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A Facile Synthesis of 4-Pyrazolylthiazoles and 4-Pyrazolylmercaptoimidazoles using [Hydroxy(tosyloxy)iodo]benzene

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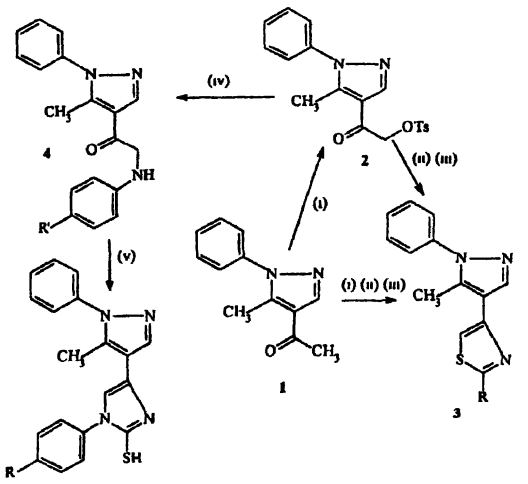
Treatment of 4-acylpyrazoles with [hydroxy(tosyloxy)iodo]benzene gives 4-(α-tosyloxyacetyl)pyrazole, which has been found to be an excellent intermediate for the synthesis of the title compounds.

Despite the biological significance of 4-acylpyrazoles and their derivatives[1-3], methods to synthesize these compounds have not received much attention. We report in this communication, a facile synthesis of 4-(pyrazol-4-yl)thiazoles (**3**) and 2-mercaptoimidazoles (**5**) starting from the corresponding 4-acetylpyrazole (**1**) through the newly discovered hypervalent iodine reagent, [hydroxy(tosyloxy)iodo]-benzene (HTIB).



	R		R'
3a	NH_2	**4,5a**	H
b	CH_3	**b**	CH_3
c	thienyl	**c**	OCH_3
d	phenyl	**d**	Cl
e	NH-Ph	**e**	F
f	NH-4-CH_3-C_6H_4	**f**	Br
g	NH-4-OCH_3-C_6H_4		
h	NH-4-Cl-C_6H_4		

Scheme 1 *Reagents* (i) HTIB/MeCN, (ii) R-$CSNH_2$/EtOH, (iii) aq NH_3, (iv) 4-R'-C_6H_4-NH_2, (v) KSCN/AcOH

Conventional route for preparing compounds **3** and **5** via α-bromination of **1**[4] was not found to be a satisfactory method because of low yields (40–48%), difficulty in purification, and its lachrymatory property. Keeping in mind the growing significance of hypervalent iodine reagents in heterocyclic synthesis[5], it was thought of interest to prepare α-tosyloxyacetyl derivative (**2**) of **1** (Scheme 1) It was found that HTIB is an excellent reagent for the preparation of α-tosyloxyacetyl derivative (**2**) which on treatment with appropriate thioamides and thioureas, and subsequent basification with aqueous ammonia gave compounds **3** in 81–84% yields. We were also successful in one-pot synthesis of **3d** in 86% yields by refluxing **2** with HTIB for 1 h followed by the addition of thiobenzamide to the resulting mixture.

Compound **2** was also found to be an intermediate of choice for the synthesis of pyrazolylmercaptoimidazoles whose synthesis, in principle, requires intermediacy of α-halogenoketones. Thus treatment of **2** with appropriate anilines gave **4** which on further reaction with KSCN in AcOH provided **5** in 70–80% yields.

All the compounds (**2-5**) were characterized by their spectral data and elemental analyses.

Experimental

M.ps. were taken in open capillaries and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 1800 insturment, ^1H nmr spectra on Bruker 300 MHz and Hitachi 60 MHz machines, and mass spectra on a Kratos MS-50 spectrometer.

4-Acetyl-5-methyl-1-phenylpyrazole (**1**) was prepared by the reported procedure[6].

4-(α-Tosyloxyacetyl)-5-methyl-1-phenylpyrazole (**2**). To a solution of **1** (1.1 g, 5.5 mmol) in acetonitrile (30 ml) was added HTIB (5.5 mmol), and the resulting solution was refluxed for 1 h. The solvent was then evaporated under reduced pressure and the solid thus obtained was crystallized from ethanol, (91%), m.p. 130° (Found : C, 61.34; H, 4.62; N, 7.88. $C_{19}H_{18}N_2O_4S$ calcd. for : C, 61.62; H, 4.86; N, 7.57%); ν_{max} (KBr) 1691 (C=O), 1405, 1188 cm^{-1} (S=O); δ($CDCl_3$) 2.45 (3H, s, Ar-CH_3), 2.54 (3H, s, pyrazoleC_5-CH_3), 4.98 (2H, s, CH_2), 7.26–7.89 (9H, m, ArH), 8.01 (1H, s, pyrazoleC_3-H), *m/z* 370 (M^+).

