SYNTHESIS OF IMIDAZOLE *N*-OXIDES IN SOLVENT-FREE CONDITIONS

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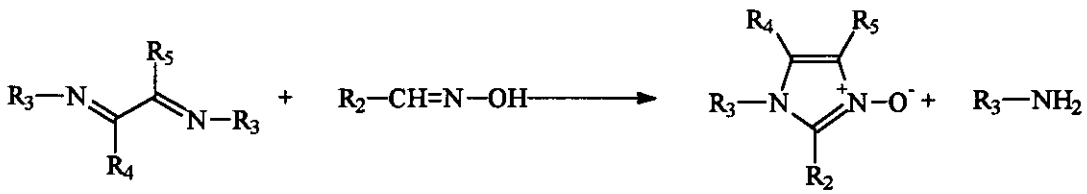
Abstract- Cyclization of 1,2-diimines with oximes was performed under solvent-free conditions using silica gel and aluminum oxide as supports and catalysts. The reaction proceeded under milder reaction conditions to give imidazole *N*-oxides. The *N*-oxides were obtained in higher yields by easier work-up procedure than in the usual reactions performed in solution.

The reaction on a solid support in solvent-free conditions resulted in milder conditions, higher selectivity, a more simple work-up procedure, and higher yields than the corresponding reactions in solution.[1] Since the use of mineral acids can be avoided by employing acidic supports, the solid supported reaction is more safe and cleaner process.[1]

The solid supports like silica gel, alumina, zeolites or clays[2] have been used in a variety of reactions such as oxidations,[3] condensations,[4] alkylations,[4] and cycloadditions.[5] However, only few examples of cyclization reactions on solid supports have been reported.[6]

Recently we described a general procedure for the cyclization of 1,2-diimines with aldoximes in solution to give 3-alkyl or 3-aryl substituted imidazole-1-oxides like ***3a***.[7] The process gives only moderate yields, the

work-up procedure is not simple and the products are sensitive and tend to decompose during work-up. This prompted us to try the cyclization under solvent-free conditions using a solid support which could act as a catalyst.



1a-c ***2a-d*** ***3a-g***

1a R_3=*p*-CH_3-C_6H_4; R_4= R_5=H ***2a*** R_2=H ***3a*** R_2=$PhCH_2$; R_3=*p*-CH_3-C_6H_4; R_4=R_5=CH_3

1b R_3=*p*-CH_3-C_6H_4; R_4=R_5=CH_3 ***2b*** R_2=CH_3 ***3b*** R_2=Ph; R_3=*p*-CH_3-C_6H_4; R_4=R_5=CH_3

1c R_3=Cyclohexyl; R_4=R_5=H ***2c*** R_2=$PhCH_2$ ***3c*** R_2=$PhCH_2$; R_3=Cyclohexyl; R_4=R_5=H

2d R_2=Ph ***3d*** R_2=R_4=R_5=H; R_3=Cyclohexyl

3e R_2=CH_3; R_3=*p*-CH_3-C_6H_4; R_4= R_5=H

3f R_2=R_4=H; R_5=CH_3; R_3=*p*-CH_3-C_6H_4

3g R_2=R_5=H; R_4=CH_3; R_3=*p*-CH_3-C_6H_4

Scheme 1

The reagents were absorbed on the support and stirred in the absence of solvent under the conditions described in Table 1. The imidazole *N*-oxides were isolated and purified by column chromatography.

The yields were influenced by the acidity of the solid support. Aromatic diimines were best cyclized using silica gel as the support. Cyclization of these diimines could not be effected using the more acidic Montmorillonite KSF probably due to protonation of the diimines to give the corresponding unreactive diiminium salts.

The more basic aliphatic diimines were not cyclized by using silica gel. However, neutral or weakly acidic alumina served satisfactorily.

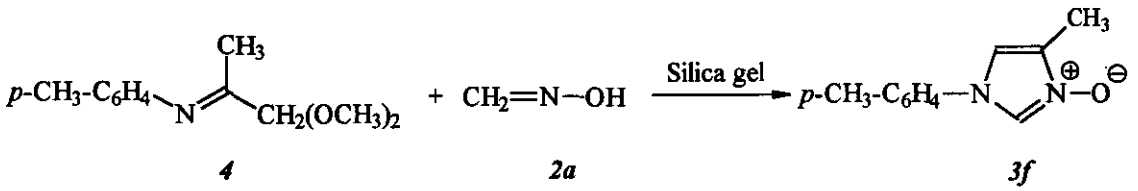
5-Methyl-3-(*p*-tolyl)imidazole-1-oxide ***(3f)*** was obtained by cyclization of 2-(*p*-tolyl)imine-2-oxopropanal dimethylacetal ***(4)***. The selectivity is similar to the observed in solution, with formation of the unexpected *N*-oxide. This result was explained by equilibration between the imine and the oxime [7] and cyclization of

the oxime with formaldehyde and *p*-toluidine as previously described [8] (Scheme 2).

