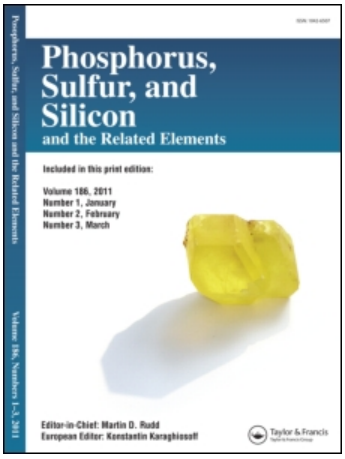

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SYNTHESIS OF BICYCLIC COMPOUNDS DERIVED FROM 1,2,4-BENZOTRIAZINES

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The synthesis of bicyclic compounds derived from benzo[1,2,4]triazines is described.

Keywords: Acetylenic esters; benzotriazines; bicyclic compounds; Pd-catalyzed cyclization

The chemistry of bicyclic compounds derived from 1,2,4-triazines[1] has been studied extensively, reflecting their wide range of pharmaceutical activities.[2] The chemistry of bicyclic compounds derived from 1,2,4-benzotriazines has received less attention.

We have been studying the chemistry of bicyclic compounds derived from 1,2,4-benzotriazine because of their easy synthesis and unique regioselectivity and have found that a number of them could be regioselectively synthesized using 3-thioxo-1,2-dihydro-1,2,4-benzotriazine.[3]

Armed with these experiences, in this article, we wish to report on the synthesis of a series of new bicyclic compounds derived from 1,2,4-benzotriazines. 3-Thioxo-1,2-dihydro-1,2,4-benzotriazines **1**[4] obtained by the fusion of substituted 1,2-diaminobenzene, was reacted with 1,2-dichloroethane in the presence of sodium methoxide to afford the corresponding 2,3-dihydrothiazolo[2,3-c]1,2,4-benzotriazine **2**.

When **1** ($R^1 = Me$, $R^2 = Me$) were reacted with propargyl bromide in the presence of sodium methoxide in methanol the corresponding thiazolo[2,3]1,2,4-benzotriazine **3** was obtained via S-alkylated product.

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Acetylenic esters have been proven to be very versatile reagents for heterocyclization and many diverse products can be prepared from the addition of this compound to nitrogen and sulfur containing heterocycles.[5] Compound (**1**, $R^1 = Me$, $R^2 = Me$) reacted readily with DMAD in methanol to give the adduct which was identified to be substituted 2-(methoxycarboxylmethylene)thiazolo[2,3-c]1,2,4-benzotriazine-3-one **4** by comparison of its spectroscopic data with those of 2-(methoxycarboxymethylene) thiazolo[2,3-b]1,2,4-triazine-3,7-dione.[6]

When (**1**, $R^1 = Me$, $R^2 = Me$) was reacted with 1,3-dibromopropane in the presence of triethylamine in methanol substituted 2,3,4 hexahydro-1,3-thiazino[2,3-c]1,2,4-benzotriazine **5** was obtained. Reaction of (**1**, $R^1 = H$, $R^2 = H$) with 1,3-dichloroacetone in the presence of trimethylamine gave 2,4-tetrahydro-1,3-thiazino[2,3-c]1,2,4-benzitriazin-3-one **6**. On the other hand reaction of (**1**, $R^2 = H$, $R^2 = H$) with epichlorohydrin in the presence of triethylamine afforded 2,4-tetrahydro-3-hydroxy-1,3-thiazino[2,3-c]1,2,4-benzotriazine **7**.

Compound (**1**, $R^1 = H$, $R^2 = H$) was condensed with allyl bromide in the presence of KOH to give the product **8**. To attempt to cyclizing the latter, it was treated with $PdCl_2(PhCN)_2$. Instead of cyclization $S \rightarrow N$ allylic rearrangment was observed to give the corresponding N-allyl compound **9**. This phenomenon has been noticed previously.

