CHEMO- AND REGIOSELECTIVE NUCLEOPHILIC REACTIONS OF (BROMOMETHYL)METHYLMALEIC ANHYDRIDE: SYNTHESIS OF α-QUINOXALINYL- AND α-BENZOTHIAZINYLACRYLIC ACIDS

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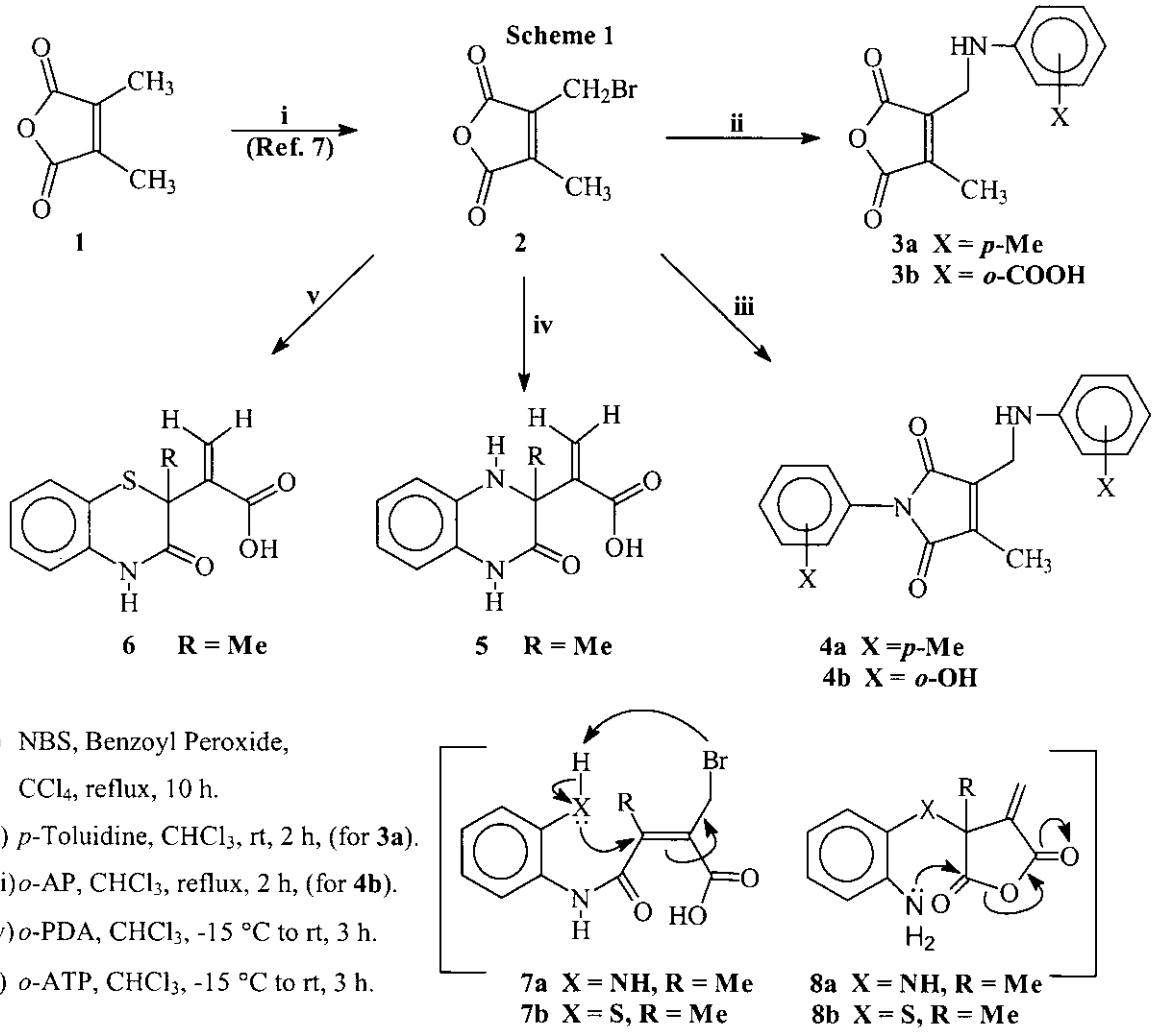
Abstract – The (bromomethyl)methylmaleic anhydride (**2**) on reaction with *o*-phenylenediamine and *o*-aminothiophenol underwent chemo- and regioselective ring opening followed by intramolecular Michael type addition and 1,4-elimination reactions to furnish kinetically controlled products α-quinoxalinylacrylic acid (**5**) and α-benzothiazinylacrylic acid (**6**) in good yields.

