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A NEW FORMYLATION REAGENT : 4-FORMYL-2-METHYL-1,3,4-THIADIAZOLIN-5-THIONE.

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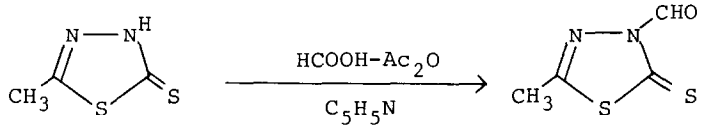
Summary: 4-Formyl-2-methyl-1,3,4-thiadiazolin-5-thione, prepared from acetic formic anhydride, is found to act as a selective formylation reagent under mild conditions. The synthesis of some N-formyl antibiotics with this reagent is reported.

The formylation of amines and alcohols is an important reaction which is used in organic synthesis, and formic acid-Ac_2O[1], formic acid-DDC[2], and N-formylimidazole[3], have been widely used as formylation reagents. In recent years, many useful formylation reagents have been reported[4], but it is necessary to perform the preparation of these reagents under strictly anhydrous conditions and moisture often can cause decomposition at room temperature.

N- or S-acyl derivatives of tautomeric cyclic thioamides such as thiazolin-2-thione[5], mercaptobenzothiazole[6], mercaptobenzoxazole[7], thiadiazolin-5-thione[8], have been utilized for the synthesis of amides and esters. We therefore attemped to synthesize and characterize stable, active formyl compounds of heterocyclic thioamides for use as formylation reagents. In this communication, we describe an N-formyl derivative of 2-methyl-1,3,4-thiadiazolin-5-thione, a new, highly reactive and stable crystalline reagent, and its use for formylation of amines and alcohols under mild conditions. 2-Methyl-1,3,4-thiadiazolin-5-thione(1) is the raw material used in our manufacture of semisynthetic cephalosporins such as cefazolin, therefore we chose this compound as an intermediate of active formyl compound.

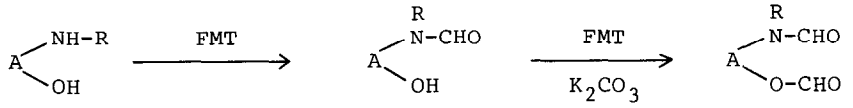


(1) (2) FMT

4-Formyl-2-methyl-1,3,4-thiadiazolin-5-thione(2:FMT) is easily prepared from 2-methyl-1,3,4-thiadiazolin-5-thione(1) and acetic formic anhydride by using a catalytic amount of pyridine in acetone or tetrahydrofuran, and is a stable crystalline compound at room temperature. Formylation of (1) might be expected to give the N- or S-formyl derivatives, but the N-formyl compound is nevertheless obtained with careful control of the reaction conditions. The structure of (2) was assigned on the basis of IR and UV spectra[9].

4-Formyl-2-methyl-1,3,4-thiadiazolin-5-thione(2:FMT). The procedure is as follows.: A solution of acetic formic anhydride, prepared from acetic anhydride (24 g) and formic acid (24 g) at room temperature under stirring for 1 h was added to 2-methyl-1,3,4-thiadiazolin-5-thione (40 g) and pyridine (2 ml) in acetone (100 ml) at 5-10 °C under stirring. After 2 h, diisopropyl ether (100 ml) was added and the precipitate was collected and washed with the same solvent to give the yellow crystalline product, 36.5 g (75 % yield). m.p. 95-96 °C. IR(nujor):cm^{-1}, 1720(C=O), 1720(C=S). NMR($CDCl_3$/TMS):ppm, 2.56(3H,s), 9.53(1H,s), UV(dioxane):λ_{max} nm, 335.

FMT reacts smoothly with primary and secondary amines in suitable solvents at room temperature or chilled conditions, to give a high yield of corresponding N-formyl compound. The formylation of hydroxy compounds requires the presence of a weak base such as potassium carbonate. Both selective N-formylation and N, O-diformylation of amino alcohols were carried out respectively in the absence or presence of potassium carbonate.



Furthermore, the procedure is very simple and the deformylated product(1) can be removed from the reaction mixture by treatment with aqueous solution of K_2CO_3 or addition of hexane or diisopropyl ether.