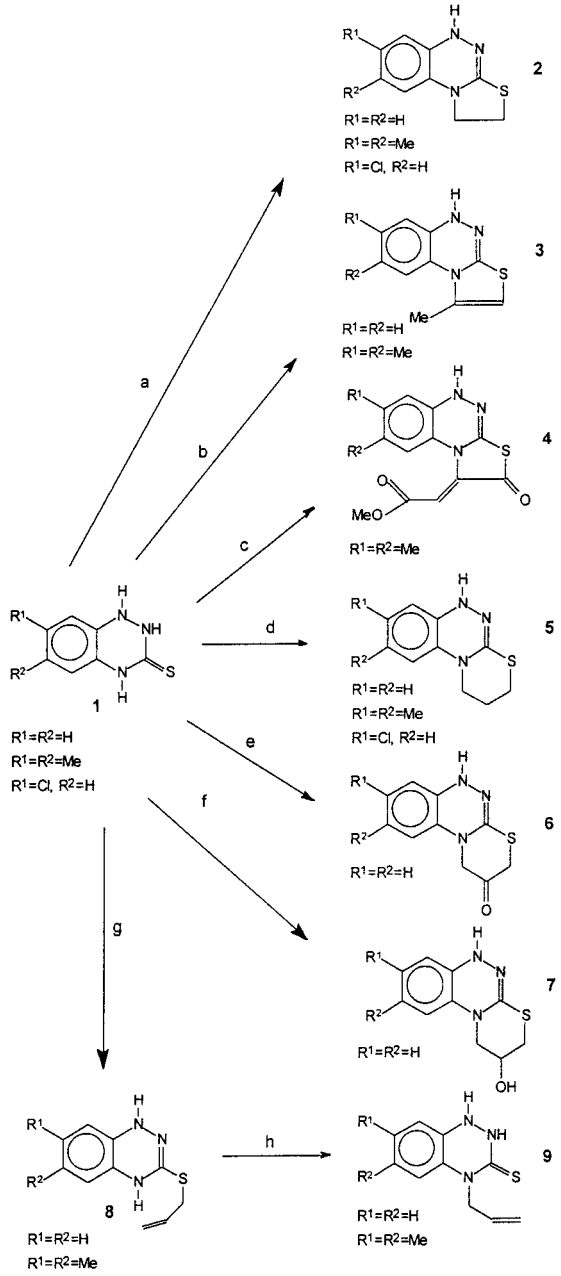
EXPERIMENTAL SECTION

General

Melting points are uncorrected and were recorded on a Kofler Heizbank Richer type 7841 melting point apparatus. IR spectra were obtained on a 4300 Shimadzu spectrometer. ^1H NMR spectra were recorded on a Varian 50A spectrometer using TMs as internal reference. Mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV.

2,3-Dihydrothiazolo[2,3-c]1,2,4-benzotriazine 2

Compound (**1**, $R^1 = R^2 = H$) (0.3 g, 2 mmol) was dissolved in sodium methoxide (0.04 g sodium in 5 mL methanol). To this solution excess 1,2-dichloroethane (0.5 mL) was added. The reaction mixture was refluxed for 4 h. The solution was neutralized by addition of 10% HCl. The solvent was evaporated to dryness and the crude product was directly subjected to column chromatography using $CHCl_3$: MeOH, 97.5: 2.5 as eluent to afford (**2**, $R^1 = R^2 = H$), yield 0.14 g (41%), m.p. 255–56°C, ^1H NMR (δ, ppm, $CDCl_3$): 3.89 (t, 2H, SCH_2), 4.25 (t, 2H, NCH_2), 7.1 (m, 2H, Ar),



SCHEME 1 (a) Dichloroethane, NaOMe/MeOH, (b) Propargyl bromide, NaOMe/MeOH, (c) Dimethyl acethylenedicarboxylate, MeOH, (d) 1,3-Dibromopropane, NEt_3/MeOH, (e) 1,3-Dichloroacetone, NEt_3/MeOH, (f) Epichlorohydrine, NEt_3/MeOH, (g) Allylbromide, KOH (MeOH/MeCN 1:1), (h) $PdCl_2(PhCN)_2$, MeOH/MeCN. 1:1).

7.6 (m, 2H, Ar). ^{13}C-NMR: δ 34.6, 43.8, 108.7, 118.8, 121.8, 121.9, 133.9, 149.6, 158.6, IR $\tilde{v}$ (KBr disc): 3100, 2900, 1600, 1500, 1450, 1400, 720 cm^{-1}; MS: m/z, (M-15, M-NH) 176.

