A new mild and selective method for oxidation of primary and secondary alcohols and amines, as well as amino acids, using a modification of Swern, Pfitzner–Moffatt and Corey–Kim

Stanislav Bayryamov

A new mild and selective method for oxidation of primary and secondary alcohols and amines, as well as amino acids, using a modification of Swern, Pfitzner-Moffatt and Corey-Kim: *The paper reveals the successful and efficient, wide functional group tolerate and selective method for oxidation of primary and secondary alcohols, amines and amino acids, using TBTU/DMSO/triethylamine as reagents for the synthesis and dichloromethane (CH_2Cl_2) as a solvent. The specific conditions, employing in the synthetic procedure has been described. The results will enable to develop and apply the methodology for successful and convenient sugar-, nucleoside- and nucleotide- aldehydes and ketones preparation. Moreover the protocols will allow for the selective and elegant production of imines of natural amino acids to be used as structural units for the synthesis of modified peptides and peptidomimetics.*

Key words: *Mild, Effective and Selective Oxidation; Primary and Secondary Alcohols and Amines; Amino Acids; TBTU; DMSO; triethylamine.*

INTRODUCTION

The main existing problem for the preparation of aldehydes, ketones and imines consists in the difficult finding and limited (confined) access of mild, effective and selective catalysts and procedures for alcohols and amines oxidation. In the classical method for selective and mild type of alcohol oxidation named Swern oxidation **(Fig.1)**, developed by Daniel Swern, the author described this process as a chemical reaction whereby a primary or secondary alcohol is oxidized to an aldehyde or ketone using oxalyl chloride, dimethyl sulfoxide (DMSO) and an organic base, where the most commonly used between them is a triethylamine [1-7] . The Swern oxidation of alcohols avoids the use of toxic metals such as chromium (as in the method of Jones oxidation, which is a chemical reaction described as the chromic acid oxidation of primary and secondary alcohols to carboxylic acids and ketones, respectively, and where the Jones reagent - a solution of chromium trioxide in concentrated sulfuric acid - is used as the oxidizing agent), and can be carried out under very mild conditions. This reaction allows for the preparation of aldehydes and ketones from primary and secondary alcohols, respectively [1-7]. Aldehydes do not react further to give carboxylic acids. A drawback is the production of the malodorous side product dimethyl sulphide. In some cases, the use of triethylamine as the base can lead to epimerisation at the carbon alpha to the newly formed carbonyl. Using the bulkier base diisopropylethylamine (i-Pr_2NEt, Hünig's base) can mitigate this side reaction. The reaction is known for its mild character and wide tolerance of functional groups. In this reaction, a dimethylchlorosulfonium chloride as an activated complex is formed, which is revealed to act as an actual oxidative unit. Dimethylchlorosulfonium ion is generated in situ from DMSO and oxalyl chloride. The first step of the Swern oxidation is the low-temperature reaction of dimethyl sulfoxide (DMSO), with oxalyl chloride. The first intermediate quickly decomposes giving off CO_2 and CO and producing dimethylchlorosulfonium chloride. After addition of the alcohol at -78°C, the dimethylchlorosulfonium chloride reacts with the alcohol to give the key alkoxysulfonium ion intermediate: alkoxysulfonium chloride. The addition of at least 2 equivalents of base — typically triethylamine, or in the case of using of optivally active primary or secondary alcohols, as well as natural amino acids - diisopropylethylamine: i-Pr_2NEt — will deprotonate the alkoxysulfonium ion to give the sulfur ylide. In a five-membered ring transition state, the sulfur ylide decomposes to give dimethyl sulfide and the desired ketone or aldehyde. In another modification of the Swern oxidation – where trifluoroacetic anhydride is used instead of oxalyl chloride, a dimethyl trifluoracetyl sulfoxonium trifluoracetate is formed as an activated complex, initializing the alcohol oxidation. The reaction conditions allow oxidation of acid-sensitive compounds,

