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A NOVEL SYNTHESIS OF 2-SUBSTITUTED 2H-IMIDAZO[1,5-*b*]ISOQUINOLINE-1,5-DIONES BY *in situ* DESULFURIZATION

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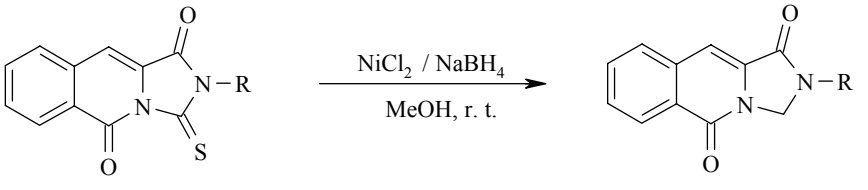
A novel synthesis of 2-substituted 2H-imidazo[1,5-b]isoquinoline-1,5-diones by reductive desulfurization of a variety of 2-substituted 3-thioxo-2H-imidazo[1,5-b]isoquinoline-1,5-diones is reported with nickel boride in dry methanol at ambient temperature.

Keywords: nickel boride, polycyclic isoquinoline, desulfurization.

Polycyclic isoquinoline compounds are well known as anticancer [1] and antitumour [2] agents, and as acetylcholinesterase [3] and human chymase inhibitors [4]. Recently, the synthesis and biological properties of isoquinolines spirofused with carbocycles and heterocycles in position 4 have been reviewed [5]. In view of their importance, we decided to explore the synthesis of a new class of substituted imidazo[1,5-*b*]isoquinoline-1,5-dione derivatives by reductive desulfurization of 2-substituted 3-thioxo-2H-imidazo[1,5-*b*]isoquinoline-1,5-diones with nickel boride. Nickel boride has been used successfully for desulfurization of the C=S group flanked by the NH group of dialkyl thioureas [6], 2(1H)-benzimidazolinethiones [6], 1,3-diaryl-2-thioxo-2H,5H-1,3-dihydropyrimidine-4,6-diones [6], 2-thioxo-4(3H)-quinazolinones [7], and 4-oxo-2-thioxo-5H-pyrano-[2,3-*d*]pyrimidines [8] by our research group besides reductions of other functionalities [9–16].

We report herein a convenient and efficient synthesis of 2-substituted 2H-imidazo[1,5-*b*]isoquinoline-1,5-diones **2a-f** with nickel boride in dry methanol at ambient temperature following a simple workup procedure. Nickel boride was prepared *in situ* from anhydrous nickel chloride and sodium borohydride in dry methanol. Various 2-substituted 3-thioxo-2H-imidazo[1,5-*b*]isoquinoline-1,5-diones **1a**–**f** underwent complete reductive desulfurization with nickel boride using a 1:7:7 or 1:9:9 molar ratio of substrate/$NiCl_2$/$NaBH_4$ in dry methanol and yielded the corresponding 2-substituted 2H-imidazo[1,5-*b*]isoquinoline-1,5-diones **2a**–**f** in nearly quantitative yields. The starting 2-substituted 3-thioxo-2H-imidazo[1,5-*b*]isoquinoline-1,5-diones were prepared by condensation of 2-formyl-benzoic acid with 3-substituted 2-thiohydantoins [17].



1a–f **2a–f**

1,2 **a** R = H, **b** R = Me, **c** R = *i*-Pr, **d** R = Ph, **e** R = CH_2Ph, **f** R = CH_2N O