2-Substituted-4-(5-methyl-1-phenylpyrazol-4-yl)thiazoles (**3a-h**). *General procedure* : To a solution of **2** (2.8 mmol) in ethanol was added an appropriate thioamide (2.8 mmol) and the reaction mixture was heated to reflux on a water-bath. A solid began to separate after 1–2 h. The reac-

tion mixture was then cooled and filtered, and the solid so obtained was treated with aqueous ammonia, filtered, washed with water, dried and crystallized from ethanol to afford **3a-h** (79–84%) : 3a (82%), m.p. 160° (Found : C, 60.62; H, 4.28; N, 21.78. $C_{13}H_{12}N_4S$ calcd. for : C, 60.94; H, 4.69; N, 21.87%); ν_{max} (KBr) 3350 cm^{-1} (NH); δ($CDCl_3$) 2.51 (3H, s, pyrazoleC_5-CH_3), 5.17 (2H, br s, NH, exchangeable with D_2O), 6.41 (1H, s, thiazole$C_{5'}$-H), 7.26–7.51 (5H, m, ArH), 7.89 (1H, s, pyrazoleC_3-H); **3b** (84%) m.p. 180° (Found : C, 65.52; H, 4.82; N, 16.36. $C_{14}H_{13}N_3S$ calcd. for : C, 65.88; H, 5.10; N, 16.47%); δ ($CDCl_3$) 2.34 (3H, s, thiazole$C_{2'}$-CH_3), 2.48 (3H, s, pyrazoleC_5-CH_3), 7.15–7.73 (6H, m, ArH and thiazole$C_{5'}$-H), 8.10 (1H, s, pyrazoleC_3-H); **3c** (81%), m.p. 128° (Found : C, 62.77; H, 3.78; N, 12.79. $C_{17}H_{13}N_3S_2$ calcd. for : C, 63.16; H, 4.02; N, 13.00%); δ($CDCl_3$) 2.62 (3H, s, pyrazoleC_5-CH_3), 7.07–7.55 (9H, m, ArH, thienyl-H and thiazole$C_{5'}$-H), 7.99 (1H, s, pyrazoleC_3-H); *m/z* 323 (M^+); **3d** (84%), m.p. 101° (Found : C, 71.88; H, 4.27; N, 13.11. $C_{19}H_{15}N_3S$ calcd. for : C, 71.92; H, 4.73; N, 13.25%); δ($CDCl_3$) 2.65 (3H, s, pyrazoleC_5-CH_3), 7.22–8.04 (12H, m, ArH, thiazole$C_{5'}$-H and pyrazoleC_3-H); *m/z* 317 (M^+); **3e** (79%), m.p. 218° (Found : C, 68 18; H, 4.54; N, 16.61. $C_{19}H_{16}N_4S$ calcd. for : C, 68.67; H, 4.81; N, 16.87%); δ ($CDCl_3$) 2.57 (3H, s, pyrazoleC_5-CH_3), 6.54 (1H, s, thiazole$C_{5'}$-H), 7.26–7.52 (11H, m, ArH and NH), 7.95 (1H, s, pyrazoleC_3-CH); **3f** : (82%), m.p. 164° (Found : C, 69.12; H, 5.01; N, 15.92. $C_{20}H_{18}N_4S$ calcd. for : C, 69.36; H, 5.20; N, 16.18%); δ($CDCl_3$ + DMSO-d_6) 2.36 (3H, s, Ar-CH_3), 2.49 (3H, s, pyrazoleC_5-CH_3), 6.55 (1H, s, thiazole$C_{5'}$-H), 7.20–7.81 (9H, m, ArH), 8.05 (1H, s, pyrazoleC_3-H), 11.80 (1H, br s, NH); **3g** (82%), m.p. 160° (Found : C, 66.32; H, 4.78; N, 15.38. $C_{20}H_{18}N_4OS$ calcd for : C, 66.30; H, 4.97; N, 15.47%); ν_{max} (KBr) 3231 cm^{-1} (NH); δ($CDCl_3$) 2.53 (3H, s, pyrazoleC_5-CH_3), 3.79 (3H, s, OCH_3), 6.45 (1H, s, thiazole$C_{5'}$-H), 6.87–7.51 (9H, m, ArH), 7.60 (1H, br s, NH, exchangeable with D_2O), 7.92 (1H, s, pyrazoleC_3-H); *m/z* 362 (M^+); **3h** (81%), m.p. 140° (Found : C, 62.18; H, 3.92; N, 15.02. $C_{19}H_{15}ClN_4S$ calcd. for : C, 62.21; H, 4.09; N, 15.28%); ν_{max} (KBr) 3237 cm^{-1} (NH); δ($CDCl_3$) 2.59 (3H, s, pyrazoleC_5-CH_3), 6.59 (1H, s, thiazole$C_{5'}$-H), 7.22–7.72 (9H, m, ArH), 7.92 (1H, s, pyrazoleC_3-H), 9.96 (1H, br s, NH, exchangeable with D_2O); *m/z* 368/366 (M^+).

