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MICHAEL ADDITIONS ON 2H-1,4-BENZOTHIAZIN-3-ONES

M. S Chande and V. Suryanarayan

Michael addition on 2H-1,4-benzothiazin-3-ones is studied in this communication. An approach towards the regioselective synthesis of Michael adducts is shown.

Keywords: Michael addition, 2H-1,4-benzothiazin-3-ones, regioselectivity.

Michael addition [1-3] is a very well-known reaction which involves the addition of an active methylene group across an α,β-unsaturated compound. This reaction has found extensive use in the synthesis of carbocyclic and heterocyclic ring systems.

Literature survey indicated that Michael additions of compounds having active methylene groups often lead to a mono adduct [4, 5] or a mixture of mono and diadducts [6, 7], especially when the β-carbon of the acceptor is unsubstituted. The formation of the adduct depends on the type of base catalyst and the acceptors used in the reaction.

Recently we explored the scope of Michael additions on various heterocyclic ring systems containing active methylene/methine groups for the synthesis of spiro compounds. The present paper is an account of our studies on the Michael addition of 2H-1,4-benzothiazin-3-one **1** [8] with acceptors, viz. methyl acrylate **2** and acrylonitrile **5**.

It was expected that under ideal conditions methyl acrylate **2** would add at position 2 of **1**, yielding either a mono-adduct or mixtures of mono- and di-adducts. When the reaction was carried out in the presence of sodamide in DMF at ambient temperature, a yellow colored semisolid was obtained. It readily decolorized the pink coloration due to phenolphthalein in a dilute alkali. This confirmed the presence of an ester linkage. Hence, it was hydrolyzed to its carboxylic acid derivative by refluxing in alcoholic potassium hydroxide. The spectral data indicated that it was the corresponding N-alkylated acid derivative **3**. The reaction was highly regioselective without the formation of any kind of side products. The N-carboxyethyl derivative **3** was further cyclized in PPA at 140°C to afford compound **4** in near quantitative yields (Scheme 1).

Based on this observation it was thought that similar results would be obtained with a different β-unsubstituted Michael acceptor. Hence, 2H-1,4-benzothiazin-3-one **1** was reacted with acrylonitrile (**5**) without any alteration in the conditions. Interestingly, two different products were obtained from the reaction. The corresponding N-alkylated nitrile derivative **6** was obtained in 28% yield. Its structure was confirmed by spectral studies and was further supported by its independent hydrolysis in acid, which furnished the N-alkylated acid derivative **3**. The other compound obtained in 64% yield was identified as Michael bisadduct **7**, with the addition taking place at position 2 of the benzothiazine ring (Scheme 1).

Department of Chemistry, The Institute of Science, 15, M Cama Road, Mumbai 400 032, India; e-mail: chandems@vsnl.com, kgsurya@vsnl.com. Published in Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1250-1254, August, 2003. Original article submitted November 26, 2001.

