Synthetic Communications®, 41: 2505–2510, 2011

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.502988

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SODIUM CYANOBOROHYDRIDE–MEDIATED DIRECT CONVERSION OF SOME HETEROCYCLIC ALDEHYDES TO ESTERS

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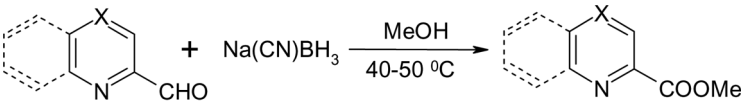
GRAPHICAL ABSTRACT



X = N or C

Abstract *An exceptional oxidizing behavior of sodium cyanoborohydride is observed where electron-withdrawing heterocyclic aldehydes are directly converted to their corresponding esters on treatment of sodium cyanoborohydride in methanol. The spectral analysis and single-crystal structure confirm the formation of esters.*

Keywords Esterification; heterocyclic aldehydes; heterocyclic esters; sodium cyanoborohydride

INTRODUCTION

Sodium cyanoborohydride is a popular reducing agent and is used to reduce a wide range of organic functional groups selectively.[1–3] Previous applications of this reagent have been reported, such as reductions of ketone, aldehyde, oxime, and enamine.[4–6] To date, the conversion of heterocyclic aldehydes to esters by the use of this reagent has not been reported.

Interestingly, we have observed that the reaction of sodium cyanoborohydride with quinoxaline aldehyde or pterin aldehyde in the presence of dry alcohol cleanly leads to the unexpected formation of esters from corresponding aldehydes instead of the usual reduction of aldehydes to alcohol (Scheme 1).

Received January 28, 2010.
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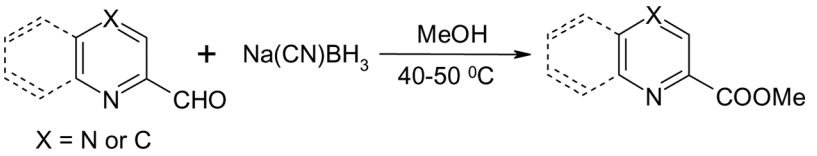
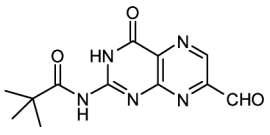
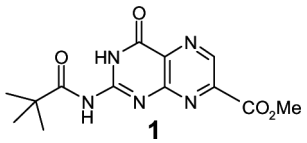
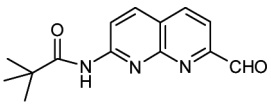
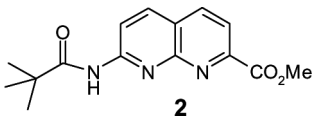
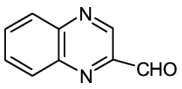
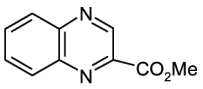
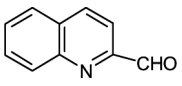
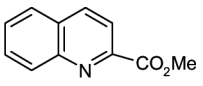
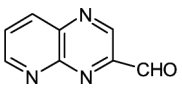
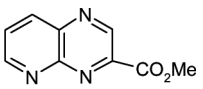


Scheme 1. One-step synthesis of heterocyclic esters from the corresponding aldehydes.

Heterocyclic esters are important compounds considering their biological and pharmaceutical aspects.[7] Only a few methods are available for the synthesis of heterocyclic esters.[8] Here, we report esterification of some electron-withdrawing heterocyclic aldehydes to esters by using sodium cyanoborohydride. The results are summarized in Table 1.

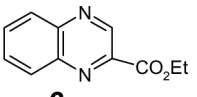
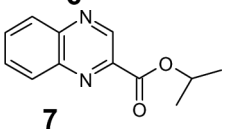
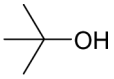
As shown in Table 1, it has been observed that more electron-deficient heterocyclic aldehydes only are converted to the corresponding esters with reasonably good yields. The time required for these reactions is 30 min to 1 h. In the case of pterin aldehyde, the reaction occurs at room temperature, whereas all the other reactions are carried out at 40–50 °C. The reaction is mild, clean, and rapid. The reactions are also carried out at pH 3–4 (methanolic solution of HCl), where we also isolate

Table 1. Synthesis of heterocyclic esters from electron-deficient heterocyclic aldehydes[a]

Entry	Aldehyde	Product	Yield (%)	Mp (°C)
a		 **1**	72	156–158
b		 **2**	68	142–144
c		 **3**	80	110–112
d		 **4**	79	62–64
e		 **5**	65	155–156

[a]Reactions were monitored by TLC analysis. Isolated yields were of chromatographically obtained pure materials.