Anilinomethyl-4-(5-methyl-1-phenyl)pyrazolylketone (**4a-f**). *General procedure* : To a solution of **2** (2.8 mmol) in ethanol (30 ml) was added aniline (5.6 mmol) in small portions and the reaction mixture was refluxed for 1 h. On cooling, a crystalline product separated out which was filtered, washed with cold ethanol and dried to afford **4a-f** in good yields : **4a** (78%), m.p. 150° (Found : C, 73.88; H, 5.72; N, 14.26. $C_{18}H_{17}N_3O$ calcd. for : C, 74.23; H, 5.84; N, 14.43%); δ ($CDCl_3$), 2.59 (3H, s, pyrazoleC_5-CH_3), 4.39 (2H, s, CH_2), 6.60–7.45 (10H, m, ArH), 8.08 (1H, s, pyrazoleC_3-H); **4b** (76%), m.p. 155° (Found : C, 74.42; H, 5.92; N, 13.88. $C_{19}H_{19}N_3O$ calcd. for : C, 74.75; H, 6.23; N, 13.77%); ν_{max} (KBr) 3380 (NH), 1659 cm^{-1} (C=O); δ ($CDCl_3$) 2.26 (3H, s, Ar-CH_3), 2.62 (3H, s, pyrazoleC_5-CH_3), 4.42 (2H, s, CH_2), 4.73 (1H, br s, NH, exchangeable with D_2O), 6.61–7.56 (9H, m, ArH), 8.11 (1H, s, pyrazole C_3-H); *m/z* 305 (M^+); **4c** (74%), m.p. 144° (Found : C, 70.88; H, 5.68; N, 12.74. $C_{19}H_{19}N_3O_2$ calcd. For : C, 71.03; H, 5.92; N, 13.08%); δ($CDCl_3$) 2.59 (3H, s, pyrazoleC_5-CH_3), 3.74 (3H, s, OCH_3), 4.38 (2H, s, CH_2), 4.67 (1H, br s, NH, exchangeable with D_2O), 6.70–6.74 (4H, dd, ArH), 7.46–7.52 (5H, m, ArH), 8.09 (1H, s, pyrazoleC_3-H); **4d** (76%), m.p. 155° (Found : C, 65.91; H, 4.82; N, 12.72. $C_{18}H_{16}ClN_3O$ calcd. for : C, 66.36; H, 4.92; N, 12.90%); ν_{max} (KBr) 3390 (NH), 1659 cm^{-1} (C=O); δ($CDCl_3$) 2.62 (3H, s, pyrazoleC_5-CH_3), 4 40 (2H, s, CH_2), 4.89 (1H, br s, NH, exchangeable with D_2O), 6.59–7.55 (9H, m, ArH), 8.10 (1H, s, pyrazoleC_3-H); **4e** (72%), m.p. 181° (Found : C, 69.88; H, 4.98; N, 13.38. $C_{18}H_{16}FN_3O$ calcd. for : C, 69.90; H, 5.18; N, 13.59%); δ($CDCl_3$ + DMSO-d_6) 2.58 (3H, s, pyrazoleC_5-CH_3), 4.39 (2H, s, CH_2), 5.45 (1H, br s, NH, exchangeable with D_2O), 6.53–7.86 (9H, m, ArH), 8.23 (1H, s, pyrazoleC_3-H); **4f** (74%), m.p. 201° (Found : C, 57.94; H, 4.02; N, 11.16. $C_{18}H_{16}BrN_3O$ calcd. for : C, 58.38; H, 4.32; N, 11.35%); δ($CDCl_3$) 2.61 (3H, s, pyrazoleC_5-CH_3), 4.40 (2H, s, CH_2), 6.50–7.81 (10H, m, ArH and NH), 8.15 (1H, s, pyrazoleC_3-H).

