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The Synthesis of Pyrimidine 1-Oxides: A New Transformation of Amide Oximes

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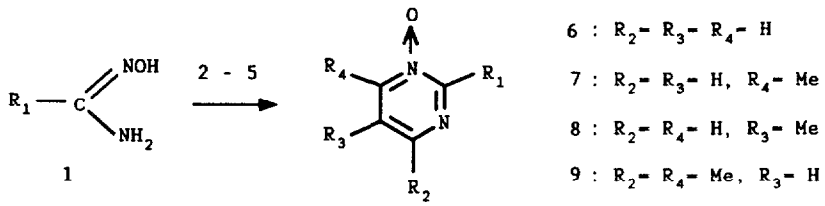
Abstract: The title N-oxides were prepared from several carboxamide oximes on treatment with 1,3-dicarbonyl derivatives.

It is known that aromatic carboxamide oximes react with ethyl or methyl acetoacetate to give 3-aryl-5-acetonyl-1,2,4-oxadiazoles[1], which are also available by another route using diketene instead of acetoacetic ester[2]. Similar products have been isolated on treatment of carboxamide oximes with other β-keto-esters[1e]. Herein, we demonstrate the utility of carboxamide oximes in the construction of pyrimidine N-oxides.

Pyrimidine N-oxides are usually obtained by N-oxidation of the corresponding pyrimidines, using hydrogen peroxide, m-chloroperbenzoic acid (MCPBA), monopermaleic acid, monoperphtalic acid or p-methylperbenzoic acid. Other methods, which include ring closure reactions, ring transformation reactions or conversion of the substituents are also known[3]. In this note we report a novel transformation of carboxamide oximes with 1,3-dicarbonyl compounds or their equivalents, leading to pyrimidine 1-oxides (Scheme). Carboxamide oximes **1** have been treated under acidic conditions with C_3 synthons such as 1,1,3,3-tetramethoxypropane (**2**), 4,4-dimethoxy-2-butanone (**3**), 3-ethoxy-2-methylpropenal (**4**) or 2,4-pentanedione (**5**). Reactions were performed under reflux in the appropriate solvent in the presence of boron trifluoride etherate, acetyl chloride or trifluoroacetic acid, to give pyrimidine 1-oxides **6** - **9**. Some typical examples presented in the Table indicate

that aliphatic, aromatic or heteroaromatic carboxamide oximes could be employed. Furthermore, this transformation is the first method for the synthesis of pyridylpyrimidine N-oxides which could not be prepared by N-oxidation of the appropriate pyridylpyrimidine. It has been shown that the treatment of 4-(4-pyridyl)pyrimidine with MCPBA gave 4-(4-pyrimidyl)-pyridine N-oxide[4].



1

6 - 9

6 : R_2- R_3- R_4- H

7 : R_2- R_3- H, R_4- Me

8 : R_2- R_4- H, R_3- Me

9 : R_2- R_4- Me, R_3- H

R_1

a: 4-pyridyl
b: 3-pyridyl
c: 2-pyridyl
d: phenyl
e: 4-nitrophenyl
f: 4-methoxyphenyl
g: methyl

2: $(MeO)_2CHCH_2CH(OMe)_2$

3: $MeCOCH_2CH(OMe)_2$

4: EtOCH=CMe-CHO

5: $MeCOCH_2COMe$

Scheme

When 2-butanone **3** is used as a C_3 synthon, one can expect the formation of 6-methylpyrimidine 1-oxides **7** or their 4-methyl analogs. The problem has been solved by NMR studies using $Eu(fod)_3$ as a shift reagent. The effect of a lanthanide reagent on the spectra of **7** has been compared with that on the spectra of pyrimidine 1-oxides **6**, **8** and **9**. Larger shift was observed on the 6 position than on the 5 or 4 position of the pyrimidine ring in all cases. This is in agreement with the studies of Yamanaka and coworkers[5,6].

In conclusion, we have developed a convenient route for the synthesis of pyrimidine N-oxides from carboxamide oximes. Our efforts are currently devoted to the extension of this method.

Table[7,8]

Entry	Amide Oxime	C_3-synthon	Reaction Conditions**	Time (h)	Product (Yield)
1	**1a**[9]	2	A	13	**6a** (40%)
2	**1a**	2	F	0.5	**6a** (79%)
3	**1a**	3	A	13	**7a** (53%)
4	**1a**	3	E	8	**7a** (76%)
5	**1a**	4	A	13	**8a** (31%)
6	**1a**	5	B	23	**9a** (14%)
7	**1b**[9]	2	A	13	**6b** (40%)
8	**1b**	3	E	5	**7b** (53%)
9	**1c**[9]	4	D	1	**8c** (75%)
10	**1c**	5	B	8	**9c** (15%)
11	**1d**[10]	2	F	1.5	**6d** (41%)
12	**1d**	2	A	4.5	**6d** (16%)
13	**1d**	3	E	8	**7d** (77%)
14	**1e**[10]	3	D	3	**7e** (76%)
15	**1e**	4	C	9	**8e** (48%)
16	**1e**	5	B	15	**9e** (61%)
17	**1f**[11]	4	D	8	**8f** (38%)
18	**1f**	5	D	13	**9f** (11%)
19	**1g**[10]	2	F	0.5	**6g** (40%)
20	**1g**	2	A	3.5	**6g** (13%)

**Reflux (solvent, catalyst): A: isopropanol, acetyl chloride; B: isopropanol-DMF, acetyl chloride; C: sec-butanol, acetyl chloride; D: isopropanol, trifluoroacetic acid; E: acetonitrile, boron trifluoride etherate; F: toluene-DMF, boron trifluoride etherate.

