SHORT COMMUNICATION

SIMPLE GRINDING-INDUCED REACTIONS OF 2-AMINOBENZYL ALCOHOL AND BENZALDEHYDE DERIVATIVES, A RAPID SYNTHETIC ROUTE TO 3,1-BENZOXAZINES

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ABSTRACT. The grinding-induced reactions of 2-aminobenzyl alcohol and benzaldehyde derivatives in the presence of 30 mol% of acetic acid to give 3,1-benzoxazines are described. The reactions were performed at room temperature affording 3,1-benzoxazines in yields above 95% and high purity when benzaldehyde and its chloro and nitro derivatives were used.

KEY WORDS: 2-Aminobenzyl alcohol, Benzaldehyde, Acetic acid, 3,1-Benzoxazines

INTRODUCTION

The development of environmentally benign methods for the synthesis of organic compounds has attracted the attention of synthetic chemists due to the increase in ecological concerns. One of the most important goals of these methods developments is the elimination or reduction of volatile organic solvents [1-4]. Solvent-free and liquid-assisted organic reactions have captured great interest not only because of their ecological importance, but also because they offer many synthetic advantages in terms of high efficiency, yield, selectivity, simplicity of the reaction procedure, mild conditions, reduction of waste, as well as their safety, and low cost [5-9].

As part of our broad interest in the chemistry of heterocyclic compounds [10, 11], the quick, environmental safe and clean synthesis of 2-phenyl-3,4-dihydro-3,1-benzoxazine derivatives from 2-aminobenzyl alcohol and benzaldehyde derivatives in the presence of minimal amount of acetic acid under grinding conditions utilizing a mortar and a pestle is described. The 3,1-benzoxazine moiety features in the natural product terresoxazine isolated from *Tribulus terrestris* [12] and many other bioactive molecules [13-15]. Although several methods for the preparation of 1,3-oxazine derivatives have previously been reported [16-21] few have been focused on the solid-solid or solid-liquid grinding method.

RESULTS AND DISCUSSION

The acetic acid-catalysed reaction of 2-aminobenzyl alcohol 1 and benzaldehyde 2 was considered as the model reaction. Thus, grinding of equivalent molar amounts of aminoacohol 1 and benzaldehyde 2 with a mortar and pestle in the presence of catalytic amount of acetic acid and monitoring the progress of the reaction by TLC (mobile phase = petroleum ether:ethyl acetate (7:3); R<sub>f</sub> value = 0.52) gave benzoxazine 6 as a white solid in 98% yield, Scheme 1. No product was detected when aminoacohol 1 and benzaldehyde 2 were ground without the organic acid. No significant difference was observed in the reaction when the amount of the acid was increased up to molar equivalent. Reducing the acid below the 30% molar equivalent threshold made grinding difficult because the reaction mixture dried relatively faster.

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To further access the scope of this procedure, the solvent-free reactions of aminoalcohol 1 with several benzaldehyde derivatives bearing electron-withdrawing groups were examined. Thus, grinding a mixture of aminoalcohol 1 and o-chlorobenzaldehyde 3 in the presence of acetic acid gave benzoxazine 7 as a yellow gum in 96% yield. m-Nitrobenzaldehyde 4 also reacted with 1 under the conditions described above to give benzoxazine 8 as a yellow solid in quantitative yield. Lastly, benzoxazine 9 was prepared in 99% yield by grinding p-nitrobenzaldehyde 5 and 1. No observable difference in reactivity exerted by -NO2 group at the m- or p-position of the benzaldehyde was noticed. The yields and reaction times were almost same.

The first step of the mechanism for the formation of the 3,1-benzoxazines is the nucleophilic attack of the amino group of 2-aminoalcohol 1 on the electrophilic carbonyl carbon of benzaldehyde derivatives to form an imine intermediate [22]. The imine intermediate then tautomerise to give the benzoxazines [23].

Benzoxazines 6-9 were obtained in pure forms that allow spectral characterization without need for any purification. The 1H NMR spectra of benzoxazines 6-9 showed typical singlet peaks in the region 5.65-6.61 ppm assigned to the proton on C-2. In addition, two doublet peaks with a germainal coupling (14.6-14.8 Hz) in the region 4.98-6.32 and 5.15-6.39 ppm which are due to the protons on carbon-4 were observed.