The nucleophilic reactions of symmetrical and unsymmetrical cyclic anhydrides have been fully investigated[1-4] as a elegant strategy for the synthesis of several structurally interesting and biologically important heterocyclic systems. It has been well established that the dimethylmaleic anhydride (**1**) on reaction with primary amine yields the corresponding imide[2] and on reaction with *o*-phenylenediamine (*o*-PDA), first the corresponding imide and then pyrrolobenzimidazole *via* intramolecular condensation,[5] while on reaction with *o*-aminothiophenol (*o*-ATP) yields benzothiazinylpropionic acid *via* ring opening and intramolecular Michael addition reaction.[6] Recently we prepared[7] the (bromomethyl)methylmaleic anhydride (**2**) by NBS bromination of dimethylmaleic anhydride (**1**) for the synthesis of chaetomellic acid A[7] and fulgenic acid.[8] In an attempt to study the nucleophilic reactions of the multifunctional unsymmetrical anhydride (**2**) with suitably *o*-substituted aniline derivatives for designing the heterocyclic skeletons, we herein report the synthesis of α-quinoxalinylacrylic acid (**5**) and α-benzothiazinylacrylic acid (**6**).

The bromo anhydride (**2**) underwent a highly chemoselective reaction with two equivalents of *p*-toluidine at room temperature to yield exclusively the (*p*-toluidinylmethyl)methylmaleic anhydride (**3a**). The anhydride (**3a**) on further reaction with *p*-toluidine in $CHCl_3$ furnished the imide (**4a**), which was also obtained by the direct reaction of **2** with excess of *p*-toluidine at room temperature in $CHCl_3$. At this stage we planned to study the reaction of *o*-aminophenol (*o*-AP), *o*-PDA and *o*-ATP with **2**, aiming for oxazepine, diazepine and thiazepine derivatives *via* nucleophilic displacement of allylic bromo atom

Scheme 1



i) NBS, Benzoyl Peroxide, CCl_4, reflux, 10 h.
ii) *p*-Toluidine, $CHCl_3$, rt, 2 h, (for **3a**).
iii) *o*-AP, $CHCl_3$, reflux, 2 h, (for **4b**).
iv) *o*-PDA, $CHCl_3$, -15 °C to rt, 3 h.
v) *o*-ATP, $CHCl_3$, -15 °C to rt, 3 h.

followed by intramolecular ring opening. In contrast to our expectation, the bromo anhydride (**2**) on reaction with *o*-PDA and *o*-ATP at -15 °C underwent highly chemo- and regioselective ring opening at unhindered carbonyl to form the unisolable intermediate acids (**7**), followed by intramolecular Michael type addition and 1,4-elimination (- HBr) reactions[9] to yield exclusively the corresponding kinetically controlled products α-quinoxalinylacrylic acid (**5**) and α-benzothiazinylacrylic acid (**6**) respectively, in very good yields. At room temperature these reactions lose their selectivities and furnish the complex mixture of products. The possibility of formation of intermediate (**8**) has been ruled out, as anhydride (**2**) did not react with thiophenol under identical set of reaction conditions. Anthranilic acid and *o*-AP on reaction with **2**, furnished respectively the thermodynamically controlled products (**3b**) and (**4b**) due to the weaker tendency of a -COOH and phenolic -OH towards Michael addition, while in our hands the reactions of ethanolamine, ethylenediamine and thioethanolamine with **2** always ended up with formation of polymeric gums.

In summary, the (bromomethyl)methylmaleic anhydride (**2**) reacts with *o*-PDA and *o*-ATP in a remarkably chemo- and regioselective fashion to yield the corresponding kinetically controlled products α-quinoxalinylacrylic acid (**5**) and α-benzothiazinylacrylic acid (**6**) respectively, in very good yields.

EXPERIMENTAL

(*p*-Toluidinylmethyl)methylmaleic anhydride (3a). To a stirred solution of *p*-toluidine (470 mg, 4.4 mmol) in chloroform (10 mL) was added a solution of anhydride (**2**) (410 mg, 2 mmol) in chloroform (10 mL) and reaction mixture was stirred at rt for 2 h. The reaction mixture was filtered, washed with chloroform (10 mL), and chloroform layer was concentrated in *vacuo*. The obtained residue on column chromatographic purification (elution with 20% ethyl acetate in petroleum ether) gave pure product (**3a**) (320 mg, 69.0%): mp 108-110 °C (ethyl acetate:petroleum ether = 1:9); IR (Nujol): ν = 3387, 1832, 1754, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ = 2.15 (s, 3H), 2.20 (s, 3H), 2.90-3.35 (br s, 1H), 4.22 (s, 2H), 6.55 (d, J = 8 Hz, 2H), 7.02 (d, J = 8 Hz, 2H); MS (*m/z*): 231, 202, 188, 158, 144, 120, 106, 91, 77, 65; Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.66; N, 6.06. Found: C, 67.31; H, 5.73; N, 5.82.