Table 2. Reactions of quinoxaline-2-aldehyde with different alcohols

Entry	Alcohol	Product	Yield (%)	Mp (°C)
a	EtOH	 **6**	72	75–76
b		 **7**	65	60–62
c		No esterification		

the corresponding esters. The products are characterized by infrared (IR), NMR, and mass spectroscopy. Heterocyclic aldehydes such as pyridine aldehyde or phenanthroline-2,9-dialdehyde are reduced to their corresponding alcohols according to the usual reducing behavior of sodium cyanoborohydride.

On the reaction of quinoxaline-2-aldehyde, we have isolated the corresponding ethyl or isopropyl esters by changing the solvent to ethanol or isopropanol, although the yields gradually decrease by the use of primary to secondary alcohols (Table 2). In the case of using tertiary butyl alcohol, no esterification occurs.

The final confirmation of the structure (i.e., formation of ester) is obtained by x-ray crystallographic investigation.[9] Here the single-crystal structure of compound **2** (methyl-7-pivaloylamino-[1,8]naphthyridine-2-carboxylate) (Fig. 1) is also presented. The naphthyridine ring (C1/N1/C2–C8/N2) lies on a crystallographic mirror plane and is planar. There are no classical hydrogen bonds. Intramolecular C3—H3···O2 and C7—H7···O3 interactions stabilize the molecular structure.

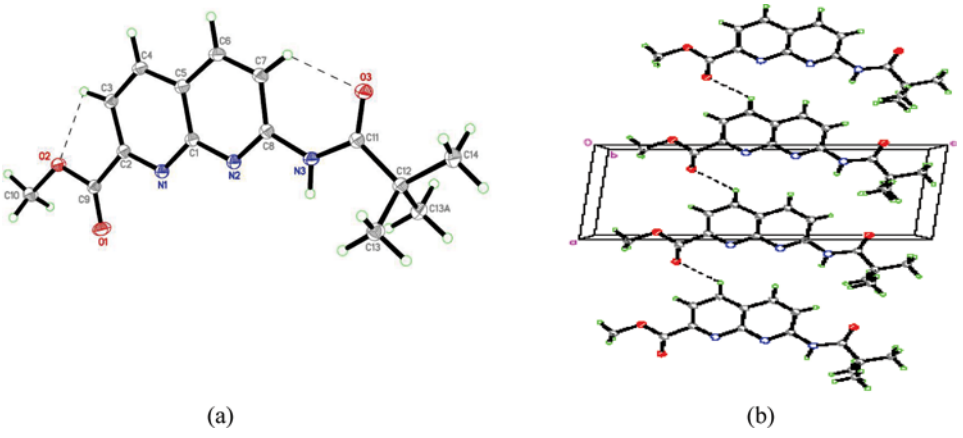


Figure 1. Illustrations of the crystal structure of compound **2**: (a) ORTEP diagram (50% probability); (b) crystal packing viewed down crystallographic *b* axis.

Intermolecular C4–H4 $\cdots$ O1 interactions build up the crystal structure, which consists of one-dimensional infinite chains along the crystallographic *a* axis. The crystal structure is further stabilized by π–π interactions [3.7466(3) Å] involving the centroids of C1/N1/C2–C5 and C1/C5–C8/N2 pyridine rings, respectively.

In conclusion, we report here that electron-withdrawing heterocyclic aldehydes are selectively oxidized by sodium cyanoborohydride to their corresponding esters. The reaction has been observed to work well with the previously mentioned heterocyclic aldehydes. The exceptional oxidative property of sodium cyanoborohydride instead of the usual reducing property has been demonstrated.

EXPERIMENTAL

General Procedure for the Direct Synthesis of Heterocyclic Ester from the Corresponding Aldehyde

Quinoxaline-2-aldehyde (160 mg, 1.01 mmol) was dissolved in dry methanol and stirred at room temperature. Sodium cyanoborohydride (purchased from Aldrich Chemical Co.) (75.4 mg, 1.2 mmol) was added slowly without further purification. The mixture was then warmed at 50–60 °C for 1 h. Excess methanol was evaporated through vacuum distillation, and the reaction mixture was quenched with saturated ammonium chloride solution. The mixture was extracted with chloroform, and the organic layer was evaporated. The compound was then purified through column chromatography by eluting with 15% ethyl acetate in petroleum ether to afford a pure crystalline solid (**3**).