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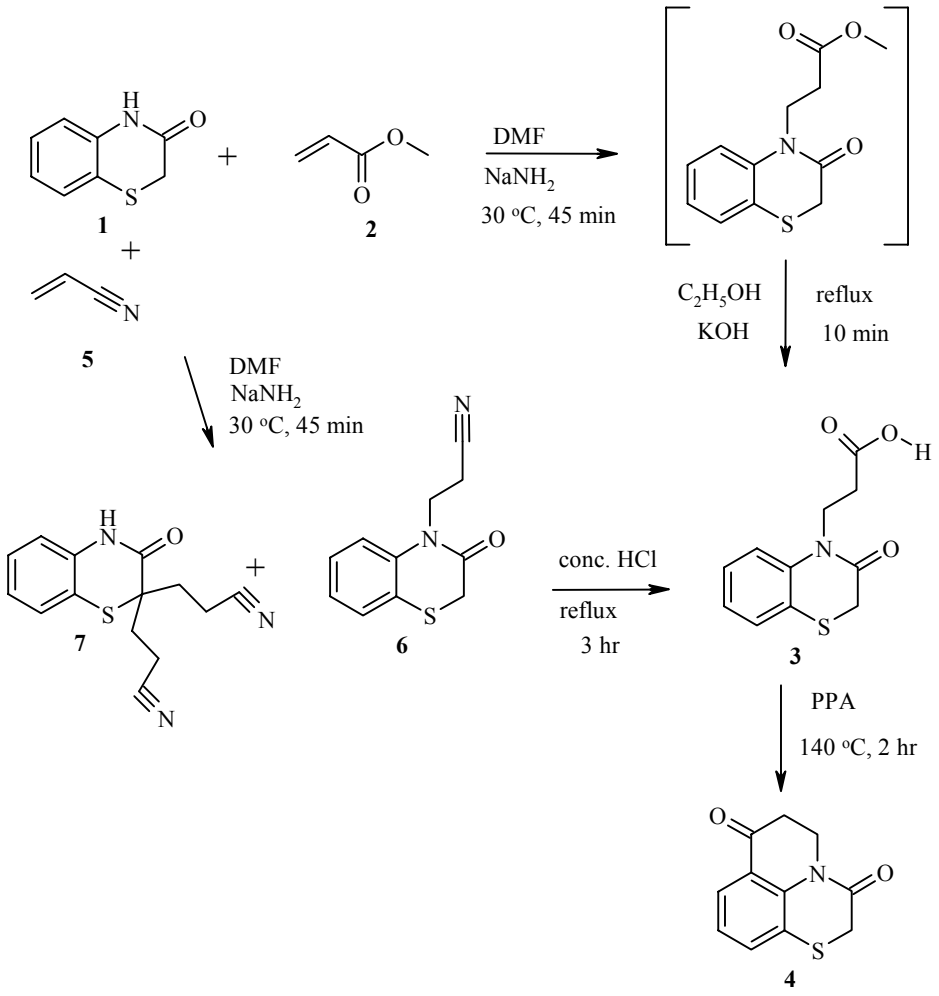
Scheme 1

