A SIMPLE AND EFFICIENT SYNTHESIS OF 4-MERCAPTO-6-PHENYLPYRIDAZIN-3(2H)-ONES

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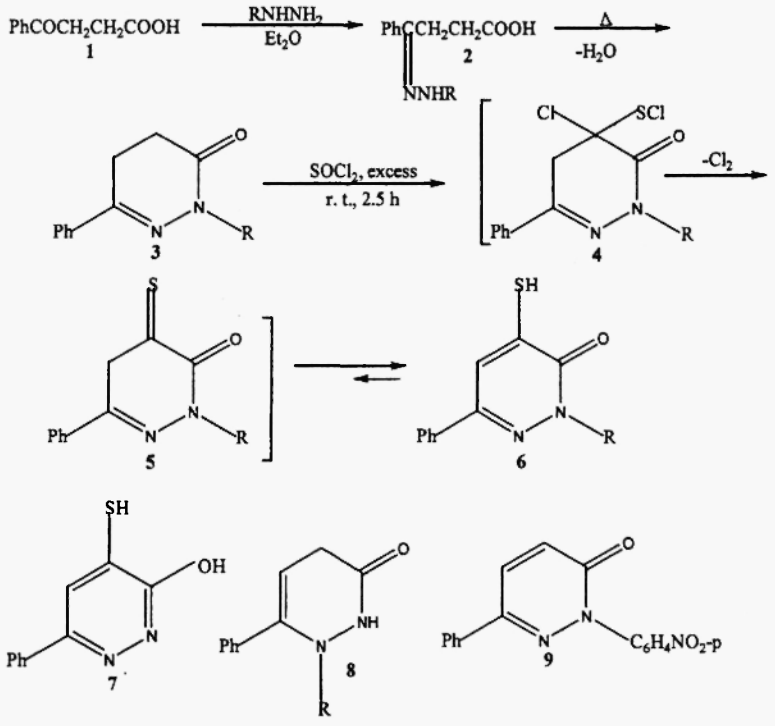
Abstract : A simple and efficient synthesis of the novel 4-mercapto-6-phenylpyridazin-3(2H)-ones from the reaction of 6-phenyl-4,5-dihydropyridazin-3(2H)-ones with excess thionyl chloride under mild conditions, is described.

3(2H)-Pyridazinone core have an ubiquitous presence in pharmaceuticals and pesticides. Three marketed selective COX-2 inhibitors, Celebrex- (celecoxib), Viox- (rofecoxib) and Bextra- (valdecoxib), effectively treat pain, infamation, and fever with improved gastroindestinal safety. All three of these drugs share a similar structural motif: a core heterocyclic ring substituted with a phenyl and a 4-(sulfonyl)phenyl ring on adjacent atoms. This structural motif was investigated[1] employing 3(2H)-pyridazinone as the core heterocycle, some active regioisomers of this report are under clinical investigation. The same core is present in many pharmaceuticals used as phosphodiesterase inhibitors[2] for treatment of different diseases among them multiple sclerosis, hypertension, Alzheimer disease, and as inhibitors of the production and transduction of cytokines.[3] 3(2H)-Pyridazinone derivatives, have been also recently referred[4] as drugs for inhibiting vascular intimal hyperplasia. Norflurazon[5], belongs to this core heterocycle with herbicidal activity inhibiting the biosynthesis of long-chain carotenoids, effecting on protein composition and chlorophyll organization in pigment-protein complex of photosystem II. Furtermore some 5-mercapto-pyridazinones have been reported as microbiocides and insecticides[6] or for treating/preventing diabetic complications.[7] Given the broad spectrum of biological activity of functionalized pyridazinones, the method desribed here could be used for the synthesis and derivatization of new compounds added to the corporate library, useful as prodrugs and/or as microbiocides or pesticides.