which might decompose under the acidic conditions of a traditional method such as Jones oxidation. Other methods for the activation of DMSO are the use of carbodiimides – in the Pfitzner–Moffatt oxidation procedure **(Fig.2)** [6-9], pyridine-sulfur trioxide complex – by the Parikh-Doering oxidation protocols **(Fig.3)** [6, 7, 10], and the activated intermediate ("active DMSO" species): N-succinimide ether of dimethyl sulfoxide (N-succinimide dimethyl sulfoxide ether, dimethyl sulfoxonium N-succinimidate), which can be prepared from dimethyl sulfide and N-chlorosuccinimide (NCS) or N-bromosuccinimide, and that species is used for the activation of the alcohol – in the Corey-Kim oxidation methodology **(Fig.4)** [11-14]. When using oxalyl chloride as the dehydration agent, the reaction must be kept colder than -60 °C to avoid side reactions. With trifluoroacetic anhydride instead of oxalyl chloride, the reaction can be warmed to -30 °C without side reactions. Although the Corey–Kim oxidation possesses the distinctive advantage over Swern oxidation of allowing an operation above –25 ºC, it is not so commonly used because of the need to employ dimethyl sulfide, a poisonous and volatile liquid with a very bad odor. In the Parikh-Doering oxidation, the procedure can be run at temperatures close to ambient (usually 0°C) without formation of significant amounts of methylthiomethyl ether side product, whereas in our developed procedure, the reaction starts at 0°C and with the time course, it rises (increases) mildly and slowly to a room temperature (resembling the Parikh-Doering oxidative procedure). All of these reactions have been largely abandoned for the Swern oxidation, which gives higher yields with fewer side products. Under Corey-Kim conditions allylic and benzylic alcohols have a tendency to evolve to the corresponding allyl and benzyl chlorides unless the alcohol activation is very quickly followed by addition of triethylamine. In fact, Corey-Kim conditions - with no addition of triethylamine - are very efficient for the transformation of allylic and benzylic alcohols to chlorides in presence of other alcohols.

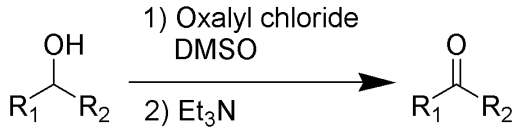


Fig.1. General reaction scheme for the method of Swern oxidation of primary and secondary alcohols, using oxalyl chloride, DMSO and triethylamine as reagents.

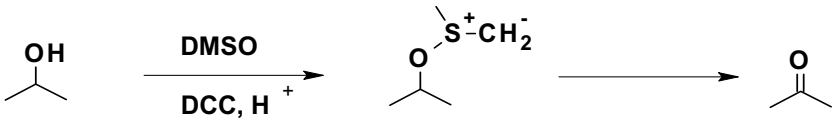


Fig.2. Scheme for the procedure of Pfitzner–Moffatt oxidation of primary and secondary alcohols, using DCC, instead of oxalyl chloride and using DMSO in acidic reaction media.

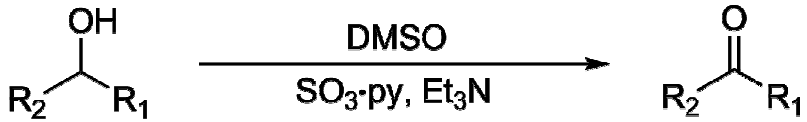


Fig.3. General scheme for Parikh-Doering oxidation of primary and secondary alcohols, using pyridine-sulfur trioxide complex (SO_3.py) instead of oxalyl chloride, and using DMSO and triethylamine as reagents.

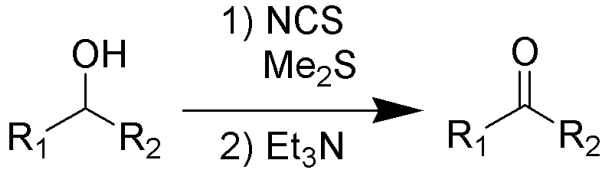


Fig.4. Reaction scheme for the procedure of Corey-Kim oxidation of primary and secondary alcohols, using N-clorosuccinimide, dimethyl sulfide and triethylamine as reagents.