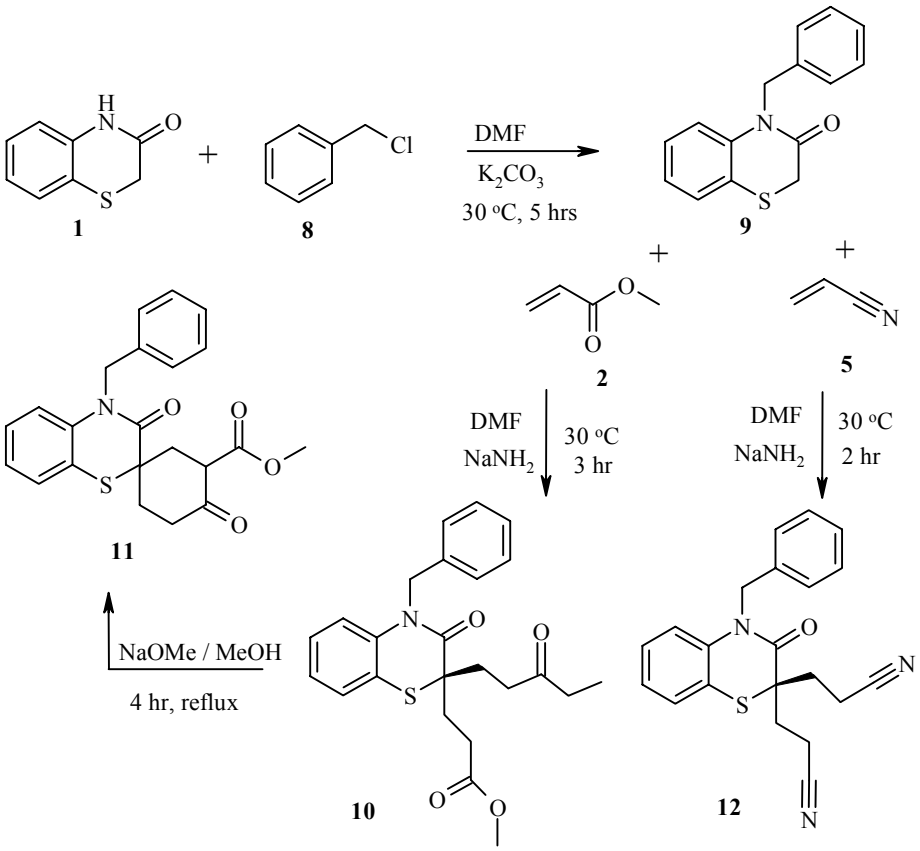


A conclusion that could be drawn based on the above reactions is that the formation of the Michael adduct depends much more on the acceptors used in the reaction than on the donors under similar reaction conditions.

Regioselective addition of Michael acceptors at position 2 of compound **1** could be achieved by blocking the amido group. It would also determine whether a mono-, di-, or mixtures of Michael adduct is obtained from the reaction. Hence, the amido proton was blocked with a benzyl group by reacting **1** with benzyl chloride **8** in DMF/K_2CO_3. The Michael addition of N-benzyl derivative **9** with equimolar proportions of methyl acrylate **2** afforded a diadduct **10** and unreacted **9** in the presence of sodamide in DMF. When the reaction was repeated with 2 moles of methyl acrylate **2**, the reaction went to completion and **10** was obtained in an extremely pure form. The formation of the mono adduct was not observed in the reaction The diadduct was obtained as a semisolid. On refluxing the diadduct with sodium ethoxide in absolute ethanol, it underwent Dieckmann condensation [8] and furnished the spirocyclohexanone derivative **11**. Similarly, **9** with acrylonitrile **5** afforded only the diadduct in excellent yields (Scheme 2).

Thus, Michael addition on 2H-1,4-benzothiazin-3-one **1** afforded selectively only the diadduct in the presence of sodamide in DMF when the amido group is blocked. These reactions have also been extended to 2H-1,4-benzoxazin-3-one [10], which gave identical results as 1,4-benzothiazin-3-one under identical reaction

Scheme 2



conditions. It seems that sodamide in DMF is a special combination which leads to the formation of a diadduct only. We have used this combination successfully on other heterocyclic systems containing active methylene group which are currently under communication.

EXPERIMENTAL

The elemental analysis of all the reported compounds had values in the range of ±0.05% of the desired calculated values.

N-(Carboxyethyl)-2H-benzothiazine-3-one (3). To sodamide (0.01 mol, 0.4 g) in DMF (15 ml) was added 2H-1,4-benzothiazin-3-one **1** at room temperature (28-30°C). This was followed by the addition of methyl acrylate **2** (0.01 mol, 0.86 g). The reaction mixture was then stirred for 45 min at the same temperature. It was then poured onto crushed ice containing a few drops of conc. HCl when a pale yellow colored semisolid separated out. It was then extracted with diethyl ether (50 ml) twice. The organic layer was then dried over anhydrous sodium sulfate. Removal of ether afforded the ester as a pale yellow colored semisolid (76%). This semisolid was then refluxed in alcoholic KOH (0.01 mol, 0.56 g in 25 ml of ethanol) for 10 min. The reaction mixture was concentrated and poured onto crushed ice containing a few drops of conc. HCl. Compound **3** separated as a colorless amorphous powder in a pure state. It was filtered off and dried. Yield 83%; mp 158°C. IR spectrum, ν, cm^{-1}: 3017 (br, OH and C–H str. merged), 1710 (C=O; carboxylic acid), 1667 (C=O; benzothiazine). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.77 (t, 2H, *J* = 8, CH_2COOH); 3.40 (s, 2H, CH_2 of

benzothiazine ring); 4.31 (t, 2H, J = 8, NCH_2); 7.03-7.39 (2t and 2d, 4H, aromatic protons). Interestingly, the peak due to the OH of carboxylic acid was not observed. ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 31.48 (CH_2 attached to carboxylic group); 32.10 (CH_2 of benzothiazine ring); 40.79 (NCH_2); 117.53, 123.85, 124.27, 127.41, 128.65, 138.88 (6 aromatic carbons); 165.52 (C=O; benzothiazine ring); 176.19 (C=O, carboxylic acid). Found, %: C 55.64; H 4.64; N 5.88; S 13.48. $C_{11}H_{11}NO_3S$. Calculated, %: C 55.68; H 4.67; N 5.90; S 13.51.

