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DI-2-PYRIDYL SULFITE. A NEW USEFUL REAGENT FOR THE PREPARATION OF N-SULFINYLAMINES, NITRILES, ISOCYANIDES, AND CARBODIIMIDES UNDER MILD CONDITIONS

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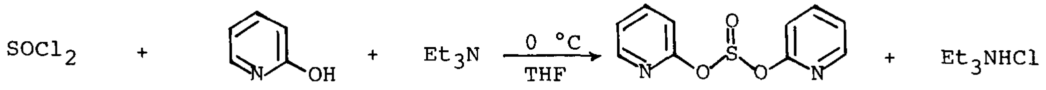
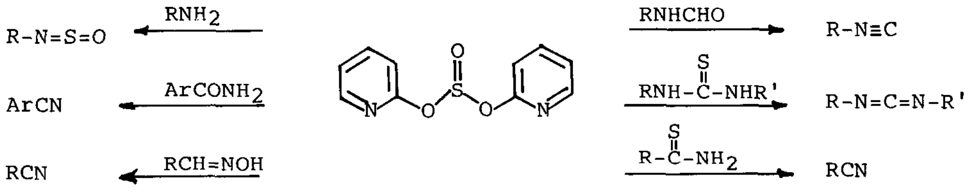
Summary: Di-2-pyridyl sulfite is a very useful reagent for the preparation of N-sulfinylamines, nitriles, isocyanides, and carbodiimides in high yields under essentially neutral conditions.

In connection with our research program directed toward development of new efficient and reliable condensing reagents utilizing 2-pyridyl moiety,[1] we have found that di-2-pyridyl sulfite is a very useful reagent for the preparation of N-sulfinylamines, nitriles, isocyanides, and carbodiimides under essentially neutral conditions.

Di-2-pyridyl sulfite was conveniently prepared in high yields by the reaction of thionyl chloride with 2 equiv of 2-hydroxypyridine and triethylamine in tetrahydrofuran at 0 °C. Since di-2-pyridyl sulfite was decomposed to some extent during aqueous workup or silica gel column chromatographic purification, di-2-pyridyl sulfite was used as a crude form after removal of triethylamine hydrochloride and subsequent solvent removal and could be stored in a refrigerator for a week without any decomposition.[2]





Scheme 1

Synthetic utility of di-2-pyridyl sulfite for functional group conversions is shown in Scheme 1 and several experimental results are summarized in Table 1. First, the use of di-2-pyridyl sulfite as a sulfinylating reagent of amines was briefly examined.[3] Reaction of amines with a stoichiometric amount of the reagent in methylene chloride at room temperature gave the corresponding N-sulfinylamines in high yields. The reaction was generally complete within 10 min at room temperature. Unlike recently reported N,N'-sulfinylbisimidazole and N-(chlorosulfinyl)imidazole,[3d] primary aliphatic carboxamides were inert to the present conditions, even in refluxing toluene for 5 h. However, primary aromatic carboxamides were cleanly converted into the corresponding nitriles in high yields in refluxing toluene within 1 h. Furthermore, the reagent was successfully utilized for the preparation of nitriles and isocyanides from aldoximes[4] and formamides,[5] respectively. Reaction of p-methoxybenzaldoxime with a stoichiometric amount of the reagent in refluxing toluene gave p-methoxybenzonitrile in 93% yield within 10 min. This reaction could be carried out in refluxing acetonitrile and was complete within 10 min, whereas the reaction in methylene chloride at room temperature required 24 h for completion of the reaction. Similarly, several formamides were smoothly converted into the corresponding isocyanides as shown in Table 1.

The use of di-2-pyridyl sulfite as a dehydrosulfurization reagent was examined using N,N'-disubstituted thioureas and primary thioamides. Reaction of N,N'-disubstituted thioureas with the reagent in methylene chloride smoothly and rapidly proceeded at room temperature, yielding the corresponding carbodiimides in high yields.[6] This method was turned out to be general for several structurally different thioureas, although N,N'-primaryl alkyl disubstituted thioureas were inert to previously reported di-2-pyridyl thionocarbonate.[1a] Similarly, primary thioamides were cleanly converted into the nitriles at room temperature using di-2-pyridyl sulfite.[7]

Although di-2-pyridyl sulfite is unstable to some extent, several noteworthy features of the reagent are apparent as compared with previously known reagents such as N,N'-sulfinylbisimidazole,[8] 2-halopyridinium salts (Mukaiyama reagent),[9] and triphenylphosphine-diethyl azodicarboxylate (Mitsunobu reagent).[10] First, since 2-hydroxypyridine, generated from the reaction, is an essentially neutral compound, the reactions described herein occur under essentially neutral conditions. For instance, the use of N,N'-sulfinylbisimidazole produces basic imidazole as a byproduct, which might cause some problems in the synthesis of base-sensitive molecules. Second, the present method is much simpler and less laborious than the conventional methods because 2-hydroxypyridine can be completely removed by the usual aqueous workup and does not normally require chromatographic separation in most cases. Therefore, we believe that di-2-pyridyl sulfite should find many useful applications in organic synthesis.

