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PREPARATION OF NITRILES FROM PRIMARY AMIDES UNDER SWERN OXIDATION CONDITIONS

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Abstract: *In order to establish a mild conversion method of primary amides to nitriles, various types of carboxamides were treated under Swern oxidation conditions, $(COCl)_2$-DMSO and Et_3N, as a dehydrating agent to obtain desired nitriles in 75-96% yields.*

In view of their importance as intermediates in organic synthesis,[1] many methods for preparation of nitriles by dehydration of carboxamides, using phosphorus pentoxide,[2] titanium tetrachloride,[3] thionyl chloride,[4] trifluoroacetic anhydride/pyridine,[5] triphenyl phosphine/carbontetrachloride,[6] have been documented in the literature. Recently, alternative reaction conditions and dehydrating reagents providing higher yields, such as diphosgene,[7] (methoxycarbonylsulfamoyl)triethylammonium hydroxide (Burgess reagent),[8] ethyl iodide/silver oxide,[9] acetic anhydride/pyridine,[10] refluxing acetonitrile with formic acid,[11] have been introduced. However, there still exists a need for the development of general and mild methods for this preparation. We report here a practically useful method for this transformation using the "activated" dimethyl sulfoxide (DMSO) species under the so-called Swern oxidation conditions,[12] $(COCl)_2$-DMSO and Et_3N. This oxidation system was reported to be a versatile reagent for oxidation of hydroxy groups and now we have applied it to the useful preparation method of nitriles from primary amides.[13]

$$\mathbf{R\text{-}CONH_2} \xrightarrow[Et_3N]{(COCl)_2\text{-DMSO}} \mathbf{R\text{-}CN}$$

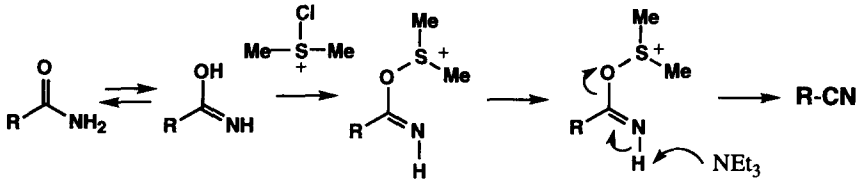
To examine this reaction species, we first optimized the dehydration conditions by using $C_6H_5CH_2CH_2CONH_2$ (**1a**). Initial studies revealed that the combination of DMSO and Et_3N was crucial for the reaction (entries 1, 2). When **1a** was treated with $(COCl)_2$ (1.2 eq.), DMSO (1.6 eq.) and Et_3N (3 eq.) in CH_2Cl_2 at -78 ℃, 87 % yield of hydrocinnamonitrile (**1b**) along with a small amount (2-3 %) of the remaining **1a** was obtained (Table I, entry 3). Complete reaction was achieved by raising the reaction temperature up to room temperature to yield **1b** in 92 % yield (entries 3, 4). Trifluoroacetic anhydride (TFAA) could also be used for the reaction to give **1b** in 85 % yield (entry 5). The use of SO_3•Py[14] as an activator of DMSO also gave nitrile, but **1b** was obtained in only 2 % yield even after 14 h (entry 6). Although Swern oxidation conditions generally require prior preparation of "activated" DMSO species before addition of the substrate, nitrile preparation could be achieved by successively adding $(COCl)_2$ and Et_3N to a mixture of amide and DMSO in CH_2Cl_2 at -78℃, which was then warmed up (if necessary) (entry 7). This is a more convenient experimental operation than the usual Swern oxidation conditions.

Table I. Conversion of $C_6H_5CH_2CH_2CONH_2$ (**1a**) to nitrile under activated DMSO conditions

Entry	Activator, eq.	DMSO, eq.	Et_3N, eq.	Temp.	Time, h	Yield, %[a]
1	$(COCl)_2$, 3	6	0	-78℃	0.25	-[b]
2	$(COCl)_2$, 3	0	9	-78℃	0.25	-[b]
3	$(COCl)_2$, 1.2	1.6	3	-78℃	0.25	87 (3)[c]
4	$(COCl)_2$, 1.2	1.6	3	-78℃ to rt.	1	92
5	TFAA, 1.2	1.6	3	-78℃	0.25	85
6	SO_3•Py, 3.3	5	15	rt.	14	2
7[d]	$(COCl)_2$, 1.2	1.6	3	-78℃ to rt.	1	90

[a] Isolation yield after chromatographic purification. [b] No reaction. [c] Parenthesis shows the recovery yield of the starting material. [d] The reaction was carried out by successive addition of $(COCl)_2$ and Et_3N at intervals of ten minutes to the CH_2Cl_2 solution of carboxamide and DMSO.