After an extensive bibliographic research we did not find 4-mercapto-substituted 3(2H)-pyridazinones and in the course of our studies on synthesis of different heterocycles and on abnormal reactions of thionyl chloride, we experimented with the incorporation of the sulfur moiety at the 4-position of this core. Based on literature reports[8a-g] and our experience,[9] on direct incorporation of chlorosulfenyl moiety, at the α-carbon atom to a carbonyl group, (ketonic or carboxylic acid's chloride), using thionyl chloride ,we proceeded by means of a mechanism which involved oxidation of a methylene carbon to the preparation of the corresponding chlorosulfenyl chloride, >C(SCl)Cl. The literature reports[8a-g,10,11,12,13,14,15] refer to such reactions under drastic conditions, in the presence of pyridine, on different carbon atoms as: methyl carbon atoms adjacent to an aromatic ring,[10,11,12] methylenes adjacent both, to an aryl and a carboxyl group,[13] active methylenes[14,15]and methylenes adjacent to enolizable carbonyl groups, (ketonic or carboxylic acid's chloride).[8a-g] The former authors suggested a mechanism which proceeded through the transformation of a methylene carbon to the corresponding chlorosulfenyl chloride. The later usually reacts as an intermediate to the formation of sulfur heterocycles[8a-g,9] or other nucleophilic displacements[14,15] while in only few cases it was isolated[8e] and characterized by ^{1}H NMR, and then heterocyclized.

In this letter we wish to disclose a simple and convenient synthesis of 4-mercapto-6-phenylpyridazin-3(2H)-ones **6** from the corresponding 6-phenyl-4,5-dihydropyridazin-3(2H)-ones **3**, a reaction of mild conditions with excess thionyl chloride, (without any of base), Scheme 1. The used pyridazinones **3** have been reported[16] (except from **3d** for which there are no data), by cyclocondensation of β-benzoylpropionic acid and the proper hydrazine. In order to overcome some experimental obscurities, perhaps connected to and/or the co-formation of the corresponding hydrazides, and to have better yields, we prepared them from the hydrazones **2**,[17] (prepared under mild condensation conditions,

from ketoacid **1** and the desired hydrazines), which then cyclodehydrated thermally to the corresponding pyridazinones **3**[18] in yields 78-86 %, excluding the probable formation of the isomeric pyridazinones **8**, (Scheme 1).



Scheme 1

4-Mercaptopyridazinones **6**, (except from **6d**), were prepared[19] in good yields, (64-71 %), from the reaction of pyridazinones **3** with excess thionyl chloride, at room temperature, and were characterized on the basis of spectroscopic data and elemental analyses.

As noted above, from the former reaction we expected the formation of the corresponding chlorosulfenyl chlorides **4**, but 4-mercaptopyridazinones **6b** and **6c**, (R=Me and Ph, respectively), and 3-hydroxy-4-mercaptopyridazine **7** (the tautomerized **6a**, R=H), were isolated instead. We can not explain, under reaction's conditions the formation of the thiol moiety, (the reduced form of a sulfenyl chloride group), on the pyridazinone ring, the only simple explanation we could give is a concomitant extrusion of chlorine from **4** to the thione **5** formation, which after enethiolization was converted to the thiol **6**, (Scheme 1). An analogous thione-thiol tautomerization in 6-arylpyridazin-3(2H)-thiones, has been reported.[20]

The failure of formation of mercaptopyridazinone **6d**, as noted above, and the formation of pyridazinone **9**[21] instead was attributed to the presence of p-nitrophenyl group, (a strong electron deficient moiety), in connection with the reactive 5-positioned pseudoallylic hydrogens. The abstraction of one of these protons, (by an elimination mechanism, upon attack of a Cl^- as base), would be favored giving an anion more stabilized than the corresponding allylic. Then the formation of C4=C5 double bond could be formed after departure of a C4-substituent, (as leaving group), which could be for example a sulfinyl chloride moiety, (-SOCl), inserted from the initial attack of thionyl chloride on C4-positioned atom of the pyridazinone ring.

In conclusion, we have developed a simple and efficient method for the synthesis of novel functionalized 3(2H)-pyridazinones, the 4-mercapto- analogs, from the reaction of excess thionyl chloride on 3(2H)-pyridazinones. This method is notable for its mild conditions, requiring no catalyst, (e.g. tertiary amine), and may be readily performed at room temperature. Furthermore, this

on is another example of methylenes oxidizable with thionyl chloride, we found no prior nce in the literature to methylenes oxidation *alfa-* to a lactamic carbonyl. The generality of the method seems to have some limitations, (e.g. the presence of strong electron deficient substituents 2-positioned to pyridazinone ring), also the mechanism by which these products were being formed has not been investigated. The expansion of the method to other 2- and/or 5-substituted-6-aryl-3(2H)-pyridazinones as well as the derivatization at sulfur atom, with suitable reagents, is in our immediate plan. All the novel compounds reported in this letter will be submitted for biological testing.