3,7-Dioxo-2H,5H,6H-(3',2':5,6'-benz)pyrido[2',1'-*c*]thiazine (4). A mixture of *o*-phosphoric acid (12.5 ml) and phosphorus pentoxide (25 g) was heated at 110°C for half an hour. Compound **3** (0.01 mol) was added and the reaction mixture was heated at 140°C for 2 h more. It was then cooled and poured onto crushed ice. Dione **4** which separated out was filtered off and purified by washing well with dilute solution of sodium bicarbonate to remove the unreacted carboxylic acid derivative. Yield 82%; mp 172°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 2.81 (t, 2H, J = 6.5, CH_2CO); 3.51 (s, 2H, CH_2 of benzothiazine ring); 4.38 (t, 2H, J = 6.5, N–CH_2); 7.11 (t, 1H, Ar–H); 7.55 (t, 1H, Ar–H); 7.92 (d, 1H, Ar–H). MS, *m/z*: 219 $[M]^+$, 190, 177, 162, 149, 135, 121, 108, 95, 81, 69, 63, 45, 31. Found, %: C 60.22; H 4.08; N 6.34; S 14.60. $C_{11}H_9NO_2S$. Calculated, %: C 60.26; H 4.10; N 6.39; S 14.62.

N-Cyanoethyl-1,4-benzothiazin-3-one (6) and 2-di(cyanoethyl)-1,4-benzothiazin-3-one (7). Compound **1** (0.01 mol, 1.65 g) was added to sodamide (0.01 mol, 0.4 g) in DMF (15 ml). This was followed by the addition of acrylonitrile (**5**) (0.01 mol, 0.53 g). The reaction mixture was stirred at room temperature (28-30°C) for 45 min. On pouring onto crushed ice an off-white compound separated which was filtered off and dried. This compound was washed thoroughly with diethyl ether. The insoluble product was identified as 2-di(cyanoethyl)-1,4-benzothiazin-3-one **7**. Removal of ether afforded N-(cyanoethyl)-1,4-benzothiazin-3-one **6**.

Compound 6. Yield 28%; mp 120°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 2.80 (t, 2H, J = 10, CH_2CN); 3.41 (s, 2H, CH_2 of benzothiazine); 4.28 (t, 2H, J = 10, NCH_2); 7.05-7.46 (m, 4H, Ar–H). Found, %: C 60.52; H 4.60; N 12.83; S 14.66. $C_{11}H_{10}N_2OS$. Calculated, %: C 60.53; H 4.62; N 12.83; S 14.69.

Compound 7. Yield 64%; mp >250°C (shrinks at 180°C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.04-2.63 (m, 8H, 4 × CH_2); 6.85-7.34 (m, 4H, Ar–H); 8.01 (s, 1H, NHCO; D_2O exchangeable). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 12.69 (2 × CH_2CN); 30.54 (2 × CH_2); 49.03 (tetrahedral carbon); 116.93 (2 × C≡N); 117.24, 118.47, 125.98, 128.12, 128,47, 136.45 (6 aromatic carbons); 167.84 (C=O). Found, %: C 61.93; H 4.82; N 15.45; S 11.81. $C_{14}H_{13}N_3OS$. Calculated, %: C 61.97; H 4.83; N 15.49; S 11.82.