(**2**, $R^1 = R^2 =$ Me), yield 0.32 g (33%), m.p.: 194–95°C, ^{1}H NMR ($CDCl_3$): 2.3 (s, 6H, 2Me), 3.9 (t, 2H, SCH_2), 4.2 (t, 2H, NCH_2), 6.9 (s, 1H, Ar), 7.3 (s, 1H, Ar); IR $\tilde{v}$ (KBr disc): 2900, 1670, 1600, 1490, 840, 810 cm^{-1}; MS: m/z (M-15, M-NH): 204.

(**2**, $R^1 =$ Cl, $R^2 =$ H), yield: 0.13 g (38%), m.p. 114–16°C, ^{1}H NMR ($CDCl_3$): 3.9 (t, 2H, SCH_2), 4.3 (t, 2H, NCH_2), 7.13 (d, 1H, Ar), 7.2 (d, 1H, Ar), 7.6 (s, 1H, Ar); IR (KBr) 3300, 3000, 1600, 1490, 1450, 800 cm^{-1}; MS, m/z (M-15, M-NH): 211.

3,6,7 Trimethylthiazolo[2,3-c]1,2,4-benzotriazine 3

Compound (**1**, $R^1 = R^2 =$ Me) (0.25 g, 13 mmol) was dissolved in sodium methoxide (0.03 g sodium, 30 mL MeOH). To this solution propargyl bromide (0.155 g, 13 mmol) was added. The reaction mixture was refluxed for 5 h. The solution was neutralized by addition of HCl (5%) and evaporated to dryness under reduced pressure. The crude residue was then directly subjected to column chromatography using $CHCl_3$/$PhCH_3$, 99:1 as eluent to afford the title compound. Yield: 0.12 g (39%), m.p. 200–201°C, ^{1}H NMR (δ, ppm, $CDCl_3$) 2.4 (s, 6H, 2Me), 2.7 (s, 3H, Me), 6.3 (s, 1H, CH of thiazole ring), 7.5 (s, 2H, Ar), IR $\tilde{v}$ (KBr disc) 3400, 1600, 1490, 1485, 940 cm^{-1}. M.S. m/z (M-15) (M-NH) 216.

6,7-Dimethyl-3-carbomethoxymethylene Thiazolo[2,3-c]-1,2,4-benzotriazine 4 ($R^1 = R^2 =$ Me)

Compound (**1**, $R^1 = R^2 =$ Me) (0.2 g, 12 mmol) was dissolved in methanol (25 mL). To this solution at room temperature dimethyl acetylenedicaboxylate (0.15 g, 12 mmol) was added. The reaction mixture was stirred at room temperature for 8 h. The orange solid was filtered, washed with water, and crystalized from methanol to afford the title compound. Yield, 0.14 g (42%), m.p. 187–188°C, ^{1}H NMR (δ, ppm, $CDCl_3$) 2.3 (s, 6H, 2Me), 3.9 (s, 3H, OMe), 7.39 (s, 1H, CH), 7.4 (s, 1H, Ar), 7.7 (s, 1H, Ar) IR, $\tilde{v}$ (KBr disc) 1730, 1690 cm^{-1}. M.S. m/z (M^+) 303.

2,3,4-Hexahydro-1,3-thiazino[2,3-c]1,2,4-benzotriazine 5

Compound (**1**, $R^1 = R^2 =$ H) (0.3 g, 2 mmol) was dissolved in acetonitrile (20 mL). To this solution 1,3-dibromopropane (0.4 g, 2 mmol) was added. The reaction mixture was refluxed for 3 h. The solvent was evaporated to dryness and the crude product was directly subjected to column chromatography using $CHCl_3$: MeOH; 97:3 as eluent to afford the product (**5**, $R^1 = R = R^2 =$ H). Yield: 0.18 g (49%), m.p. 139–141°C,

^{1}H NMR (δ ppm, $CDCl_3$) 2.4 (m, 2H, CH_2), 3.2 (t, 2H, SCH_2), 4.1 (t, 2H, NCH_2), 7.2 (m, 2H, Ar), 7.6 (m, 2H, Ar), IR $\tilde{\upsilon}$ (KBr disc) 3000, 1600, 1480, 750 cm^{-1}. M.S. m/z (M-15) 190.