Table 1. Comparison between cyclization of diimines (1a-c) with oximes (2a-e) in the solid phase and in solution.

Diimine	Oxime	*N*-Oxide	Time (T)	Solvent	Acid or support	Ratio[a]	(%)
1b	***2c***	***3a***	8 h (120 °C)	Toluene	CF_3COOH	1:1:4	31[b]
1b	***2c***	***3a***	24 h (20°C)	CH_2Cl_2	Silica gel	1:1:4	31
1b	***2c***	***3a***	24 h (20°C)	none	Silica gel	1:1:4	47
1b	***2d***	***3b***	10 h (120 °C)	Toluene	*p*-CH_3-C_6H_4-SO_3H	1:1:4	traces[b]
1b	***2d***	***3b***	2 h (100 °C)	none	Silica gel	1:1:4	18
1c	***2c***	***3c***	6 h (120 °C)	Toluene	*p*-CH_3-C_6H_4-SO_3H	1:1:0.2	traces
1c	***2c***	***3c***	24 h (20°C)	none	Silica gel	1:1:4	traces
1c	***2c***	***3c***	24 h (20°C)	none	Alumina (pH=3.75)	1:1:4	12
1c	***2a***	***3d***	24 h (20°C)	CH_2Cl_2	-----	1:1	32[b]
1c	***2a***	***3d***	14 h (20°C)	none	Alumina (pH=7)	1:1:4	42
1a	***2a***	***3e***	14 h (20°C)	none	Alumina (pH=7)	1:1:4	36

[a]molar ratio diimine : oxime : acid or support (w/w); [b] reference 7.



4 *2a* *3f*

Scheme 2

The synthesis of imidazole *N*-oxides using supported reagents represents one the first examples of a cyclization reaction of two solid-supported reagents.

In conclusion, cyclization of 1,2-diimines with aldoximes produce higher yields when performed under solvent-free conditions on a solid support than in solution. In addition, the reaction conditions are milder and the work-up procedures simpler by the solid phase method. Finally, the solid phase method permits the synthesis of imidazole-1-oxides devoid of substituents at C-4 and C-5. Such *N*-oxides are very difficulty accessible by other methods, including oxidation of the corresponding imidazoles at the nitrogen atom.

EXPERIMENTAL

The solid supports were purchased from the following sources: silica gel (Merck 60, 70-230 mesh), neutral alumina (Merck 90, 70-230 mesh, activity I), and Montmorrilonite KSF (Aldrich). Acidic alumina, pH = 3.75, was prepared by stirring of neutral alumina with 0.1 M hydrochloric acid (10 mg/g) followed by removal of the water and drying at 150 °C. The pH was determined from a 10 % slurry of the alumina in water using a CRISON micropH 2000 pH meter. The silica gel Merck 60 (70-230 mesh) was used for chromatographic purification.

Cyclizations using benzaldoxime or phenylacetaldoxime

The aldoxime and the diimine were adsorbed on the support by addition of its dichloromethane solution (5 ml/mmol) to the support followed by removal of the dichloromethane *in vacuo*. The supported reagents were stirred with a magnetic stirrer under the conditions stated in Table 1. Subsequent elution and filtration through silica gel (10 g/mmol) followed by removal of the solvent afforded the pure imidazole-1-oxide. In this way, 2,3-dimethyl-1,4-bis(*p*-tolyl)-1,4-diaza-1,3-butadiene ***(1b)*** (264 mg, 1 mmol) and phenylacetaldoxime ***2c*** (135 mg, 1 mmol) on silica gel (1.6 g) followed by elution with ethyl acetate-ethanol (2:1) afforded *2-benzyl-4,5-dimethyl-3-(p-tolyl)imidazole-1-oxide* ***(3a)*** (141 mg, 47%) (R_f= 0.15). mp 113-115°C (from ethyl acetate).[7] Similarly, 2,3-dimethyl-1,4-bis(*p*-tolyl)-1,4-diaza-1,3-butadiene ***(1b)*** (264 mg, 1 mmol) and benzaldoxime ***(2d)*** (121 mg, 1 mmol) on silica gel (1.54 g) followed by elution with ethyl acetate-ethanol (2:1) afforded 2-phenyl-*4,5-dimethyl-3-(p-tolyl)imidazole-1-oxide* ***(3b)*** (50 mg, 18%) (R_f=0.19), mp 165-166°C (from dichloromethane : light petroleum) (Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.7; H, 6.5; N, 10.1. Found: C, 77.4; H, 6.5; N, 10.1). ^{1}H-Nmr δ (ppm) 2.05 (s, 3H, CH_3-4); 2.30 (s, 3H, CH_3-5); 2.39 (s, 3H, CH_3-4'); 7.00-7.24 (AA'BB', *J* = 8 Hz, 4H, H-2', H-3', H-5', H-6'); 7.25-7.28 (m, 3H, H-3'', H-4'', H-5''); 7.52-7.55 (m, 2H, H-2'', H-6''). ^{13}C-Nmr δ (ppm) 7.6 (CH_3-5); 9.5 (CH_3-4); 21.1 (CH_3-4'); 121.9 (C-4); 124 (C-5); 126.5 (C-1''); 127.9 (C-3', C-5'); 128.8 (C-4''); 129.1 (C-2'', C-6''); 130.3 (C-3', C-5'); 132.6 (C-1'); 134 (C-2); 139.4 (C-4'). Similarly, 1,4-dicyclohexyl-1,4-diaza-1,3-