Scheme 1. Reactions of aminoalcohol 1 with benzaldehyde and its derivatives 3, 4 and 5.

Next, to further delineate the scope of this procedure, the reactions of aminoalcohol 1 and benzaldehyde derivatives bearing electron-donating hydroxyl or methoxy groups under the grinding conditions were studied. In the event, o-hydroxybenzaldehyde 10 reacted with aminoalcohol 1 in 30 minutes of grinding to give imine 13 as the only detectable product in 98% yield. Attempts to cyclise imine 13 to benzoxazine 14 by grinding for 1 hour and adding more acetic acid were futile. Interestingly and somewhat surprisingly, grinding of aminoalcohol 1 with m-hydroxybenzaldehyde 11 gave a yellow gum in 88% yield (Scheme 2). The 1H NMR spectrum of the product revealed that it was a 4:1 tautomeric mixture of benzoxazine 16 and imine 15 respectable. The proportion of the tautomers was determined by integration of the well separated H-2 of the benzoxazine 16 and the –N=CH- proton of imine 15. Likewise, p-methoxybenzaldehyde 12 reacted under the same conditions to yield a 3:1 mixture of benzoxazine 18 and imine 17 in 97% yield. Attempts to separate these mixtures by column chromatography were futile suggesting that the benzoxazines and their imine tautomers existed in equilibrium [23].

Scheme 2. Reactions of aminoalcohol 1 with hydroxyl- and methoxybenzaldehyde derivatives.

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CONCLUSION

In conclusion, benzaldehyde, o-chloro-, m-nitro- and p-nitro-substituted derivatives of benzaldehyde reacted with 2-aminobenzyl alcohol in the presence of catalytic amount of acetic acid under grinding conditions at room temperature to give the corresponding 1,3-benzoxazines in short reaction times with high yields and purity. In contrast, o-hydroxybenzaldehyde reacted with 2-aminobenzyl alcohol to give the corresponding imine while m-hydroxy- and p-methoxy-substituted derivatives of benzaldehyde reacted under the conditions described above to give an equilibrium mixture of the corresponding benzoxazines and imines.

EXPERIMENTAL

General experimental conditions. All reagents were purchased from Merck and Aldrich and used without further purification. Thin layer chromatography experiments were performed on TLC silica gel 60 aluminium plates and a mixture of petroleum ether and ethyl acetate (7:3) was used as the mobile phase. Melting points were recorded using a Stuart scientific melting point apparatus and are uncorrected. The NMR spectra were acquired on a Bruker DPX 300 spectrometer using TMS as the internal standard. The mass spectra were obtained on a GCT Premier instrument.

General procedure for the synthesis of 3,1-benzoxazines. A mixture of 2-aminobenzyl alcohol (1 mmol), benzaldehyde derivative (1 mmol) and acetic acid (0.3 mmol) was mixed thoroughly in a mortar followed by grinding with a pestle till the completion of the reaction as indicated by TLC (5-30 min). The product was then allowed to stand in a fumehood over night to allow the acetic acid to evaporate and the product was then characterized.

2-Phenyl-1,2-dihydro-4H-3,1-benzoxazine (6). White solid, m.p. 94-96 °C. 

1H NMR (300 MHz, CDCl3): 4.72 (1H, s, NH), 4.99 (1H, d, J = 14.7 Hz, H-4), 5.17 (1H, d, J = 14.7 Hz, H-4), 5.65 (1H, s, H-2), 6.76 (1H, d, J = 7.5 Hz, H-8), 6.91 (1H, dd, J = 7.5 and 7.8 Hz, H-6), 7.03 (1H, d, J = 7.5 Hz, H-5), 7.14 (1H, dd, J = 7.5 and 7.8 Hz, H-7), 7.44 (3H, m, H-3', 4' and 5'), 7.60 (2H, m, H-2' and 6'); 13C (75 MHz, CDCl3): 67.7 (C-4), 82.8 (C-2), 115.7(C-8), 122.3 (C-6), 125.9 (C-5), 126.4 (C-4'), 126.8 (C-2' and 6'), 128.5 (C-3' and 5'),128.8 (C-7), 134.7 (C-4a), 140.5 (C-1'), 145.1 (C-8a). HRMS (EI): m/z calcd for C14H13NO (M+): 211.2590; found: 211.2593.

