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4,4-Dibromo-3-methylpyrazol-5-one: New Applications for Selective Monobromination of Phenols and Oxidation of Sulfides to Sulfoxides

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Abstract: Dibromopyrazolone **1**, a stable, crystalline solid effects *para* selective monobromination of phenols and aniline substrates under mild conditions. Selective oxidation of sulfides to sulfoxides can also be accomplished by using **1** in high yields.
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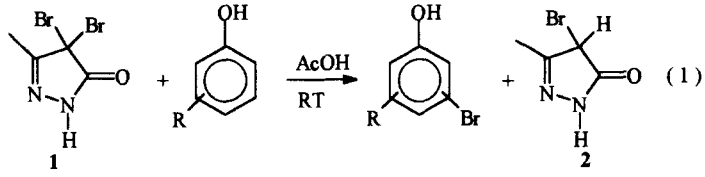
Selective monobromination and regiochemical control in the nuclear bromination of reactive aromatics using molecular bromine is generally difficult to achieve[1]. On the other hand, indirect methods available[2] to effect nuclear brominations are multisteps, cumbersome and not always practical. In recent years, a number of electrophilic bromine carriers namely, tetramethylammonium bromide[3a,b], 1,8-diazabicyclo [5.4.0] undec-7-enehydrobromide perbromide[3c], 2,4,4,6-tetrabromocyclohexa-2,5-dienone[3d,e], hexabromocyclopentadiene[3f] and N-bromosuccinamide[3g] showing moderate to high regioselective monobromination have been reported. However, problems of contamination with di-and polybromoproducts, toxicity or low stability of the reagents and attainment of high level of regioselectivity are some of the issues that need to be satisfactorily resolved.

4,4-dibromo-3-methylpyrazol-5-one **(1),** a well known, stable, crystalline solid and readily accessible in multigram quantity by bromination of 3-methylpyrazol-5-one[4a], has been exploited in functional group transformations and in heterocyclic fields[4]. However, its potential as a brominating agent does not appear to have been described in the literature. It occurred to us that under appropriate conditions, protonation or hydrogen bonding of either the imine-nitrogen or the amide carbonyl of **1** might polarize and thereby weaken the C-Br bond to render **1** as an electrophilic bromine carrier. We now report that **1** can indeed be employed as a mild, general and selective monobrominating agent for phenolic substrates as depicted in the generalized equation (1).



1 2 (1)

The Table shows our results on the bromination of various phenols with **1** in glacial acetic acid at room temperature.Under these conditions, phenol reacted with **1** to produce a total of 94% monobromination comprising of 90% of the *para* and 10% of the *ortho* bromoproducts. Of the several solvents examined, acetic acid as a reaction medium allowed for relatively faster conversions and produced the highest *para* selectivity. For instance, the bromination of phenol with **1** in methanol and acetonitrile resulted in comparatively lower *para* selectivity (*o/p* ratios of ca. 17/83 and 19/81, respectively). Use of 2 and 3

Table. Bromination of phenols with 4,4-dibromopyrazolone (1)[a]

Entry	Phenols	Bromophenols[e]	Time/h	Yield%[f]
1.	Phenol	4-bromophenol (85%)	20	94
		2-bromophenol (9%) +		
		2,4-dibromophenol (3%)		
2.	4-Methylphenol	2-bromo-4-methylphenol (92%) +	16	95
		2,6-dibromo-4-methylphenol (5%)		
3.	4-Bromophenol	2,4-dibromophenol	24	90
4.	4-hydroxybenzaldehyde[b]	2-bromo-4-hydroxybenzaldehyde	30	88
5.	2-Methylphenol	4-bromo-2-methylphenol (86%) +	18	90
		6-bromo-2-methylphenol (7%) +		
		2,4-dibromo-6-methylphenol (3%)		
6.	3-Methylphenol	4-bromo-3-methylphenol (86%) +	20	92
		2-bromo-5-methylphenol (9%) +		
		2,4-dibromo-5-methylphenol (<2%)		
7.	2-Bromophenol	2,4-dibromophenol	24	94
8.	Eugenol	6-bromoeugenol (90%) +	24	87
		Eugenol (10%)		
9.	2.6-dimethylphenol	4-bromo-2,6-dimethylphenol	16	91
10.	1-Naphthol	2-bromo-1-naphthol (95%) +	20	95
		2,4-dibromo-1-naphthol (5%)		
11.	2-Naphthol	1-bromo-2-naphthol	20	94
12.	Bisphenol A[c,d]	2,2-dibromobisphenol-A (>95%)	24	88

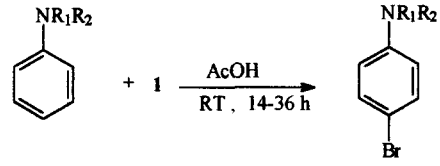
[a] Reactions carried out using 5 mmol each of the phenol and 1 in 15 ml of glacial acetic acid at room temperature except where noted. [b] Reaction was done in methanol. [c] Bisphenol A is 4,4-isopropylidenephenol. [d] 2 equivalents of 1 were used. [e] Isomeric ratios determined by g.l.c using an internal standard. All monobromination products isolated and characterized by mp and or spectral data. Dibromination products identified by g.l.c comparisons with authentic samples. [f] Yields not optimised. 0-3% phenols remain unreacted.

