, 3H), 3.90 (s, 3H); MS (ES+) m/z: 245.2$[M+H]^+$.

2g. 2-bromo-4,6-difluorobenzaldehyde

Yield: 80.93%; Colorless liquid; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.18 (s, 1H), 7.74 (dt, J = 8.4 Hz, 2.0 Hz, 1H), 7.60 (td, J = 9.2 Hz, 2.4 Hz, H).

2 h. 2-bromo-3-hydroxy-4-methoxybenzaldehyde

Yield: 41.0%; White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.11 (s, 1H), 9.93 (s, 1H), 7.41 (s, 1H), 7.15 (s, 1H), 3.93 (s, 3H); MS (ES+) m/z: 229.11$[M+H]^+$.

2j. Acetophenone

Yield: 96.22%; Colorless liquid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00 (d, J = 7.2 Hz, 2H), 7.61 (t, J = 7.2 Hz, 1H), 7.51 (d, J = 7.6 Hz, 2H), 2.65 (s, 3H).

2k. Benzophenone

Yield: 95.0%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 7.2 Hz, 4H), 7.64 (t, J = 7.2 Hz, 2H), 7.53 (t, J = 7.6 Hz, 4H).

2l. 1-(4-chlorophenyl)propan-1-one

Yield: 87.49%; Off-white solid; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.99 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 3.06 (q, J = 7.2 Hz, 2H), 1.08 (t, J = 7.2 Hz, 3H).

2m. 1-(5-bromo-2-methylphenyl)ethan-1-one

Yield: 79.0%; White Solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (d, J = 2.2 Hz, 1H), 7.63 (dd, J = 8.2, 2.2 Hz, 1H), 7.27 (d, J = 8.2 Hz, 1H), 2.56 (s, 3H), 2.36 (s, 3H).

2n. 1-(4-bromophenyl)ethanone

White solid; Yield: 93.10%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.86 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 2.63 (s, 3H).

2s. 3-bromoisonicotinaldehyde

Yield: 51.0%; White solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.41 (s, 1H), 8.95 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 7.75 (d, J = 4.8 Hz, 1H); MS (ES+) m/z: 264.1$[M+2H]^+$

2t. 1-(3-bromo-6-methylpyridin-2-yl)ethan-1-one

Yield: 61.0%; Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.2 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H), 2.71 (s, 3H), 2.57 (s, 3H); MS (ES+) m/z: 216.1$[M+2H]^+$.

2u. di(pyridin-2-yl)methanone

Yield: 91.40%; Off-white crystal; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, J = 4.4 Hz, 2H), 8.14 (d, J = 7.6 Hz, 2H), 7.94 (t, J = 7.6 Hz, 2H), 7.54 (dd, J = 7.2 Hz, 4.4 Hz, 2H); MS(ES+) m/z: 186.3$[M+H]^+$.

2v. 5-methylthiophene-3-carbaldehyde

Yield: 46.0%; black oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H), 7.72 (d, J = 3.6 Hz, 1H), 6.92 (d, J = 3.6 Hz, 1H) 2.77 (s, 3H); MS (ES+) m/z: NS

2w. 1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde

Yield: 41.0%; Off-white to yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.72 (s, 1H), 9.39 (s, 1H), 8.49 (s, 1H), 8.41 (d, J = 7.6 Hz, 1H), 8.38 (d, J = 4.8 Hz, 1H), 7.30 (dd, J = 8.0 Hz, 3.6 Hz, 1H); MS (ES+) m/z: 147.05$[M+H]^+$.

2y. isoquinoline-4-carbaldehyde

Yield: 47.0%; light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.44 (s, 1H), 9.39 (s, 1H), 8.04 (d, J = 5.6 Hz,1H), 8.77 (d, J = 5.2 Hz, 1H), 8.36–8.20 (m, 2H), 7.83 (t, J = 8.0 Hz, 1H); MS (ES+) m/z: 157.2$[M+H]^+$.

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