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Concise and Efficient Synthesis of 1H-Pyrazoles: Reaction of [Hydroxy(tosyloxy)iodo]benzene with Ethyl 2,3-Dioxobutanoate-2-arylhydrazones

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CONCISE AND EFFICIENT SYNTHESIS OF 1*H*-PYRAZOLES: REACTION OF [HYDROXY(TOSYLOXY)IODO]BENZENE WITH ETHYL 2,3-DIOXOBUTANOATE-2-ARYLHYDRAZONES

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ABSTRACT: Ethyl 2,3-dioxobutanoate-2-arylhydrazones **1** on treatment with [hydroxy(tosyloxy)iodo]benzene **2** at reflux temperature and followed by heating in the presence of *N*-ethyldiisopropylamine afforded the cyclized ethyl 1-aryl-4-hydroxy-1*H*-3-pyrazolecarboxylates **4** in good yield.

Pyrazole derivatives have attracted much attention due to their diverse biological properties.[1] A number of relatively simple pyrazole and pyrazolone derivatives have been described as potential analgesics, antipyretics, antiinflammatories, germicides and antifungals.[2] Extensive work has been done on the synthesis of these classes of compounds.[3] These observations and our continued interest[4] in the synthesis of pyrazoles and evaluation of their biological activity led us to develop new methodology for the synthesis of 1*H*-pyrazoles. In this communication we wish to report efficient

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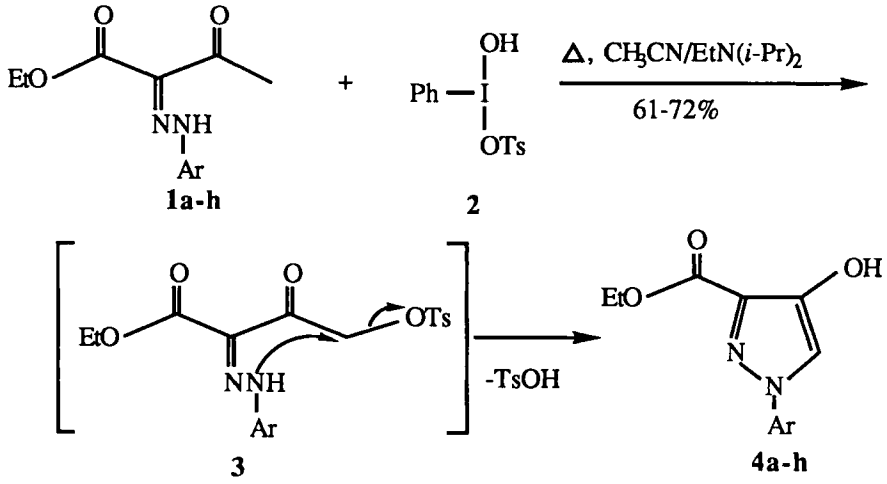
and concise synthesis of hydroxy-1*H*-pyrazoles by reacting [hydroxy(tosyloxy)iodo]benzene with ethyl 2,3-dioxobutanoate-2-arylhydrazones.

In recent years, there has been considerable interest in hypervalent iodine(III) compounds as reagents for organic synthesis.[5] It is well known that, ketones and silyl enol ethers react with [hydroxy(tosyloxy)iodo]benzene (HTIB) to give α-tosyloxy ketones.[6] A remarkable feature of HTIB is its ability to introduce the formal equivalent of the tosyloxenium ion directly onto carbon. We



1,4	Ar	1,4	Ar
a	C_6H_5	e	3,5-$Cl_2C_6H_3$
b	4-BrC_6H_4	f	3,5-$Br_2C_6H_3$
c	2-$NO_2C_6H_4$	g	2,4,6-$Cl_3C_6H_2$
d	4-$NO_2C_6H_4$	h	2,4,6-$Br_3C_6H_2$

Scheme

report herein the ready adaptation of the ∝-tosyloxylation of ketone using HTIB to the preparation of hydroxy-1*H*-pyrazoles.

The ethyl 2,3-dioxobutanoate-2-arylhydrazones[7] **1a-h** treated with [hydroxy(tosyloxy)iodo]benzene[8] (**2**, HTIB) in acetonitrile at reflux temperature for 50 min and further treated with *N*-ethyldiisopropylamine for 10 min to afford the directly cyclized ethyl 1-aryl-4-hydroxy-1*H*-3-pyrazolecarboxylates[9] **4a-h** in good yield (Table). Reactions were also conducted in dichloromethane or acetonitrile at room temperature gave the product but in very poor yield. HTIB is not very soluble in either acetonitrile or dichloromethane at room temperature but dissolves in acetonitrile at reflux temp. Hence it is convenient to carry out the reaction at reflux temperature.