2-(2'-Chlorophenyl)-1,2-dihydro-4H-3,1-benzoxazine (7). Yellow gum.

1H NMR (300 MHz, CDCl3): 4.18 (1H, br, NH), 5.02 (1H, d, J = 14.6 Hz, H-4), 5.23 (1H, d, J = 14.6 Hz, H-4), 6.04 (1H, s, H-2), 6.76 (1H, d, J = 7.8 Hz, H-8), 6.93 (1H, t, J =7.44 and 7.56 Hz, H-6) 7.04 (1H, d, J = 7.44 Hz, H-5) 7.17 (1H, dd, J = 7.56 and 7.8 Hz, H-7), 7.43 (3H, m, H-4', 5' and 6'), 7.84 (1H, dd, J = 7.5 and 2.6 Hz, H-3); 13C NMR (75 MHz, CDCl3): 68.0 (C-4), 81.8 (C-2), 116.7 (C-8), 121.7 (C-6), 124.2 (C-5), 127.4 (C-3'), 127.6 (C-6'), 128.1 (C-7), 129.2 (C-3'), 130.5 (C-2'), 132.7 (C-4a), 136.7 (C-1'), 142.1 (C-8a). HRMS (EI): m/z calcd for C14H12NOCl (M+) 245.0668; found: 245.0632.

2-(3'-Nitrophenyl)-1,2-dihydro-4H-3,1-benzoxazine (8). Yellow solid, m.p. 80-82 °C. 

1H NMR (300 MHz, CDCl3): 5.99 (1H, br, NH), 6.32 (1H, d, J = 14.8 Hz, H-4), 6.39 (1H, d, J = 14.8 Hz, H-4), 6.61 (1H, s, H-2), 7.04 (1H, d, J = 7.9 Hz, H-8), 7.08 (1H, dd, J = 7.3 and 7.0 Hz, H-6), 7.12 (1H, d, J = 7.0 Hz , H-5), 7.17 (1H, dd, J = 7.3 and 7.9 Hz , H-7), 7.35 (1H, dd, J = 8.2 and 7.6 Hz, H-5'), 7.49 (1H, d, J = 8.2 Hz, H-6'), 7.60 (1H, d, J = 7.6 Hz, H-4'), 7.69 (1H, s, H-2'); 13C NMR (75 MHz, CDCl3): 67.3 (C-4), 83.8 (C-2), 117.9 (C-8), 120.7 (C-6), 122.0 ( C-4') 122.4 (C-2'), 123.9 (C-5), 124.9 (C-5'), 127.7 (C-6'), 129.7 (C-4a), 132.9 (C-7), 141.9 (C-1'), 141.8 (C-1').
141.3 (C-8a), 148.4 (C-3'). HRMS (EI): m/z calcd for C_{14}H_{12}N_{2}O_{3} (M^+) 256.25668; found: 256.25664.

2-(4'-nitrophenyl)-1,2-dihydro-4H-3,1-benzoxazine (9). Yellow solid, m.p. 102-104 °C. ^1H NMR (300 MHz, CDCl3): 4.21 (1H, br, NH), 4.98 (1H, d, J = 14.7 Hz, H-4), 5.15 (1H, d, J = 14.7 Hz, H-4), 5.74 (1H, s, H-2), 6.83 (1H, d, J = 8.0 Hz, H-8), 6.98 (1H, dd, J = 7.2 and 6.9 Hz, H-6), 7.03 (1H, dd, J = 6.9 Hz, H-5), 7.19 (1H, d, J = 6.9 Hz, H-6), 7.82 (2H, d, J = 8.6 Hz, H-2' and 6'), 8.31 (2H, d, J = 8.6 Hz, H-3' and 5'); ^13C NMR (75 MHz, CDCl3): 67.2 (C-4), 83.9 (C-2), 118.0 (C-8), 120.8 (C-6), 122.5 (C-5), 123.9 (C-2' and 6'), 125.1 (C-7), 127.7 (C-3' and 5'), 140.8 (C-4a), 145.9 (C-1' and 8a), 148.3 (C-4'); HRMS (EI): m/z calcd for C_{14}H_{12}N_{2}O_{3} (M^+) 256.2568; found 256.2572.

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