1-Aryl-4-(5-methyl-1-phenylpyrazol-4-yl)-2-mercaptoimidazoles (**5a-f**). *General procedure* : Potassium thiocyanate (2.5 mmol) was added to solution of **4** (2.5 mmol) in glacial acetic acid (10 ml) and the reaction mixture was refluxed gently for 20–30 min On cooling, a crystalline solid separated out which was filtered, washed with water and crystallized from acetic acid to yield compounds **5a-f** in excellent yields : **5a** (79%), m.p. 160° (Found : C, 68.52; H, 4.62; N, 16.51. $C_{19}H_{16}N_4S$ calcd. for : C, 68.67; H, 4.82; N, 16.87%); ν_{max} (KBr) 2390 cm^{-1} (SH); δ($CDCl_3$ + DMSO-d_6) 2.47 (3H, s, pyrazoleC_5-CH_3), 7.00 (1H, s, imidazole$C_{5'}$-H), 7.40–7.84 (10H, m, ArH), 8.05 (1H, s, pyrazoleC_3-H), 12.76 (1H, br s, SH, exchangeable with D_2O); **5b** (80%), m.p. 245° (Found : C, 69.24; H, 4.88; N, 15.87. $C_{20}H_{18}N_4S$ calcd. For : C, 69.36; H, 5.20; N, 16.18%); ν_{max} (KBr) 2400 cm^{-1} (SH); δ($CDCl_3$) 2.40 (3H, s, Ar-CH_3), 2.41 (3H, s, pyrazoleC_5-CH_3), 6.81 (1H, s, imidazole$C_{5'}$-H), 7.26–7.53 (9H, m, ArH), 7.89 (1H, s, pyrazoleC_3-H), 12.24 (1H, br s, SH, exchangeable with D_2O); *m/z* 346 (M^+); **5c** (76%), m.p. 268° (Found : C, 65.91; H, 4.56; N, 15.17. $C_{20}H_{18}N_4OS$ calcd. for : C, 66.30; H, 4.97; N, 15.47%); δ($CDCl_3$ + DMSO-d_6) 2.42 (3H, s, pyrazoleC_5-CH_3), 3.85 (3H, s, OCH_3), 6.93 (1H, s, imidazole$C_{5'}$-H), 6.99–7.56 (9H, m, ArH), 8.04 (1H, s, pyrazoleC_3-H), 12.71 (1H, br s, SH, exchangeable with D_2O); **5d** : (80%), m.p. 260° (Found : C, 62.12; H, 3.98; N, 14.92. $C_{19}H_{15}ClN_4S$ calcd. for : C, 62.21; H, 4.09; N, 15.28%); ν_{max} (KBr) 2360 cm^{-1} (SH); δ ($CDCl_3$ + DMSO-d_6) 2.41 (3H, s, pyrazoleC_5-CH_3), 6.88 (1H, s, imida-

zole C_5-H), 7.46–7.67 (9H, m, ArH), 8.05 (1H, s, pyrazoleC_3-H), 12.77 (1H, br s, SH); *m/z* 368/366 (M^+); **5e** (78%), m.p. 285° (Found : C, 64.72; H, 4.12; N, 15.82. $C_{19}H_{15}FN_4S$ calcd. for : C, 65.14; H, 4.28; N, 16.00%); ν_{max} (KBr) 2362 cm^{-1} (SH); δ ($CDCl_3$ + DMSO-d_6) 2.41 (3H, s, pyrazoleC_5-CH_3), 6.81 (1H, s, imidazoleC_5-H), 7.19–7.66 (9H, m, ArH), 7.84 (1H, s, pyrazoleC_3-H), 11.26 (1H, br s, SH); **5f** (72%), m.p. 250° (Found : C, 55.21; H, 3.42; N, 13.21. $C_{19}H_{15}BrN_4S$ calcd. for : C, 55.47; H, 3.65; N, 13.62%); ν_{max} (KBr) 2390 cm^{-1} (SH); δ($CDCl_3$ + DMSO-d_6) 2.42 (3H, s, pyrazoleC_5-CH_3), 6.97 (1H, s, imidazoleC_5-H), 7.34–7.73 (9H, m, ArH), 8.04 (1H, s, pyrazoleC_3-H), 12.81 (1H, br s, SH); *m/z* 412/410 (M^+).

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