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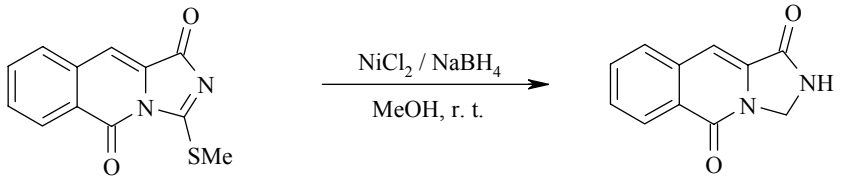
With lower ratios of substrate to nickel chloride to sodium borohydride, the reaction was incomplete. The reaction of 2H-imidazo[1,5-*b*]isoquinoline-1,5-dione proceeded very slowly and was incomplete even after 24 h, when carried out with nickel boride in dry dichloromethane, tetrahydrofuran, dimethylformamide, and dioxane using a 1:9:9 molar ratio. Thus dry methanol was considered as a solvent of choice and was employed in all the reactions. The reaction of compound **1a** with nickel boride using hydrated nickel chloride and ordinary methanol using a 1:9:9 molar ratio also proceeded very slowly and was incomplete even after 24 h. There was no reaction of compound **1a** with anhydrous nickel chloride alone, and the starting material was recovered unchanged. Also, reaction of compound **1a** with sodium borohydride alone yielded a mixture of products along with the starting material. It is obvious therefore that the desulfurization is undoubtedly proceeding due to the involvement of nickel boride formed *in situ*. The reaction of 3-(methylthio)imidazo-[1,5-*b*]isoquinoline-1,5-dione (**1g**) also yielded 2H-imidazo[1,5-*b*]isoquinoline-1,5-dione (**2a**). These results are summarized in Table 1.



1g **2a**

The reagent shows a high selectivity towards desulfurization in these reactions and does not affect the amide carbonyl group, as confirmed by the IR spectra which show the characteristic peaks for the two different carbonyls around 1670 and 1710 cm^{-1} for all the products. Also, the double bond in position 10 remains unaffected, as confirmed by the peak at δ 7.2 due to CH=C in the ^1H NMR spectra for all the products. No hydrogenolysis of the benzyl group was observed in the reaction of compound **1e** with nickel boride in either of the attempted molar ratios. Also colloidal sulfur was not formed in any of these reactions; instead the smell of H_2S was observed during the reactions. Desulfurization is proceeding *via* a transition state in which nickel coordinates with sulfur and weakens the C=S bond, resulting in *in situ* generation of a –CH–SH intermediate.

TABLE 1. Reactions of 2-substituted 3-thioxo-2H-imidazo[1,5-*b*]isoquinoline-1,5-diones with nickel boride in dry methanol at ambient temperature

Substrate (S)	Molar ratio S:$NiCl_2$:$NaBH_4$	Time, h	Product	Yield, %
1a	1:9:9	2	**2a**	75
1b	1:7:7	1.5	**2b**	78
1c	1:7:7	1.5	**2c**	74
1d	1:7:7	1.5	**2d**	76
1e	1:7:7	1	**2e**	78
1f	1:7:7	24	—	—*
1f	1:9:9	2	**2f**	78
1g	1:9:9	3	**2a**	76

* Reaction was incomplete.

This subsequently undergoes hydrogenolysis to yield the desired product. This is also evidenced by the reductive desulfurization of compound **1g**.

We conclude that 2-substituted 2H-imidazo[1,5-*b*]isoquinoline-1,5-diones can be prepared by nickel boride mediated reductive desulfurization of 2-substituted 3-thioxo-2H-imidazo[1,5-*b*]isoquinoline-1,5-diones. The procedure offers several advantages like mild reaction conditions, chemoselectivity, and clean reaction products, which makes it a useful process for the synthesis of novel polycyclic isoquinoline-1,5-dione derivatives.

EXPERIMENTAL

All the melting points were recorded on Tropical Labequip apparatus and are uncor- rected. IR spectra were recorded on Perkin-Elmer FT-IR SPECTRUM-2000 (nujol) and ^{1}H NMR spectra were recorded in DMSO-d_6 on Brucker Avance Spectrospin dpx (300 MHz) with TMS as an internal standard. Mass spectra were recorded on KC-455-TOF mass spectrometer (Micromass, Manchester, U.K.). Analytical data were obtained on Gmbh Vario EL V3 instrument.