Similarly the reaction of anhydride (**2**) (410 mg, 2 mmol) with anthranilic acid (548 mg, 4 mmol) in Et_2O (20 mL) furnished pure (**3b**) (330 mg, 63%): mp 181-183 °C (ethyl acetate:petroleum ether = 1:2); IR (Nujol): ν = 3382, 1857, 1765, 1656 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz) δ = 1.90 (s, 3H), 4.18 (d, J = 6 Hz, 2H,), 6.38 (dd, J = 8 and 2 Hz, 1H), 6.50 (dt, J = 8 and 2 Hz, 1H), 7.17 (dt, J = 8 and 2 Hz,1H), 7.78 (dd, J = 8 and 2 Hz, 1H), 8.15 (br t, J = 6 Hz, 1H); MS (*m/z*): 261, 243, 214, 197, 170, 142, 132, 116, 92, 78, 66, 53; Anal. Calcd for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.25; N, 5.36. Found: C, 59.44; H, 4.39; N, 5.09.

In a similar way the reaction of anhydride (**2**) (410 mg, 2 mmol) with excess of *p*-toluidine (642 mg, 6 mmol) and the anhydride (**3a**) (462 mg, 2 mmol) with *p*-toluidine (429 mg, 4 mmol) in chloroform (20 mL) at rt for 3 h furnished the imide (**4a**) (190 mg, 59%): mp 115-117 °C (ethyl acetate:petroleum ether = 1:9); IR (Nujol): ν = 3386, 1769, 1704, 1619 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ = 1.40-1.75 (br s, 1H), 2.15 (s, 3H), 2.25 (s, 3H), 2.38 (s, 3H), 4.23 (s, 2H), 6.60 (d, J = 9 Hz, 2H), 7.05 (d, J = 9 Hz, 2H), 7.18 (d, J = 6 Hz, 2H), 7.25 (d, J = 6 Hz, 2H); MS (*m/z*): 320, 277, 214, 186, 158, 144, 120, 106, 91, 77, 65; Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.69; H, 6.43; N, 8.89.

***o*-Hydroxy-*N*-phenyl-3-(*o*-hydroxyanilinomethyl)-4-methylmaleimide (4b).** To stirred solution of *o*-aminophenol (764 mg, 7 mmol) in chloroform (25 mL) was added slowly the solution of **2** (410 mg, 2 mmol) in chloroform (10 mL) and the reaction was refluxed for 7 h. The reaction mixture was filtered, and the residue was washed with chloroform and organic layer was concentrated in *vacuo* to furnish (**4b**) (325 mg, 50%): mp 155-157 °C (chloroform) ; IR (Nujol): ν = 3380, 3169, 1796, 1691, 1620, 1605 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz) δ = 2.05 (s, 3H), 4.17 (s, 2H), 6.50-7.35 (m, 8H); MS (*m/z*):

324, 306, 281, 264, 231, 215, 199, 188, 170, 160, 144, 120, 108, 81, 65, 52; Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.51; H, 5.13; N, 8.42.

α-(2-Methyl-2,3-dihydro-3-oxoquinoxalin-2-yl)acrylic acid (5). To a stirred solution of *o*-phenylenediamine (432 mg, 4 mmol) in chloroform (10 mL) at -15 °C was added a solution of **2** (410 mg, 2 mmol) in chloroform (10 mL) and the reaction mixture was allowed to reach rt for 3 h. The reaction mixture was filtered, the residue was washed with chloroform and the organic layer was concentrated in *vacuo*. Silica gel column chromatographic purification (elution with petroleum ether:ethyl acetate:methanol = 12:7:1) of residue furnished pure (**5a**) (400 mg, 86%): mp 233-235 °C ($CHCl_3$); IR (Nujol): ν = 3352, 3190, 1711, 1662, 1613 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz) δ = 1.65 (s, 3H), 5.10-5.25 (br s, 1H), 5.55 (s, 1H), 6.10 (s, 1H), 6.50-6.75 (m, 4H), 9.55-9.75 (s, 1H); ^{13}C NMR ($CDCl_3$+ DMSO-d_6, 50 MHz) δ = 22.5, 59.0, 112.8, 113.7, 117.6, 121.7, 124.1, 125.0, 132.0, 139.9, 166.0, 166.7; MS (*m/z*): 232, 217, 199, 171, 161, 143, 133, 118, 105, 92, 77, 64; Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.00; H, 5.39; N, 11.83.

α-(2-Methyl-2,3-dihydro-3-oxo-1,4-benzothiazin-2-yl)acrylic acid (6) was prepared similarly using *o*-ATP, 90% yield: mp 195-197 °C (ethyl acetate:petroleum ether = 2:8); IR (Nujol): ν = 3162, 1684, 1635, 1563 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz) δ = 1.70 (s, 3H), 5.57 (s, 1H), 6.13 (s, 1H), 6.80-7.15 (m, 4H), 10.20 (s, 1H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ = 22.5, 48.0, 116.5, 119.1, 122.8, 126.2, 126.5, 126.8, 136.2, 139.1, 166.3, 167.9; MS (*m/z*): 249, 231, 203, 175, 160, 151, 123, 109, 96, 80, 69, 53; Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.81; H, 4.49; N, 5.62 Found: C, 57.63; H, 4.73; N, 5.51.

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