Selected Data

Methyl-2-pivaloylaminopteridine-7-carboxylate (1). Mp 156–158 °C. IR (KBr): 3163, 2982, 1732, 1682, 1542, 1224, 770 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) (ppm): 12.56 (bs, 1H), 9.32 (s, 2H), 4.07 (s, 3H), 1.36 (s, 9H). MS (LCMS): m/z (%): 306.2 [$(M+H)^+$, 100]. Anal. calcd. for $C_{13}H_{15}N_5O_4$: C, 51.15; H, 4.95; N, 22.94; Found: C, 51.27; H, 4.81; N, 22.85.

Methyl-7-pivaloylamino-[1,8]naphthyridine-2-carboxylate (2). Mp 142–144 °C. IR (KBr): 3432, 2960, 1744, 1692, 1620, 1325, 860 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) (ppm): 8.67 (d, 1H, $J = 8.92$ Hz), 8.53 (bs, 1H), 8.30 (d, 1H, $J = 8.24$ Hz), 8.25 (d, 1H, $J = 8.92$ Hz), 8.19 (d, 1H, $J = 8.23$ Hz), 4.06 (s, 3H), 1.36 (s, 9H). MS (LCMS): *m/z* (%): 288.2 [$(M+H)^+$, 100], 289.2 [$(M+2H)^+$, 20], 204.1 (15).

Crystallographic data of compound 2. $C_{15}H_{17}N_3O_3$; $Mr = 287.32$; monoclinic, $P2_1/m$; block, colorless; $Z = 2$; $F(000) = 304$; $D = 1.385$ g/cm^3; $V = 688.97(3)$ Å^3; Cu $K\alpha$ radiation; $\lambda = 1.54178$ Å; a = 6.45930(10) Å; b = 6.7201(2) Å; c = 15.9665(3) Å; $\alpha = 90°$; $\beta = 96.2290(10)°$; $\gamma = 90°$; $\mu = 0.810$ mm^{-1}; $\theta = 7.16–67.25°$; crystal size = 0.13 × 0.18 × 0.41; $T = 100$ K. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center (CCDC), No. 762718.

Methyl quinoxaline-2-carboxylate (3). Mp 110–112 °C. IR (KBr): 2998, 2950, 1715, 1496, 1435, 1320, 1101, 786 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) (ppm):

9.55 (s, 1H), 8.30 (d, 1H, $J = 8.00$ Hz), 8.19 (d, 1H, $J = 8.80$ Hz), 7.89 (m, 2H), 4.13 (s, 3H). MS (LCMS): m/z (%): 189.1 [$(M + H)^+$, 100], 175.1 (15), 147.1 (75).

Methyl pyrido[2,3-b]pyrazine-3-carboxylate (5). Mp 155–156 °C. IR (KBr): 3063, 2965, 1714, 1574, 1337, 1122, 972 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) (ppm): 9.65 (s, 1H), 9.31 (s, 1H), 8.55 (d, 1H, $J = 8.50$ Hz), 7.84 (d, 1H, $J = 6.23$ Hz), 5.30 (s, 3H). MS (LCMS): m/z (%): 190.1 [$(M + H)^+$, 50]. Anal. calcd. for $C_9H_7N_3O_2$: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.02; H, 3.96; N, 22.13.

Isopropyl quinoxaline-2-carboxylate (7). Mp 60–62 °C. IR: 3433, 2919, 1705, 1636, 1468, 1383, 1098, 776 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) (ppm): 9.51 (s, 1H), 8.32 (d, 1H, $J = 8.50$ Hz), 8.18 (d, 1H, $J = 8.50$ Hz), 7.87 (m, 2H), 5.44 (t, 1H, $J = 12.50$ Hz), 1.50 (d, 6H, $J = 6.50$ Hz). MS (LCMS): m/z (%): 217.2 [$(M + H)^+$, 25], 175.1 (100). Anal. calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.79; H, 5.46; N, 13.07.

ACKNOWLEDGMENTS

We thank the Council of Scientific and Industrial Research (CSIR) [No. 01(2292)/09/EMR-II], government of India, for financial support. A. H. thanks the CSIR, government of India, for a research fellowship. The authors also thank the Malaysian Government and Universiti Sains Malaysia (USM) for Research University Golden Goose Grant No. 1001/PFIZIK/811012. J. H. G. thanks the USM for a fellowship.

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