Methanol (S. D. Fine) was used after drying by the reported procedure [18]. Nickel(II) chloride hexahydrate (Thomas Baker Chemicals) was dried by heating in a crucible till golden yellow. It was then allowed to cool at room temperature and stored over calcium chloride in a desiccator. Sodium borohydride (E. Merck) was used in all the reactions. 2-Formylbenzoic acid (Sigma-Aldrich) was used as such for the preparation of starting materials. Glycine (S. D. Fine) was used as such. Substituted 2-thiohydantoins [19] and 2-substituted 3-thioxo-2H-imidazo[1,5-*b*]isoquinoline-1,5-diones **1a–f** [17] were prepared by the reported procedures.

A new compound **1c** has also been prepared by the reported procedure as given below.

2-Isopropyl-3-thioxo-2H-imidazo[1,5-*b*]isoquinoline-1,5-dione (**1c**). 2-Formylbenzoic acid (1.415 g, 9.43 mmol), anhydrous sodium acetate (2.631 g, 32.08 mmol), and 3-isopropyl-2-thiohydantoin (1.5 g, 9.43 mmol) were taken in glacial acetic acid in a round-bottomed flask. The reaction mixture was refluxed for 4 h. After cooling to room temperature, the reaction mixture was poured into cold water (~50 ml). The separated crystals were collected by filtration and recrystallized from ethanol to give a pale yellow crystalline solid which was identified to be compound **1c** (1.9249 g, 75%); mp 198°C. IR spectrum, ν_{max}, cm^{-1}: 3077.8 (Ar–H), 2924.5 (C–H methyl), 1743.7, 1694.0 (2×C=O), 1597.6 (C=S), 1460.5 (ring), 1386.0 (C<u>H</u>CH$_3$), 755.7 (*o*-disubstituted ring). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.24–1.26 (6H, d, *J* = 6.1, 2CH$_3$); 4.67-4.84 (1H, m, C<u>H</u>CH$_3$); 7.39 (1H, s, H-10); 7.65 (1H, t, *J* = 7.3, H-8); 7.71 (1H, t, *J* = 7.7, H-7); 7.79 (1H, d, *J* = 6.7, H-9); 8.17 (1H, d, *J* = 6.7, H-6). Mass spectrum, *m/z* (I_{rel}, %): found 272 [M]$^+$(100), calculated 272 [M]$^+$. Found, %: C 61.73; H 4.45; N 10.29; S 11.78. $C_{14}H_{12}N_2O_2S$. Calculated, %: C 61.74; H 4.44; N 10.28; S 11.77.

Desulfurization of 2-Substituted 3-Thioxo-2H-imidazo[1,5-*b*]isoquinoline-1,5-diones 1 (General Method). In a typical procedure, compound **1a** (0.1 g, 0.44 mmol) and dry MeOH (5 ml) were placed into a 100 ml round-bottomed flask. The flask was mounted over a magnetic stirrer and the contents were stirred. Anhydrous $NiCl_2$ (0.505 g, 3.91 mmol) was added to the flask followed by cautious addition of $NaBH_4$ (0.149 g, 3.91 mmol) at room temperature. Addition of $NaBH_4$ is highly exothermic. The contents were stirred vigorously. After complete disappearance of starting material as monitored by TLC (petroleum ether–ethyl acetate, 70:30, v/v), the reaction mixture was filtered off through a Celite pad (~2.5 cm). Nickel boride precipitate was washed with methanol (1×15 ml). The combined filtrate was diluted with water (~50 ml) and extracted with ethyl acetate (3×10 ml). The combined ethyl acetate extract was dried over anhydrous $MgSO_4$, filtered off, and the solvent was removed on a rotary evaporator followed by vacuum drying to afford 2H-imidazo[1,5-*b*]isoquinoline-1,5-dione (**2a**). Yield 0.065 g (75%) as white powder; mp 250°C dec. IR spectrum, ν_{max}, cm^{-1}: 3160.2 (NH), 1722.8,