butadiene ***(1c)*** (220 mg, 1 mmol) and phenylacetaldoxime ***(2c)*** (135 mg, 1 mmol) on acidic alumina (pH = 3.75, 1.42 g) followed by elution with ethyl acetate-ethanol (1:1) afforded *2-benzyl-3-cyclohexylimidazole-1-oxide* ***(3c)*** (30 mg, 12 %) (R_f = 0.21), mp 132-133 °C (from ethyl acetate : ether) (Anal. Calcd for $C_{16}H_{20}N_2O$: C, 75.0; H, 7.9; N, 10.9. Found: C, 74.6; H, 7.8; N, 10.8). ^{1}H-Nmr δ (ppm) 1.00-2.20 (m, 10H, 5 CH_2); 3.71 (tt, J = 1.4 and 3.8 Hz, 1H, H-1'a); 4.30 (s, 2H, CH_2); 6.80 (d, J = 1.9 Hz, 1H, H-4); 7.05-7.27 (m, 5H, C_6H_5); 7.28 (d, J = 1.9 Hz, 1H, H-5). ^{13}C-Nmr δ (ppm) 24.6 (C-4'); 25.2 (C-3', C-5'); 27.8 (CH_2); 33.1 (C-2', C-6'); 57 (C-1'); 112.1 (C-4); 120.5 (C-5); 127.1 (C-4''); 128 (C-2'', C-6''); 128.8 (C-3'', C-5''); 135 (C-1''); 136.4 (C-2).

Cyclizations using formaldoxime or acetaldoxime

The diimine was absorbed on the support and the dichloromethane was removed as described above. Then the aldoxime dissolved in ethanol (0.6 ml/mol) was added. Stirring was performed as stated in Table 1 and the mixture worked up as above. In this way, 1,4-dicyclohexyl-1,4-diaza-1,3-butadiene ***(1c)*** (220 mg, 1 mmol) and formaldoxime ***(2a)*** in ethanol (0.6 ml, *ca.* 1 mmol) on neutral alumina (1.3 g) followed by elution with ethyl acetate-ethanol (1:1) afforded *3-cyclohexylimidazole-1-oxide* ***(3d)*** (70 mg, 42 %) (R_f = 0.13). mp 132-133 °C (from ethyl acetate : dichloromethane). [7] Similarly, 1,4-bis(*p*-tolyl)-1,4-diaza-1,3-butadiene ***(1a)*** (236 mg, 1 mmol) and acetaldoxime ***(2b)*** in ethanol (0.6 ml, *ca.* 1 mmol) on neutral alumina (1.48 g) followed by elution with ethyl acetate-methanol (1:1) afforded *2-methyl-3-(p-tolyl)imidazole-1-oxide* ***(3e)*** (67 mg, 36 %) (R_f = 0.22), mp 154-156 °C (from dichloromethane : ethyl acetate) (Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4; N, 14.9 Found: C, 70.4; H, 6.2; N, 14.6). ^{1}H-Nmr δ (ppm) 2.45 (s, 6H, CH_3-2, CH_3-4'); 6.85 (d, J = 2, 1H, H-4), 7.17-7.33 (AA'BB', J = 8.6, 4H, H-2', H-3', H-5', H-6'); 7.27 (d, J = 2, 1H, H-5). ^{13}C-Nmr δ (ppm) 8.8 (CH_3-2), 21.1 (CH_3-4'), 115.6 (C-4), 121.5 (C-5), 125 (C-2', C-6'), 130.5 (C-3', C-5'), 133.9 (C-1'), 134.7 (C-2), 139.6 (C-4'). Similarly, 2-methyl-3-(*p*-tolyl)-3-azapropenal dimethyl acetal ***(4)*** (260 mg, 1 mmol) and formaldoxime ***(2a)*** in ethanol (0.6 ml, *ca.* 1 mmol) on silica gel (1.46 g) followed by elution with ethyl acetate-ethanol (1:1) afforded *5-methyl-3-(p-*

tolyl)imidazole-1-oxide (3f) (56 mg, 30 %) (R_f= 0.25). mp 197-199°C (from dichloromethane).[7]

ACKNOWLEDGEMENT

Financial support from Spanish DGICyT (project PB94-0742) and the Danish Council for Technical and Industrial Research is gratefully acknowledged.

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Received, 12th March, 1996