In variance with other alcohol oxidation using "activated DMSO," the reactive oxidizing species is not generated by reaction of DMSO with an electrophile. Rather, it is formed by oxidation of dimethyl sulfide with an oxidant (NCS).

In this paper we present and describe a new method for oxidation of primary and secondary alcohols and amines, as well as amino acids, prepared in good yields (65-90%), to be used as reagents in the organic (peptide-, carbohydrate-, nucleoside-, nucleotide- and oligonucleotide chemistry) synthesis [15-21], using successful effective and selective, mild and elegant procedure, whose protocols may be applied for industrial purposes **(Fig.5)**. The procedure consists in the using of TBTU/DMSO as reagents for the preparation of initially oxidative complex (complex with oxidative capacity), and triethylamine as organic base **(Fig.6)**. In the case of utilization of optically active alfa-carbon atom to the newly formed carbonyl or imine, or carbonyl atom located at a beta-position near the oxidizing functional group (hydroxyl group or amino group) diisopropylethylamine (i-Pr_2NEt) is used as organic tertiary base. Also, in the case of natural amino acids oxidizing - diisopropylethylamine as a base is used also.

EXPOSITION

Materials and methods

All reagents and solvents were purchased and used without further purification. TLC analyses were performed on silica plates UV_{260}, purchased from Merck, using the following solvent systems: system A - CH_2Cl_2 : CH_3OH-9:1; system B - CH_2Cl_2 : CH_3OH-9,5:0,5 (19:1); system C – hexane : ethyl acetate-2:3; system D – hexane : ethyl acetate-3:7; system E – hexane : ethyl acetate-1:1; system F – hexane : ethyl acetate-3:2; system G – hexane : ethyl acetate-7:3; system H – hexane : ethyl acetate-8:2. For the spots labeling and virtual detection on TLC plates, a 5% solution of H_2SO_4 in methanol or ethanol was employed, also – an alcohol solution of ninhydrin was used, as well as a solution of phosphorus-molybdenum acid. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II+ 600MHz spectrometer using BBO or TBI probeheads. Chemical shifts are expressed in ppm and coupling constants in Hz. The precise assignments of the ^{1}H and ^{13}C NMR spectra were accomplished by measurement of 2D homonuclear correlation (COSY), DEPT-135 and 2D inverse detected heteronuclear (C–H) correlations (HSQC and HMBC). Chemical shifts are reported in δ (ppm). The analysis of first order multiplets in ^{1}H NMR spectra was speed up by the use of FAFOMA program [22]. The elemental analysis was carried out and organic compounds were determined using the automatic analyzers: *Carlo Erba* Elemental *Analyzer* Model 1106 with automatic sampler for 53 samples (Carlo Erba, Milan, Italy) and **Perkin-Elmer** Elemental **Analyzer** Model 240 (Perkin-Elmer Corp., Norwalk, Connecticut).

Experimental procedure

A general working procedure for the preparation of aldehydes and ketones from primary and secondary alcohols, as well as imines from primary or secondary amines and natural amino acids.

To a solution of 1 equiv. TBTU in DMSO/CH_2Cl_2* at $0^0C^{Ø}$ – 1 equiv. of alcohol (primary or secondary) or nucleoside (nucleotide) and 2 equiv. of triethylamine were added. When an optically active alcohol or amine (amino acid ester or amide) was used, the DIPEA (diisopropylethylamine: i-Pr_2NEt) was employed as a base to avoid the undesired side epimerization reactions. The reaction mixture was slowly leaved and allowed to increase to room temperature and thus was allowed to stand at a room temperature for 24 hours^{Ø}. After the reaction was complete (TLC), the mixture was diluted with CH_2Cl_2 and washed 3 times with 0,5 N HCl, 3 times with saturated solution of $NaHCO_3$ (10% $NaHCO_3$) and brine^. In the case of amine or amino acid oxidation - the reaction mixture was washed by the same manner, with exception of acid solution. After that, the organic phase was dried over Na_2SO_4 or $MgSO_4$ and evaporated under vacuo. Also the reaction product (aldimine or ketimine, as well as alfa-imine of the methyl ester or alfa-imine of the amide of an amino acid) was able to be purified by washing of the organic phase 2-3 times with 0,2 N HCl or diluted solution of $NaHSO_4$, and then – by alkalization of the combined water phases and extraction with organic solvent. However, sometimes, when we used this purification procedure, the reaction products were disturbed.