equivalents of **1** with one equivalent of phenol readily gave 87% and 91% of 2,4-dibromo- and 2,4,6-tribromophenols, respectively in high purity. Bromination of the *para* substituted phenols (entries 2,3) with **1** resulted in excellent yields of the corresponding *o*- bromophenols, whereas *o*- and *m*-cresols predominantly exhibited para selective bromination. In the bromination reactions (Table), dibromo products if at all formed do not exceed 5% of the total product mixture. The product isolation consists of filtering the precipitated **2** (recovery 80-85%), diluting the filtrate with water, neutralization and

extractive work-up with 1:1 hexane-Et_2O. The spent reagent **2** can be readily brominated by the known procedure[4a] to regenerate **1**.

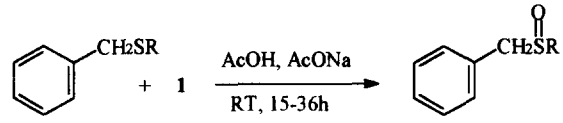
Noteworthy are the brominations of phenolic aldehyde and eugenol (entries 4 and 8) which exclusively led to the corresponding nuclear bromination products in high yields without detectable carbonyl group or double bond being affected in the reaction. In other examples cited in the Table (entries 7,9,10,11 and 12) the monobromination products are isolated after work-up in good purity and excellent yields. Simple aromatics such as benzene, toluene, and anisole failed to participate in the attempted bromination with **1**, thereby suggesting that the nucleus must be sufficiently activated for the reaction to occur. Similar observation has also been made by Mitchell[3g] in the context to the bromination of aromatics with NBS in DMF solvent.

Bromination of highly reactive aniline and N,N-dimethylaniline with **1** (eqs 2 and 3) also proved highly successful affording ca. 90% *para* bromination, accompanied by small amounts of the unreacted anilines and polybromo-products. Acetanilide and benzanilide were cleanly brominated with **1** to give the corresponding *para* bromoproducts in exellent yields (eqs. 4 and 5). We presume that the protonation of **1** should activate one of its C-Br bonds towards nucleophilic attack by the reactive arenes, the latter reacting through their relatively unencumbered *para* positions (and further assisted by +M effect of the -OH or NR_2 groups) to give the expected bias for *para* regioselectivity[1,5].



$R_1=R_2=H$	90%	(2)
$R_1=R_2=Me$	90%	(3)
$R_1=H; R_2=NHCOCH_3$	93%	(4)
$R_1=H; R_2=NHCOC_6H_5$	87%	(5)

Because of the importance of sulfoxides in C-C bond formations and functional group transformations, newer methods for the selective oxidation of sulfides to sulfoxides are continued to be investigated[6]. Although not studied in as much detail, we have found that under a slightly modified condition, reagent **1** neatly trasforms sulfides into sulfoxides in 79-92% isolated yields without contamination from sulfones (eqs. 6 to 9). Triphenylphosphine was also oxidised by **1** in less than an hour to triphenylphosphine oxide in quantitative yield.



R=Me	89%	(6)
$R=C_6H_5$	79%	(7)
$R=CH_2C_6H_5$	92%	(8)
$R=CH_2CO_2C_2H_5$	84%	(9)

Preparation of 1-bromo-2-naphthol. General procedure: To a solution of 2-naphthol (720mg,5mmol) in glacial acetic acid (15ml) was added **1** (1.28gm,5mmol) in small portions during 30 min. The reaction was left at room temperature for 20 h. The precipitated **2** was filtered off and washed with little cold acetic acid. The combined filtrate was diluted with water, cooled in ice and neutralized with aq.$NaHCO_3$. Extractive work-up with 1:1 hexane- Et_2O followed by solvent removal afforded the product (1.05gm,94%) which was recrystallised from aq.ethanol, mp 79-80°C, lit[7] mp 81-82°C.

Preparation of dibenzyl sulfoxide. General procedure: Dibenzyl sulfide (1.07gm,5mmol), **1** (1.30gm,5.1mmol) and anhydrous sodium acetate (1gm) were added to glacial acetic acid (15ml) and the reaction stirred for 18 h at room temperature. The reaction was cooled in ice and basified with 10% aq. NaOH. The precipitated dibenzyl sulfoxide was collected by filtration (1.06gm,92%), and recrystallized from aq.ethanol, mp 133-34°C, lit[8] mp 137.5°C.

In summary, we have recognised **1** as a convenient, stable and highly useful electrophilic bromine carrier capable of effecting regioselective monobromination of a variety of phenols and aniline substrates. In addition, **1** is able to selectively oxidize sulfides to sulfoxides in high yields.

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