We proposed the reaction mechanism and stoichiometry based on these experimental results[15,16] as shown in the following Scheme 1.

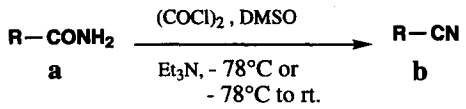


Scheme 1

Although the secondary and tertiary amides were unreactive under these conditions, dehydration of primary amides proceeded to afford high yield of nitriles. This method was applied to several substrates with various functional and protecting groups, such as simple substrates (entries 1-10), sugar derivatives (entries 11,12), protected amino acid derivatives (entries 13-16), tartaric acid derivatives (entries 18-20) and optically active synthetic intermediates (entries 17, 21-25). Table II summarizes the results of dehydration of carboxamides. It is noteworthy that both acid-sensitive (epoxide, acetonide, silyl, NBoc, NcbZ) and alkaline-sensitive groups (Ac, Bz, ester, silyl) were completely unaffected because of the mild reaction conditions. Neither any racemization of the α-carbon nor β-elimination of the nitrile groups were observed by chiral HPLC analyses.[17] Structures of all the products gave satisfactory spectral (^{1}H-NMR, ^{13}C-NMR, and MS) and analytical data (EI and HRMS).

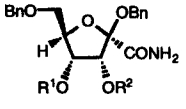
A typical procedure: Preparation of nitrile **25b** (Table II, entry 25). A solution of $(COCl)_2$ (67 μL, 0.77 mmol) in CH_2Cl_2 (0.5 mL) was added to the solution of **25a** (142.0 mg, 0.55 mmol) and DMSO (78 μL, 1.1 mol) in CH_2Cl_2 (1.5 mL) at -78℃. After stirring for 15 min. at -78℃, Et_3N (0.23 mL, 1.65 mmol) was added dropwise to the mixture. After the reaction mixture was stirred for 15 min. at -78℃, the mixture was quenched by addition of water (5 mL). After this mixture was warmed to room temperature, the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), then filtered. Concentration of the filtrate *in vacuo* followed by purification by silica gel column chromatography (hexane/EtOAc, 2/1) and Kugelrohr distillation to gave nitrile **25b** as a colorless oil (123.3 mg, 93 %).[18]

Table II. Conversion of primary amides to nitriles under Swern oxidation conditions

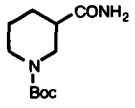


Entry	Amide	$(COCl)_2$, eq.	DMSO, eq.	Et_3N, eq.	Yield, %[a]
1	$C_6H_5CH_2CH_2CONH_2$ (**1a**)	1.2	1.6	3.0	90[c]
2	Cl_3CCONH_2 (**2a**)	1.2	1.6	2.4	86
3	c-$C_6H_{11}CONH_2$ (**3a**)	1.2	3.5	3.0	80
4	*trans*-Cinnamide (**4a**)	1.2	1.4	2.4	80
5	$C_6H_5CCCONH_2$ (**5a**)	1.2	1.6	3.0	84
6	4-$MeOC_6H_4CONH_2$ (**6a**)	1.2	1.6	3.0	93
7	2,6-$Cl_2C_6H_3CONH_2$ (**7a**)	1.2	1.6	3.0	87
8	3,5-$(O_2N)_2C_6H_3CONH_2$ (**8a**)	3.0	6.0	9.0	93
9	2-Naphthalenecarboxamide (**9a**)	1.2	1.8	3.0	83
10	Nicotinamide (**10a**)	1.5	2.5	3.0	75
11	**11a**	1.2	3.5	3.0	95
12	**12a**	1.2	1.6	3.0	94
13	**13a**	1.2	1.6	3.0	89
14	**14a**	1.2	1.6	3.0	66 (16)[b]
15	**15a**	1.3	1.7	3.2	81
16	**16a**	1.2	6.4	7.1	Mess
17	**17a**	1.2	1.6	3.0	87[c]
18	**18a**	2.5	4.0	6.0	80
19	**19a**	1.5	2.0	3.0	94
20	**20a**	1.5	3.0	4.5	91
21	**21a**	1.5	2.0	3.0	90[c]
22	**22a**	1.5	2.0	3.0	91[c]
23	**23a**	1.5	2.0	3.0	75[c]
24	**24a**	1.4	2.0	3.0	96[c]
25	**25a**	1.5	2.0	3.0	93[c]

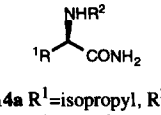
[a] Isolation yield after chromatographic purification. [b] Parenthesis shows the recovery yield of the starting material. c Reaction run at -78°C.