Illustrative example for the formylation is as follows.: N-formylation. To a solution of N-(2-hydroxyethyl)piperazine (6.5 g, 0.05 mol) in acetone (50 ml) at 0-5 °C was added FMT (8.8 g, 0.055 mol). The reaction mixture was stirred at the same temperature for 1 h and evaporated to dryness under reduced pressure. The residue was treated with water and filtered to remove (1). The filtrate was evaporated and extracted with benzene, dried over anhydrous M_gSO_4. The benzene solution was evaporated to dryness and distilled to afford N-formyl-N'-(2-hydroxyethyl)piperazine, 7.4 g (93 % yield). b.p. 165-170 °C/6-7 torr. IR(CCl_4):cm^{-1}, 3420(OH), 1700(C=O). NMR($CDCl_3$/TMS):ppm, 2.5-2.9(6H,m), 3.4-3.9(6H,m), 6.1(1H,OH), 8.1(1H,s). M^+(158).

N, O-Formylation. To a solution of the above compound (1.5 g, 0.01 mol) and K_2CO_3 (1.38 g, 0.01 mol) in acetone (15 ml) was added FMT (1.76 g, 0.01 mol) and stirred at room temperature for 1 h. After removing the solvent, the residue was extracted with benzene and the solution was washed with aqueous K_2CO_3, water, dried over M_gSO_4, and evaporated. The residue was treated with column chromatography on Merk Kieselgel 60 using CH_2Cl_2 as solvent to give N-formyl-N'-(2-formyloxyethyl)piperazine, 1.38 g (78 % yield). IR(CCl_4):cm^{-1}, 1740, 1690, 1660(shol). NMR($CDCl_3$/TMS):ppm, 2.4-2.9(6H,m), 3.3-3.8(4H,m), 4.2-4.5(2H,t), 8.1-8.2(2H,S). M^+(186).

The results of the formylation are listed in the Table.

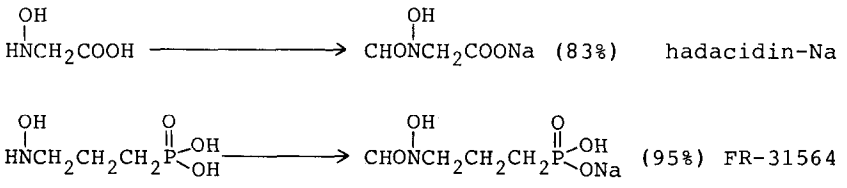
Table Formylation with FMT

RR'NH, ROH	Solvent	Product	Yield(%)[a]
$C_6H_5NH_2$	acetone	C_6H_5NHCHO	87
$2\text{-}ClC_6H_4CH_2NH_2$	acetone	$2\text{-}ClC_6H_4CH_2NHCHO$	85
HN◯NCH$_2$CH$_2$OH	acetone	CHON◯NCH$_2$CH$_2$OH	93
$C_6H_5NHCH_3$	acetone	$C_6H_5N(CHO)CH_3$	84
$C_6H_4(CO)_2NH$	DMF	$C_6H_4(CO)_2NCHO$	83[b]
$4\text{-}NO_2C_6H_4CH_2OH$	acetone	$4\text{-}NO_2C_6H_4CH_2OCHO$	89[b]
CHON◯NCH$_2$CH$_2$OH	acetone	CHON◯NCH$_2$CH$_2$OCHO	78[b]
$C_6H_5CH(OH)COOH$	acetone	$C_6H_5CH(OCHO)COOK$	84[b]

a: Refers to isolated products of 1 h reaction.

b: Carried out with equiv. K_2CO_3.

It is well known that N-formyl-N-hydroxyglycine (hadacidin)[10] is an antitumor antibiotic and 3-(N-formyl-N-hydroxyamino)propylphosphonic acid (FR-31564)[11] is a superior and clinically useful phosphonic acid antibiotic. We applied this selective formylation to the systhesis of hadacidin and FR-31564. N-Hydroxyamino acid was treated with 1.1 mol of FMT in N,N-dimethylformamide (DMF) at room temperature. After 2 h, the solution was treated with 1.1 mol of NaOH-EtOH solution and a high yield of the Na salt was obtained.



In general, formylation reagents are so unstable that formylation must be carried out cautiously. FMT, however, is a very stable crystal at room temperature and for this reason, the reagent in this present study is particularly interesting.

Further studies on the synthetic utility of this reagent are in progress.

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