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7. Typical procedure: Appropriate solvent (25 ml, Table) was treated at room temperature with catalyst (7.5-10 mmol), followed by the addition of the corresponding C_3 synthon **2** - **5** (7.5 mmol) and carboxamide oxime **1** (7.2 mmol). Reaction mixture was heated under reflux, evaporated to dryness, dissolved in water, neutralized with sodium carbonate, extracted with chloroform, dried over anhydrous sodium sulfate and evaporated to dryness. Pyrimidine 1-oxides have been in some cases purified by flash chromatography[12](entries: 1, 2, 3, 4, 6, 10, 11, 12, 13).

Selected data (mp; ^{1}H NMR, 90 MHz, $CDCl_3$): **6a:** mp= 160 - 161 °C; ^{1}H NMR: δ= 8.81(dd, 2H, H-2′ and H-6′, J= 4.6 and 1.7 Hz), 8.36 - 8.56(m, 4H, H-4, H-6, H-3′ and H-5′), 7.33(dd, H-5, J= 6.6 and 4.6 Hz). **6b:** mp= 147 - 150 °C; ^{1}H NMR: δ= 9.71(d, 1H,H-2′, J= 1.7 Hz), 8.97(td, 1H, H-4′, J= 8.3 Hz and 1.7 Hz), 8.74(dd, 1H, H-6′, J= 4.9 and 1.7 Hz), 8.51(dd, 1H, H-6, J= 6.6 and 1.5 Hz), 8.39(dd, 1H, H-4, J= 4.5 and 1.5 Hz), 7.44(dd, 1H, H-5′, J= 8.3 and 4.9 Hz), 7.29(dd, 1H, H-5, J= 6.6 and 4.5 Hz). **7a:** mp= 114 - 116 °C; ^{1}H NMR: δ= 8.79(dd, 2H, H-2′ and H-6′, J= 4.6 and 1.7 Hz), 8.39(dd, 2H, H-3′ and H-5′, J= 4.6 and 1.7 Hz), 8.25(d, 1H, H-4, J= 4.6 Hz), 7.31(d, 1H, H-5, J= 4.6 Hz), 2.6(s, 3H, Me). **7b:** mp= 82 - 84 °C; ^{1}H NMR: δ= 9.77(d, 1H, H-2′, J=2Hz), 9.03(td, 1H,H-4′, J= 8.1 and 2 Hz), 8.8(dd, 1H, H-6′, J= 5.5 Hz), 8.33(d, 1H, H-4, J= 4.6 Hz) 7.46(dd, 1H, H-5′, J= 8.1 and 5.5 Hz), 7.35(d, 1H, H-5, J= 4.6 Hz), 2,63(s, 3H, Me). **7d:** mp= 91 - 95 °C; ^{1}H NMR: δ= 8.43 - 8.50(m, 2H, H-2′ and H-6′), 8.19(d, 1H, H-4, J= 4.3 Hz), 7.45 - 7.52(m, 3H, H-3′, H-4′ and H-5′), 7.21(d, 1H, H-5, J= 4.3 Hz), 2.58(s, 3H, Me). **8a:** mp= 150 - 152 °C; ^{1}H NMR: δ= 8.79(dd, 2H, H-2′ and H-6′, J= 4.6 and 1.7 Hz), 8.25 - 8.44(m, 4H, H-4, H-6, H-3′ and H-5′), 2.38(s, 3H, Me). **8f:** mp= 122 - 125 °C; ^{1}H NMR: δ= 8.61(d, 2H, H-2′ and H-6′, J= 9.0 Hz), 8.19 and 8.35(d, 2H, H-4 and H-6, J= 1.5 Hz), 7.0(d, 2H, H-3′ and H-5′, J= 9.0 Hz), 3.88(s, 3H, OMe), 2.32(s, 3H,Me). **9c:** mp= 115 - 117 °C; ^{1}H NMR: δ= 8.9(dd, 1H, H-6′, J= 5.1 and 1.9 Hz), 8.53(dd, 1H, H-3′, J= 8.0 and 1.2 Hz), 7.87(dt, 1H, H-4′, J= 8.0 and 1.9 Hz), 7.43(ddd, 1H, H-5′, J= 8.0, 5.1 and 1.2 Hz), 7.23(s, 1H, H-5), 2.60(s, 6H, 2x Me). **9e:** mp= 215 - 218 °C; ^{1}H NMR: δ= 8.63(d, 2H, H-2′ and H-6′, J= 9.0 Hz), 7.05(s, 1H, H-5), 6.98(d, 2H, H-3′ and H-5′, J= 9.0 Hz), 3.89(s, 3H, OMe), 2.56 and 2.51 (s, 6H, 2x Me).

8. The structures of all new compounds were confirmed by IR, ^{1}H NMR, MS spectra and by CHN analysis or high resolution mass spectrometric data. Pyrimidine 1-oxides **6d** and **6g** were identical with the samples obtained by known procedure[13].

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