1672.0 (2×C=O), 1464.4 (ring). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.25 (2H, s, H-3); 7.24 (1H, s, H-10); 7.63 (1H, t, *J* = 7.6, H-8); 7.8 (1H, t, *J* = 7.0, H-7); 7.90 (1H, d, *J* = 8.0, H-9); 8.27 (1H, d, *J* = 8.0, H-6); 9.62 (1H, s, NH). Mass spectrum, *m/z* (I_{rel}, %): found 201 $[M + H]^+$ (100), calculated 201 $[M + H]^+$. Found, %: C 65.98; H 4.03; N 13.97. $C_{11}H_8N_2O_2$. Calculated, %: C 65.99; H 4.02; N 13.99.

2H-Imidazo[1,5-*b*]isoquinoline-1,5-dione (**2a**) from compound **1g**. Yield 0.066 g (76%); mp 252°C (dec.). IR spectrum, ν_{max}, cm^{-1}: 3160.2 (NH), 2924.0 (Ar-H), 2854.5 (CH), 1722.8, 1672.0 (2×C=O), 1464.3 (ring), 766.4 (ring). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.34 (2H, s, H-3); 7.33 (1H, s, H-10); 7.73 (1H, t, *J* = 7.8, H-8); 7.88 (1H, t, *J* = 7.8, H-7); 8.00 (1H, d, *J* = 7.8, H-9); 8.36 (1H, d, *J* = 7.8, H-6); 9.70 (1H, s, NH). Mass spectrum, *m/z* (I_{rel}, %): found 201 $[M + H]^+$ (100), calculated 201 $[M + H]^+$. Found, %: C 65.98; H 4.03; N 13.97. $C_{11}H_8N_2O_2$. Calculated, %: C 65.99; H 4.02; N 13.99.

Compounds 2b–f were obtained in a similar manner.

2-Methyl-2H-imidazo[1,5-*b*]isoquinoline-1,5-dione (**2b**). Yield 0.068 g (78%); mp 210°C. IR spectrum, ν_{max}, cm^{-1}: 2924.3 (CH, Ar), 2854.9 (C–H), 1712.0, 1692.1 (2×C=O), 1464.8 (ring), 766.35 (*o*-disubstituted ring). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.16 (3H, s, CH_3); 5.34 (2H, s, H-3); 7.62 (1H, t, *J* = 7.7, H-8); 7.78 (1H, t, *J* = 7.5, H-7); 7.84 (1H, d, *J* = 7.7, H-9); 7.23 (1H, s, H-10); 8.34 (1H, d, *J* = 7.7, H-6). Mass spectrum, *m/z* (I_{rel}, %): found 215 $[M + H]^+$ (100), calculated 215 $[M + H]^+$. Found, %: C 67.29; H 4.70; N 13.07. $C_{12}H_{10}N_2O_2$. Calculated, %: C 67.28; H 4.70; N 13.07.

2-Isopropyl-2H-imidazo[1,5-*b*]isoquinoline-1,5-dione (**2c**). Yield 0.066 g (74%); mp 240–242°C. IR spectrum, ν_{max}, cm^{-1}: 2924.1 (Ar-H), 2854.5 (CH), 1703.3, 1667.6 (2× C=O), 1462.9 (ring), 1318.0 ($CHCH_3$), 768.3 (*o*-disubstituted ring). ^{1}H NMR spectrum, δ, ppm (*J*, Hz):1.29-1.31 (6H, d, $2CH_3$); 4.37-4.42 (1H, m, $C\underline{H}CH_3$); 5.32 (2H, s, H-3); 7.27 (1H, s, H-10); 7.65 (1H, t, *J* = 7.1, H-8); 7.81 (1H, t, *J* = 7.1, H-7); 7.93 (1H, d, *J* = 7.9, H-9); 8.30 (1H, d, *J* = 7.9, H-6). Mass spectrum, *m/z* (I_{rel}, %): found 243 $[M + H]^+$ (100), calculated 243 $[M + H]^+$. Found, %: C 69.41; H 5.81; N 11.57. $C_{14}H_{14}N_2O_2$. Calculated, %: C 69.40; H 5.82; N 11.56.