(**5**, $R^1 = R^2 =$ Me), yield: 0.37 g (58%), m.p. 206–208°C, ^{1}H NMR (δ, ppm, $CDCl_3$) 2.3 (s, 6H, 2Me), 2.4 (m, 2H, CH_2), 3.2 (t, 2H, SCH_2), 4.1 (t, 2H, NCH_2), 7.0 (s, 1H, Ar), 7.4 (s, 1h, Ar).

(**5**, $R^1 =$ Cl, $R^2 =$ H), yield: 0.20 g (55%), m.p. 96–98°C, ^{1}H NMR (δ, ppm, $CDCl_3$) 2.5 (m, 2H, CH_2), 3.2 (t, 2H, SCH_2), 4.1 (s, 2H, NCH_2), 7.12–7.21 (m, 3H, Ar).

2,4-Dihydro-1,3-thiazino[2,3-c]1,2,4-benzotriazin-3-one (6, $R^1 = R^2 =$ H)

Compound (**1**, $R^1 = R^2 =$ H) (0.7 g, 4 mmol) was dissolved in methanol (30 mL) and triethylamine (0.5 mL). To this solution 1,3-dichloroacetone (0.51 g, 4 mmol) was added. The reaction mixture was stirred at room temperature for 30 min. The solution was neutralized by the addition of 5% HCl. The solvent was evaporated under reduced pressure and the crude was directly subjected to column chromatography to afford the titile compound. Yield: 0.48 g (52%), m.p. 185–187°C, ^{1}H NMR (δ, ppm, $CDCl_3$), 3.8 (s, 2H, SCH_2), 4.5 (s, 2H, NCH_2), 7.3 (m, 2H, Ar), 7.75 (m, 2H, Ar), IR $\tilde{\upsilon}$ (KBr disc) 3400, 1720 cm^{-1}. M.S. m/z (M-15) 204.

2,4-Dihydro-3-hydroxy-1,3-thiazino[2,3-c]1,2,4-benzotriazine (7, $R^1 = R^2 =$ H)

Compound (**1**, $R^1 = R^2 =$ H) (0.7 g, 7 mmol) was dissolved in methanol (30 mL) and triethylamine (2 mL). To this solution excess of epichlorohydrine (3 mL) was added. The reaction mixture was refluxed for 14 h. The solution was neutralized by the addition of 5% HCl. The solvent was evaporated under reduced pressure and the crude residue was directly subjected to column chromatography using $CHCl_3$:MeOH; 97:3 as eluent to afford the title compound. Yield: 0.5 g (53%), m.p. 140–141°C, ^{1}H NMR (δ ppm, $CDCl_3$), 3.02–3.18 (dd, 2H, CH_2), 3.88–4.04 (dd, 2H, CH_2), 4.27 (m, 1H, CH), 5.55 (d, 1H, OH), 6.9 (m, 2H, Ar), 7.25 (m, 2H, Ar), 10.4 (s, 1H, NH), 13°C NMR (δ, ppm, $CDCl_3$) 31.3, 48.1, 108.4, 108.5, 116.9, 120.3, 120.7, 121.6. IR $\tilde{\upsilon}$ (KBr disc) 3400, 3100, 600, 490 cm^{-1}. M.S. m/z (M-15) 206.

3-Allylmercapto-1,2,4-benzotriazine 8

Compound (**1**, $R^1 = R^2 =$ H) (0.5 g, 3 mmol) was dissolved in ethanol (25 mL) and KOH (0.17 g, 3 mmol). To this solution allyl bromide (0.36 g, 3 mmol) was added dropwise. The reaction mixture was stirred at 30°C for 4 h. The solution was neutralized by the addition of 10% HCl. The solvent was evaporated under reduced pressure and the crude residue

was directly subjected to column chromatography using $CHCl_3$:MeOH; 95:5. Yield: 0.42 g (68%), m.p. 163–165°C, ^{1}H NMR (δ, ppm, $CDCl_3$), 3.95 (t, 2H, SCH_2), 5.3 (m, 2H, $=CH_2$), 6.05 (m, 1H, =CH), 7.25 (m, 4H, Ar), IR $\tilde{v}$ (KBr disc) 3100, 1640 cm^{-1}. M.S. m/z M-15) 189.