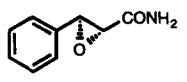
11a R^1=R^2=CMe_2
12a R^1=R^2=Ac



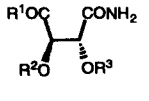
13a



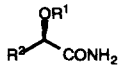
14a R^1=isopropyl, R^2=cbZ
15a R^1=Ph, R^2=Boc
16a R^1=isopropyl, R^2= H



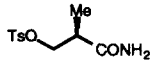
17a



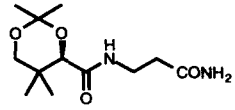
18a R^1=NH_2, R^2=R^3=TBDPS
19a R^1=NMe_2, R^2=R^3=Bz
20a R^1=OEt, R^2=R^3=Ac



21a R^1=Ac, R^2=Ph
22a R^1=Ac, R^2=CH_2CH_2Ph
23a R^1=TMS, R^2=CH_2CH_2Ph



24a



25a

In conclusion, the method presented in this report is believed to be operationally simple and useful for the conversion of primary amides to nitriles as well as oxidation of alchols to carbony compounds. The dehydration of other functional groups, such as aldoxime, urea and carbamate, and more mechanistic details will be reported in due course.

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13. We have observed before that the amide alcohol was easily converted into the nitrile aldehyde under Swern oxidation conditions in the synthetic study of (±)-Epiderstatin, Ubukata, M.; Sonoda, T.; Isono, K. *Natural product Letters*, **1992**, *1*, 149.
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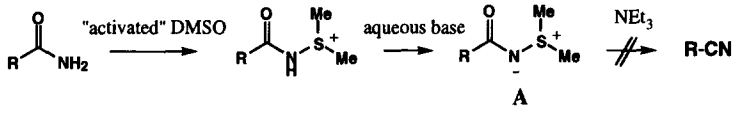
15. We observed interesting results concerning this reaction mechanism. The *anti*-oxime gave nitrile in moderate yield under the same reaction conditions for amide while the *syn*-oxime gave no reaction product at -78℃.
16. Swern reported the formation of iminosulfuranes **A** from "activated" DMSO reagents and carboxamides under aqueous alkaline base conditions.[12d,e] However, isolated 4-nitrobenziminosulfurane, mp. 219.5-222.0℃ [lit[12c]. mp. 220-223℃], prepared from 4-nitrobenzamide and DMSO "activated" by TFAA was not converted into 4-nitrobenzonitrile by the treatment of Et_3N.



A

Vorbruggen *et al.* also discussed the mechanism of the *N*-chlorosulfonylamide into the corresponding nitriles by the treatment of Et_3N. Vorbruggen, H; Krolikiewicz, K. *Tetrahedron*, **1994**, *50*, 6549.
17. The enantiomeric excess (ee %) was monitored by HPLC system [GILSON FastPCLC, and measurement of UV 254 nm absorbance] by comparison of retention time with synthetic racemic samples. ᵗR-(*2R,3S*-**17b**, 26.0 min, ᵗR-(*2S, 3R*-**17b**, 31.8 min (Daicel Chiralcel 25 cm OJ 10 mm, hexane/^{i}PrOH, 98/2, 0.8 mL/min.); ᵗR-(*R*)-**21b**, 9.2 min., ᵗR -(*S*)-**21b**, 11.0 min. (Daicel Chiralcel 15 cm OD-H 10 mm, hexane/^{i}PrOH, 99/1, 1.0 mL/min.); ᵗR-(*S*)-**22b**, 11.4 min.; ᵗR-(*R*)-**22b**, 12.6 min. (Daicel Chiralcel 15 cm OD-H 10 mm, hexane/^{i}PrOH, 97/3, 0.8 mL/min.).
18. Data for (+)-**25b**: $[\alpha]^{D}_{22}$ = + 44.9° (*c* = 1.0, $CHCl_3$); IR (neat, cm^{-1}) 3378 (m, NH), 2994 (m), 2957 (m), 2251 (w), 1673 (s), 1526 (s), 1379 (s), 1260 (s), 1223 (m), 1198 (s), 1161 (m), 1100 (s), 1049 (m); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.00 (1H, br d, NH), 4.13 (1H, s, HC(5)), 3.71 (1H, d, *J* = 11.7, HC(7)), 3.65-3.56 (1H, m, HC(3)), 3.56-3.46 (1H, m, HC(3)), 3.32 (1H, d, *J* = 11.7, HC(7)), 2.72-2.60 (2H, m, HC(2)), 1.50 (3H, s, Me), 1.46 (3H, s, Me), 1.06 (3H, s, Me), 1.03 (3H, s, Me); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 170.4, 117.9 (CN), 99.1, 77.0, 71.2, 34.9, 32.9, 29.3, 21.9, 18.8, 18.6, 18.1; Anal. Calcd for $C_{12}H_{20}N_2O_3$ (240.30): C, 59.98; H, 8.39; N, 11.66. Found: C, 60.13; H, 8.45; N, 11.46.

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