***** Sometimes pure DMSO was added instead of the mixed solvent mixture (DMSO/CH_2Cl_2). In the case of oxidation of alcohols, which oxidative products have had low boiling points (acetaldehyde, acetone), only DMSO was presented in the reaction as a solvent and at the same time as a reagent, to avoid the complication of the working-up procedure.

Ø When we used ethyl alcohol as starting reagent, the reaction was carried out at 0^0C to avoid the acetaldehyde evaporation from reaction mixture, which was obtained as a reaction product (B.p.- 20,2 °C). In the case – to prepare the pure product, only distillation of the product from the reaction mixture was sufficient.

^ When easily evaporated aldehydes or ketones, with low boiling points (acetaldehyde, acetone) were prepared as reaction products, they were only distilled from the reaction mixture.

Acetaldehyde: Yield: 28.634g (38.338ml, d_4^{20}=0.788 g/cm^3), (65%), b.p. = 20.2 °C, **^{1}H NMR (600 MHz, $CDCl_3$, 25°C):** δ=2.207(d, 3H, CH_3), 9.789(m, 2.9 Hz, 1H, CHO). **^{13}C NMR (150 MHz, $CDCl_3$, 25^0C):** δ=30.89(CH_3), 199.94(CHO). Elemental analysis: Anal. Calculated for C_2H_4O: (M_w = 44.053g/mol); C-54.545%, H-9.091%; found: C- 54.467%, H-8.984%.

Benzaldehyde: Yield: 85.96g (82.535ml, d_4^{20}=1.0415 g/cm^3), (81%), b.p. = 178.1 °C, **^{1}H NMR (600 MHz, $CDCl_3$, 25°C):** δ=7.514(dt, 2H, 3-CH and 5-CH), 7.603(t, 1H, 4-CH), 7.871(dd, 2H, 2-CH and 6-CH), 10.002(s, 1H, CHO). **^{13}C NMR (150 MHz, $CDCl_3$, 25^0C):** δ = 128.97(3-CH, 5-CH), 129.68(2-CH, 6-CH), 134.45(4-CH), 136.49(1-CH), 192.22(CHO). Elemental analysis: Anal. Calculated for C_7H_6O: (M_w = 106.124g/mol); C-79.245%, H-5.66%; found: C-78.931%, H-5.617%.

2',3'-O-Isopropylidene-N^6-[Bz(NO_2)]-5'- Oxo Adenosine: Yield: 358.179g (79%). Rf-0.343 (system A), Rf-0.276 (system B), Rf-0.125 (system C), Rf-0.413 (system D). **^{1}H NMR (600 MHz, DMSO-d6, 25°C):** δ = 1.322(s, 3H, CH_3) and 1.542(s, 3H, CH_3), 4.210(dt, J=2.6, 4.8 Hz, 1H, 4'-H), 4.959(dd, J=2.4, 6.1 Hz, 1H, 3'-H), 5.336(dd, J=3.1, 6.1 Hz, 1H, 2'-H), 6.114(d, J=3.1 Hz, 1H, 1'-H), 8.105(d, J=8.8 Hz, 2H, 3-CH and 5-CH), 8.149(s, 1H, 2-H), 8.334(d, J=8.8 Hz, 2H, 2-CH and 6-CH), 8.341(s, 1H, 8-H), 9.396(s, broad, 1H, 6-NH), 9.734 (s, 1H, 5`-CH, CHO). **$^{13}$C NMR (150 MHz, DMSO-d6, 25°C):** $\delta$ = 25.14($CH_3$), 27.04($CH_3$), 77.37(C), 81.31(3`-CH), 83.15(2`-CH), 86.28(4`-CH), 89.56(1`-CH), 113.01(C), 119.04(5-C), 123.48(3-CH and 5-CH), 128.92(2-CH and 6-CH), 139.54(1-C), 139.66(8-CH), 148.75(4-C), 149.05(4-C), 152.61(2-CH), 156.10(6-C), 169.94(NHCO), 192.74(5`-CH, CHO). Elemental analysis: Anal. Calculated for C_2H_4O: (M_w = 453.391g/mol); C-52.983%, H-3.779%, N-18.536%; found: C-52.768%, H-3.725%, N-18.398%.