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17. General procedure for the preparation of β-benzoylpropionic acid hydrazones **2**. To a stirred and ice cooled suspension of β-benzoylpropionic acid 5 g (28.06 mmol) in 50 ml diethyl ether, 29.5 mmol of the proper hydrazine were added gradually. After a half an hour stirring in this temperature the thick slurry was stirred at room temperature for additional half an hour. The product was filtered and washed with cold ether to give a pure solid of the hydrazone **2**, (as revealed from ^{1}H NMR). Recrystallization from diethyl ether gave an analytical sample of the hydrazone **2**. Compound **2a**: Yield 81 %, mp 80-81 ^{0}C. Anl. Calcd for $C_{10}H_{12}N_2O_2$: C,62.49; H, 6.29; N; 14.57. Found: C, 62.27; H, 6.45; N, 14.47. IR (Nujol mull, cm^{-1}): 3380, 1713, 1682, 1602, 1595. ^{1}H NMR ($CDCl_3$): 2.60 and 3.30 (two t, J=6.5 Hz, 4H, -CH_2CH_2-), 4.20 (br s, 2H, -NH_2), 7.20-7.83 (m, 5H, arom.), 12.47 (br s, 1H, -COOH). Compound **2b**: Yield 87 %, mp 110-112 ^{0}C. Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: 64.21; H, 6.78; N, 13.69. IR (Nujol mull, cm^{-1}): 3385, 1711, 1685, 1600, 1595. ^{1}H NMR ($CDCl_3$): 2.65 and 3.40

(two t, J=6.5 Hz, 4H, $-CH_2CH_2-$), 3.43 (s, 3H, $-CH_3$), 4.11 (br s, 1H, >NH), 7.34-8.07 (m, 5H, arom.), 11.81 (s, 1H, -COOH). Compound **2c**: Yield 85 %, mp 64-65 ^{0}C. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.80; H, 6.11; N, 10.37. IR (Nujol mull, cm^{-1}): 3383, 1709, 1675, 1602, 1595. ^{1}H NMR ($CDCl_3$): 2.70 and 3.30 (two t, J=7 Hz, 4H, $-CH_2CH_2-$), 5.20 (br s, 1H, >NH), 7.20-7.85 (m, 10H, arom.), 12.37 (s, 1H, -COOH). Compound **2d**: Yield 81%, mp 148-150 ^{0}C. Anal. Calcd for $C_{16}H_{15}N_3O_4$: C, 61.34; H, 4.82; N, 13.41. Found: C, 61.47; H, 4.91; N, 13.35. IR (Nujol mull, cm^{-1}): 3395, 1706, 1670, 1600, 1592. ^{1}H NMR ($CDCl_3$): 2.76 and 3.11 (two t, J=7 Hz, 4H, $-CH_2CH_2-$), 7.20-8.50 (m, 10H, 9 arom. and >NH), 12.51 (s, 1H, -COOH).

18. General procedure for the preparation of 6-phenyl-4,5-dihydropyridazin-3(2H)-ones **3**. A round bottom flask containing 20 mmol of hydrazone **2** was heated under stirring in an oil bath 140-150 ^{0}C, (160-170 ^{0}C for compound **3d**), until the exhaust of water vapors was ceased. The crystalline product obtained after cooling to room temperature, was proved to be almost pure (^{1}H MR) compound **3**. After recrystallization from ethanol an analytical sample was obtained. Compound **3a**: Yield 80 %, mp 150-151 ^{0}C, lit.[16b] 150 ^{0}C, lit.[16d] 145 ^{0}C. IR (Nujol mull, cm^{-1}): 3350, 1680. ^{1}H NMR ($CDCl_3$): 2.78 (m, 4H, $-CH_2CH_2-$, A_2B_2), 7.01-7.72 (m, 5H, arom.), 9.23 (br s, 1H, >NH, exchangeable). Compound **3b**: Yield 84 %, mp 106-107 ^{0}C, lit.[16c] mp 106-107.5 ^{0}C, lit.[16d] 90 ^{0}C. IR (Nujol mull, cm^{-1}): 1680. ^{1}H NMR ($CDCl_3$): 2.75 (m, 4H, $-CH_2CH_2-$, A_2B_2), 3.46 (s, 3H, $-CH_3$), 7.10-8.00 (m, 5H, arom.). Compound **3c**: Yield 86 %, mp 97-98 ^{0}C, lit.[16a] mp 97-98 ^{0}C, lit.[16d] 97-98 ^{0}C. IR (Nujol mull, cm^{-1}): 1680. ^{1}H NMR ($CDCl_3$): 2.91 (m, 4H, $-CH_2CH_2-$, A_2B_2), 7.20-7.95 (m, 10H, arom.). Compound **3d**: Yield 78 %, mp 111-112 ^{0}C. Anal. Calcd for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.15; H, 4.52;, N, 14.11. IR (Nujol mull, cm^{-1}): 1675. ^{1}H NMR ($CDCl_3$): 2.98 (m, 4H, $-CH_2CH_2-$, A_2B_2), 7.33-846 (m, 9H, arom.).