2-Phenyl-2H-imidazo[1,5-*b*]isoquinoline-1,5-dione (**2d**). Yield 0.041 g (76%); mp 250°C (dec.). IR spectrum, ν_{max}, cm^{-1}: 2924.5 (Ar-H), 2855.0 (CH), 1711.1, 1669.0 (2×C=O), 1463.0 (ring), 761.7 (*o*-disubstituted ring), 700.1 (monosubstituted ring). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.96 (2H, s, H-3); 7.39 (1H, s, H-10); 7.42–7.61 (5H, m, C_6H_5); 7.76 (1H, t, *J* = 7.8, H-8); 7.85 (1H, t, *J* = 7.8, H-7); 7.94 (1H, d, *J* = 8.6, H-9); 8.09 (1H, d, *J* = 7.6, H-6). Mass spectrum, *m/z* (I_{rel}, %): found 278 $[M + 2H]^+$ (100), calculated 278 $[M + 2H]^+$. Found, %: C 73.91; H 4.38; N 10.14. $C_{17}H_{12}N_2O_2$. Calculated, %: C 73.9; H 4.37; N 10.13.

2-Benzyl-2H-imidazo[1,5-*b*]isoquinoline-1,5-dione (**2e**). Yield 0.043 g (78%); mp 243–245°C (dec.). IR spectrum, ν_{max}, cm^{-1}: 2924.4 (Ar-H), 2854.6 (CH), 1704.0, 1665.7 (2×C=O), 1461.4 (ring), 763.3 (ring), 637.5. ^{1}H NMR spectrum, δ, ppm (*J*, Hz):4.78 (2H, s, CH_2, benzyl); 5.24 (2H, s, H-3); 7.33 (1H, s, H-10); 7.38-7.39 (5H, m, Ar-H); 7.63 (1H, t, *J* = 7.4, H-8); 7.79 (1H, t, *J* = 7.4, H-7); 7.91 (1H, d, *J* = 8.1, H-9); 8.29 (1H, d, *J* = 8.1, H-6). Mass spectrum, *m/z* (I_{rel}, %): found 291 $[M + H]^+$ (100), calculated 291 $[M + H]^+$. Found, %: C 74.45; H 4.87; N 9.67. $C_{18}H_{14}N_2O_2$. Calculated, %: C 74.46; H 4.86; N 9.66.

2-(4-Morpholinomethyl)-2H-imidazo[1,5-*b*]isoquinoline-1,5-dione (**2f**). Yield 0.063 g (78%); mp 280-282°C (dec.). IR spectrum, ν_{max}, cm^{-1}: 2924.6 (Ar-H); 2855.0 (CH), 1716.7, 1671.6 (2×C=O), 1464.3 (ring), 767.0 (C=C ring). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.98–2.52 (4H, m, 2H-2', 2H-6', morpholino); 3.30–3.78 (4H, m, 2H-3', 2H-5', morpholino); 4.63 (2H, s, CH_2, morpholinyl methylene); 5.28 (2H, s, H-3); 7.22 (1H, s, H-10); 7.64 (1H, t, *J* = 7.7, H-8); 7.77 (1H, t, *J* = 7.0, H-7); 7.87 (1H, d, *J* = 7.9, H-9); 8.32 (1H, d, *J* = 8.0, H-6). Mass spectrum, *m/z* (I_{rel}, %): found 300 $[M + H]^+$ (100), calculated 300 $[M + H]^+$. Found, %: C 64.21; H 5.73; N 14.02. $C_{16}H_{17}N_3O_3$. Calculated, %: C 64.20; H 5.72; N 14.03.

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