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Table 1. Preparation of N-Sulfinylamines, Nitriles, Isocyanides, and Carbodiimides Using Di-2-pyridyl Sulfite.

Compound	Method[a]	Time, min	Product[b]	Yield, %[c]
$C_6H_5-NH_2$	A	5	$C_6H_5-N=S=O$	90
$p-Cl-C_6H_4-NH_2$	A	5	$p-Cl-C_6H_4-N=S=O$	85
$c-C_6H_{11}-NH_2$[d]	A	5	$c-C_6H_{11}-N=S=O$	88
$(CH_3)_3C-NH_2$	A	5	$(CH_3)_3C-N=S=O$	85
$CH_3(CH_2)_6-CONH_2$	B	5 h	$CH_3(CH_2)_6-CN$	0[e]
$p-CH_3O-C_6H_4-CONH_2$	B	60	$p-CH_3O-C_6H_4-CN$	83
$p-CH_3-C_6H_4-CONH_2$	B	60	$p-CH_3-C_6H_4-CN$	87
$p-Br-C_6H_4-CONH_2$	B	30	$p-Br-C_6H_4-CN$	89
$p-CH_3O-C_6H_4-CH=NOH$	B	10	$p-CH_3O-C_6H_4-CN$	93
$CH_3(CH_2)_7-CH=NOH$	B	10	$CH_3(CH_2)_7-CN$	95
$C_6H_5CH=CH-CH=NOH$	B	30	$C_6H_5CH=CH-CN$	89
$c-C_6H_{11}-NHCHO$	B	15	$c-C_6H_{11}-NC$	78
$C_6H_5CH_2-NHCHO$	B	15	$C_6H_5CH_2-NC$	82
$p-CH_3O-C_6H_4-NHCHO$	B	15	$p-CH_3O-C_6H_4-NC$	70
$o-CH_3-C_6H_4-NHCHO$	B	15	$o-CH_3-C_6H_4-NC$	71
$C_6H_5NH-CS-NHC_6H_5$	A	10	$C_6H_5-N=C=N-C_6H_5$	85
$C_6H_5NH-CS-NH-c-C_6H_{11}$	A	10	$C_6H_5-N=C=N-c-C_6H_{11}$	92
$c-C_6H_{11}NH-CS-NH-c-C_6H_{11}$	A	10	$c-C_6H_{11}-N=C=N-c-C_6H_{11}$	90
$n-C_4H_9NH-CS-NH-n-C_4H_9$	A	10	$n-C_4H_9-N=C=N-n-C_4H_9$	76
$CH_3(CH_2)_6-CSNH_2$	A	20	$CH_3(CH_2)_6-CN$	92
$p-CH_3-C_6H_4-CSNH_2$	A	30	$p-CH_3-C_6H_4-CN$	86
$C_6H_5CH_2-CSNH_2$	A	20	$C_6H_5CH_2-CN$	88
$p-Cl-C_6H_4-CSNH_2$	A	30	$p-Cl-C_6H_4-CN$	83

[a] Method A: in CH_2Cl_2 at room temperature. Method B: in refluxing toluene.

[b] Spectral and physical data of the products are in accord with reported data.

[c] The yields refer to isolated products. [d] $c-C_6H_{11}$ indicates cyclohexyl group.

[e] 88% of the starting material was recovered.

References and Notes

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2. To a stirred solution of 2-hydroxypyridine (2.66 g, 28 mmol) and triethylamine (4.05 ml, 29 mmol) in tetrahydrofuran (80 ml) at 0 °C under nitrogen was slowly added thionyl chloride (1.05 ml, 14.5 mmol). After the reaction mixture was stirred at 0 °C for 1 h, triethylamine hydrochloride was removed by filtration and solvent removal under reduced pressure afforded di-2-pyridyl sulfite (2.84 g, 86%) as a yellow solid. mp 73-74 °C; NMR($CDCl_3$) δ6.80-7.36 (m, 2H), 7.63-8.03 (m, 1H), 8.13-8.40 (m, 1H); IR(KBr) 1665, 1590, 1440, 1250, 1160, 1110, 980, 780 cm^{-1}.
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