19. General procedure for the preparation of 4-mercaptopyridazin-3(2H)-ones 6. A solution of pyridazinone **3** (10 mmol) in freshly distilled thionyl chloride (20 ml), was stirred at room temperature for two and a half hours, in a flask protected with a calcium chloride tube. The excess thionyl chloride was then removed under vacuum and the solid residue was recrystallized from the proper solvent to give an analytically pure sample of the product 6. Compound **6a**:[22] Yield 67 %, red-yellow solid mp 290 ^{0}C, (from DMF). Anal. Calcd for $C_{10}H_8N_2OS$: C, 58.80; H, 3.95; N,13.71; S, 15.70. Found: C, 58.63; H, 3.69; N, 13.70; S, 15.47. IR (Nujol mull, cm^{-1}): 3280, 2580, 1640, 1560. ^{1}H NMR (DMSO-d_6): 3.40 (s, 1H, -SH, exchangeable), 6.82 (s, 1H, =CH-), 7.46 (s, 5H, arom.), 13.20 (bs s, 1H, -OH, exchangeable). ^{13}C NMR ($CDCl_3$): 113.30, 127.51, 128.84, 129.32, 133.15, 150.43, 151.04, 151.74. HRMS (EI) calcd for $C_{10}H_8N_2OS$: 204.0357. Found: 204.0346. Compound **6b**: Yield 71 %, mp 191-192 ^{0}C, (from MeOH). Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83; S, 14.69. Found: C, 60.46; H, 4.46; N, 12.80; S, 14.81. IR (Nujol mull, cm^{-1}): 2585, 1663, 1570. ^{1}H NMR ($CDCl_3$): 2.92 (br, 1H, -SH, exchangeable), 3.83 (s, 3H, $-CH_3$), 6.80 (s, 1H, =CH-), 7.58 (s, 5H, arom.). ^{13}C NMR ($CDCl_3$): 36.13, 128.92, 129.25, 131.15, 132.04, 133.20, 136.05, 155.22, 157.61. HRMS (EI) calcd for $C_{11}H_{10}N_2OS$: 218.0514. Found: 218.0511. Compound **6c**: Yield 64 %, mp 149-151 ^{0}C, (from EtOH). Anal. Calcd for $C_{16}H_{12}N_2OS$: C, 68.55; H, 4.31; N, 9.99; S, 11.44. Found: C, 68.31; H, 4.31; N, 10.21; S, 11.27. IR (Nujol mull, cm^{-1}): 2580, 1673, 1600. ^{1}H NMR ($CDCl_3$): 3.5 (s, 1H, -SH, exchangeable), 7.12 (s, 1H, =CH-), 7.26-7.83 (m, 10H, arom.). ^{13}C NMR ($CDCl_3$): 121.64, 124.42, 128.80, 129.03, 129.25, 131.11, 132.04, 133.28, 136.07, 137.83, 155.27, 157.93. HRMS (EI) calcd for $C_{16}H_{12}N_2OS$: 280.0670. Found: 280.0668.

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21. Compound 9: Yield 65 %, mp 204-206 ^{0}C, (from DMF). Anal. Calcd for $C_{16}H_{11}N_3O_3$: C, 65.53; H, 3.78; N, 14.33. Found: C, 65.36; H, 3.69; N, 14.41. IR (Nujol mull, cm^{-1}): 1690, 1620, 1600. ^{1}H NMR (DMSO-d_6): 7.53-8.66 (m, 11H, 9H arom. and 2H =CH-). ^{13}C NMR ($CDCl_3$): 121.37, 122.53, 128.94, 129.28, 131.16, 133.25, 143.94, 144.08, 145.64, 155.26, 164.08. HRMS (EI) calcd for $C_{16}H_{11}N_3O_3$: 293.0800. Found: 293.0763.

22. The tautomeric form **7** of compound **6a** was obtained instead.

Received on November 1, 2006.