S → N Allylic Rearrangement of 8 to 9

Compound (**8**, $R^1 = R^2 = H$) (025 g, 1 mmol) was dissolved in acetonitrile (5 mL) and methanol. To this solution $PdCl_2(PhCN)_2$ was added and the reaction mixture was refluxed for 8 h. The solvent was evaporated under reduced pressure and the crude product was directly subjected to column chromatography using $CHCl_3$ as eluent to afford N-allyl derivative (**9**, $R^1 = R^2 = H$). Yield: 0.04 g (16%), m.p. 243–244°C, ^{1}H NMR (δ, ppm, $CDCl_3$), 4.9 (d, 2H, NCH_2), 5.3 (m, 2H, $C{=}CH_2$), 6.0 (m, 1H, =CH–), 7.2 (m, 4H, Ar), IR $\tilde{v}$ (KBr disc) 3200, 1640 cm^{-1}. M.S. m/z (M-15) 189.

REFERENCES

[1] a) M. Mizutani, Y. Sanomitsu, Y. Tamaru, and Z. I. Yashida, *Tetrahedron*, 305 (1986); b) M. M. Heravi and M. Bakavoli, *J. Chem. Res.*, **11,** 480 (1995); c) M. M. Heravi, M. Shafaie, M. Bakavoli, M. M. Sadeghi, and A. R. Khoshdast, *Indian J. Chem.*, **B53,** 1260 (1996); d) M. M. Heravi, K. Aghapoor, and M. A. Nooshabadi, *Synth. Commun.*, **28,** 233 (1998); e) M. M. Heravi, M. M. Mojtahedi, and M. Bolourtchian, *Indian J. Chem.*, **37,** 590 (1998).

[2] a) J. Mohan, *Indian J. Chem.*, **29,** 645 (1990); b) D. L. Trepanier, E. P. Krieger, U.S. Pat. 3,641,019, *CA* **76,** 127024K (1972); c) L. C. March, G. S. Bajwa, K. Wasti, and M. M. Jollie, *J. Medicinal Chem.*, **19,** 845 (1976); d) R. Rohme and Z. E. Hans, *Greifs Med. Reihe*, **37,** 122 (1989); *CA* **112,** 16053 m, (1990).

[3] a) M. M. Heravi, M. S. Alameh, and M. Bakavoli, *J. Sci. I. R. Iran*, **8,** 239 (1997); *CA* **129,** 260362y (1998); b) M. M. Heravi, K. Aghapoor, M. A. Nooshabadi, and M. M. Mojtahedi, *Monatsh. Chem.*, **128,** 1143 (1997); c) M. M. Heravi, Z. Tavalaie, and O. Sabzevari, *Indian J. Chem.*, **37,** 589 (1998); d) M. M. Heravi, K. Aghapoor, M. M. Mojtahedi, and H. A. Oskooie, *J. Sci. I. R. Iran* (in press).

[4] S. Bala, M. L. Sachdeva, R. N. Handa, and H. K. Pujari, *Heterocycles*, **4,** 149 (1980).

[5] a) R. M. Acheson and N. F. Elmer, *Adv. Heterocycl. Chem.*, **23,** 263 (1978); b) F. Barka and F. B. Batemero, *Synthesis*, **5,** 55 (1994); c) R. M. Acheson and J. D. Wallis, *J. Chem. Soc.*, 415 (1981); d) P. J. Bhayar, K. C. Lekhok, and J. S. Sandhu, *Tetrahedron Lett.*, **49,** 1793 (1999).

[6] L. Gianvala, G. Giammina, and S. Palazzo, *J. Chem. Soc., Perkin Trans. I*, 2707 (1984).

[7] a) M. Mizutani, Y. Sanemitsu, Y. Tamaru, and Z. Yashida, *J. Org. Chem.*, **48,** 4585 (1983); b) M. Mizutani, Y. Sanemitsu, Y. Tamaru, and Z. Yashida, *Tetrahedron*, 5289 (1984).