N-Benzyl-1,4-benzothiazin-3-one (9). Benzylchloride (0.012 mol, 1.26 g) was added to a mixture of **1** (0.01 mol) and potassium carbonate (0.01 mol, 1.38 g) in DMF (15 ml). The reaction mixture was stirred at room temperature (28-30°C) for 5 h. The contents were poured onto crushed ice containing a few drops of conc. HCl. The product which separated was filtered, dried, and recrystallized from 50% ethanol. Yield 90%; mp 110°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.54 (s, 2H, CH_2 of benzothiazine ring); 5.24 (s, 2H, N–CH_2–Ph); 6.84-7.31 (m, 9H, Ar–H). Found, %: C 70.55; H 5.08; N 5.47; S 12.53. $C_{15}H_{13}NOS$. Calculated, %: C 70.58; H 5.09; N 5.49; S 12.54.

N-Benzyl-2-(dicarbomethoxyethyl)-1,4-benzothiazin-3-one (10). N-Benzyl-1,4-benzothiazin-3-one **(9)** (0.01 mol) was stirred in DMF in the presence of sodamide (0.02 mol, 0.8 g) at room temperature (28-30°C). Methyl acrylate (**2**) (0.02 mol, 1.72 g) was added dropwise to this mixture. The reaction mixture was stirred for 3 h more. It was then poured onto crushed ice containing a few drops of conc. HCl. A yellow colored semisolid separated out which was extracted with diethyl ether (25 ml, 2 times). The ethereal layer was dried over anhydrous sodium sulfate. Removal of ether under reduced pressure afforded a pale yellow semisolid which was used directly for further reactions. Yield 82%. IR spectrum ($CHCl_3$), ν, cm^{-1}: 3066, 3017 (C–H str.), 1728 (C=O, ester), 1667 (C=O, benzothiazine). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.69-3.39 (m, 8H, 4 × CH_2); 3.55 (s, 6H, 2 × OCH_3); 5.24 (s, 2H, NCH_2); 6.96-7.35 (m, 9H, Ar–H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 31.55 (2 × $\underline{C}H_2$–CH_2); 36.72 (2 × $\underline{C}H_2$–CO); 40.92 (N–CH_2); 48.50 (tetrahedral carbon); 51.89 (2 × OCH_3); 117.60-136.61 (12 aromatic carbons); 163.00 (C=O, benzothiazine); 171.69, 174.87 (2 × C=O, ester carbonyl).

4-Aza-1-thia-2,3-benz-5,9-dioxo-8-carbomethoxy-4-phenylspiro[5,5]undecane (11). Compound **10** (0.01 mol) was refluxed in freshly prepared sodium methoxide (0.01 mol) in methanol (30 ml) for 4 h. The excess methanol was removed under reduced pressure. The residue was poured onto crushed ice containing a few drops of conc. HCl. Compound **11** separated as a yellow solid which was filtered off, washed well with water and hexane, and recrystallized from 50% methanol. Yield 78%; mp 92°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.92-2.25 (br. m, 6H, 3 × CH_2); 3.54 (s, 3H, OCH_3); 4.31-4.35 (m, 1H, CH); 5.24 (s, 2H, CH_2); 6.98-7.32 (m, 9H, Ar–H). Found, %: C 67.10; H 6.12; N 3.37; S 7.78. $C_{22}H_{21}NO_4S$. Calculated, %: C 66.81; H 5.35; N 3.55; S 8.11.

N-Benzyl-2-(dicyanoethyl)-1,4-benzothiazin-3-one (12). Compound **9** (0.01 mol) was stirred with sodamide (0.02 mol, 0.8 g) in DMF (15 ml) at room temperature (28-30°C). Acrylonitrile **5** (0.02 mol) was added and the reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was then poured onto crushed ice containing a few drops of HCl. The product **12** separated as a brown colored amorphous solid in its pure form. Yield 91%; mp >250°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.05-2.68 (m, 8H, 4 × CH_2); 5.24 (s, 2H, NCH_2); 6.92-7.42 (m, 9H, Ar–H). Found, %: C 69.77; H 5.27; N 11.61; S 8.83. $C_{21}H_{19}N_3OS$. Calculated, %: C 69.78; H 5.30; N 11.62; S 8.87.

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