It seems plausible that the cyclization process probably occurs through the formation of ∝-tosyloxy ketone *in situ*. Treatment of ketone **1** with HTIB **2** may form ∝-tosyloxy ketone(**3**) which in turn may undergo intramolecular nucleophilic attack by the nitrogen atom to give hydroxy-1*H*-pyrazole **4** (Scheme).

The ease and moderate generality of the synthesis reported herein provides convenient access to 4-hydroxy-1*H*-pyrazoles.

Experimental

Melting points were determined using a Buchi 510 apparatus and are uncorrected. IR spectra was recorded on a Perkin-Elmer FT-IR 1600 instrument. ^{1}H NMR spectra were obtained on a Varian XL-200, 200MHz spectrometer using TMS as an internal standard. A

Table : Ethyl 1-aryl-4-hydroxy-1*H*-3-pyrazolecarboxylates **4a-h**

No	Yield[@] (%)	m.p.[Lit] (^{0}C)	^{1}H NMR(CDCl$_3$:TMS) δ(ppm)	MS m/z(%)
4a	64	83-84 [84][9a]	1.08(t, *J*=7Hz, 3H, CH_2CH_3), 4.21 (q, *J*=7Hz, 2H, CH_2CH_3), 8.15(s, 1H, C=CH); 7.48(m, 6H, ArH, OH)	216(12)
4b	68	136-37 [136-37][4c]	1.07(t, *J*=7Hz, 3H, CH_2CH_3), 4.23 (q, *J*=7Hz, 2H, CH_2CH_3), 8.21(s, 1H, C=CH); 7.68(m, 5H, ArH, OH)	295(16)
4c	61	152-53 [153][9b]	1.08(t, *J*=7Hz, 3H, CH_2CH_3), 4.22 (q, *J*=7Hz, 2H, CH_2CH_3), 8.23(s, 1H, C=CH); 7.79(m, 5H, ArH, OH)	261(23)
4d	65	220-22 [220-21][4c]	1.11(t, *J*=7Hz, 3H, CH_2CH_3), 4.25 (q, *J*=7Hz, 2H, CH_2CH_3), 8.15(s, 1H, C=CH), 7.61(s, 1H, OH), 7.51 (d, *J*=8Hz, 2H, ArH); 8.31 (d, *J*=8Hz, 2H, ArH)	261(27)
4e	62	153-54 [154][9c]	1.08(t, *J*=7Hz, 3H, CH_2CH_3), 4.22 (q, *J*=7Hz, 2H, CH_2CH_3), 8.08(s, 1H, C=CH); 7.57(m, 4H, ArH, OH)	285(16)
4f	63	152-54 [154][9c]	1.11(t, *J*=7Hz, 3H, CH_2CH_3), 4.23 (q, *J*=7Hz, 2H, CH_2CH_3), 8.11(s, 1H, C=CH); 7.52(m, 4H, ArH, OH)	374(19)
4g	68	157-58 [158][9d]	1.09(t, *J*=7Hz, 3H, CH_2CH_3), 4.21 (q, *J*=7Hz, 2H, CH_2CH_3), 8.07(s, 1H, C=CH); 7.58(s, 1H, OH); 7.48 (s, 2H, ArH)	319(15)
4h	72	160 [160][4c]	1.11(t, *J*=7Hz, 3H, CH_2CH_3), 4.26 (q, *J*=7Hz, 2H, CH_2CH_3), 8.06(s, 1H, C=CH); 7.61(s, 1H, OH); 7.45 (s, 2H, ArH)	452(18)

[@] All the compounds were purified by column chromatography using silica gel as stationary phase and gave satisfactory analytical figures and were characterized by spectroscopic means(i.r., mass and NMR).

Jeol-JMS-OISG-2 mass spectrometer was employed for recording low resolution 75eV mass spectra.

Ethyl 1-aryl-4-hydroxy-1*H*-3-pyrazolecarboxylates(**4a-h**)

General procedure

To a hot solution of arylhydrazone **1**(8 mmol) in CH_3CN(25 ml) was added a hot solution of HTIB **2**(8.01 mmol) in CH_3CN(50 ml). Reaction mixture was refluxed for 50 min and to this was added *N*-ethyldiisopropylamine and further refluxed for 10 min. Solvent was removed under vacuo and residual material was dissolved in dichloromethane(50 ml). The dichloromethane solution was washed with water(3X80 ml), brine(50 ml) and dried over $MgSO_4$. Removal of solvent under reduced pressure followed by column chromatography over silica gel using EtOAc:hexane(3:7) as eluent gave hydroxy 1*H*-pyrazole **4**; which was further purified by crystallization from appropriate solvent.

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