Acetone: Yield: 51.691g (65.225ml, d_4^{20}=0.7925 g/cm^3), (89%), b.p. = 56.53 °C, **^{1}H NMR (600 MHz, $CDCl_3$, 25°C):** δ =2.165(s, 6H, $2CH_3$). **^{13}C NMR (150 MHz, $CDCl_3$, 25^{0}C):** δ =28.23(CH_3), 29.82(CH_3), 206.55(CO). Elemental analysis: Anal. Calculated for C_3H_6O: (M_w = 58.08g/mol); C-62.069%, H-10.345%; found: C-62.023%, H-10.017%.

Acetaldimine: Yield: 31.009g (72%). Rf-0.743 (system A), Rf-0.676 (system B), Rf-0.535, (system C), Rf-0.634 (system D), Rf-0.429 (system E), Rf-0.395 (system F), Rf-0.167 (system G), Rf-0.133 (system H). **^{1}H NMR (600 MHz, $CDCl_3$, 25°C):** δ =2.174(d, 3H, CH_3), 9.135(m, J = , 2.9 Hz, 1H, CH=N), 9.945(s, broad, 1H, C=NH). **^{13}C NMR (150 MHz, $CDCl_3$, 25^{0}C):** δ=29.08(CH_3), 193.34(CHNH). Elemental analysis: Anal. Calculated for C_2H_5N: (M_w = 43.068g/mol); C-55.814%, H-11.628%, N-32.558%; found: C-55.334%, H-11.478%, N-32.323%.

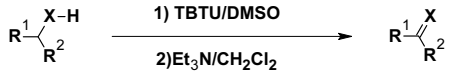
Benzaldimine: Yield: 78.854g (75%). Rf-0.786 (system A), Rf-0.712 (system B), Rf-0.643, (system C), Rf-0.694 (system D), Rf-0.581 (system E), Rf-0.436 (system F), Rf-0.323 (system G), Rf-0.256 (system H). **^{1}H NMR (600 MHz, $CDCl_3$, 25°C):** δ=7.298(dt, 2H, 3-CH and 5-CH), 7.536(t, 1H, 4-CH), 7. 781(dd, 2H, 2-CH and 6-CH), 8.992(s, broad, 1H, CH=N), 9.968(s, broad, 1H, C=NH). **^{13}C NMR (150 MHz, $CDCl_3$, 25^{0}C):** δ = 128.33(3-CH, 5-CH), 129.04(2-CH, 6-CH), 133.92(4-CH), 136.01(1-CH), 183.47(CHNH). Elemental analysis: Anal. Calculated for C_7H_7N: (M_w = 105.139g/mol); C-79.967%, H-6.711%, N-13.322%; found: C-79.876%, H-6.703%, N-13.216%.

Acetonimine: Yield: 39.396g (69%). Rf-0.817 (system A), Rf-0.802 (system B), Rf-0.651, (system C), Rf-0.765 (system D), Rf-0.742 (system E), Rf-0.402 (system F), Rf-0.342 (system G), Rf-0.315 (system H). **^{1}H NMR (600 MHz, $CDCl_3$, 25°C):** δ =1.986(s, 3H, CH_3), 2.017(s, 3H, CH_3). **^{13}C NMR (150 MHz, $CDCl_3$, 25^{0}C):** δ =26.76(CH_3), 27.33(CH_3), 189.98(CNH). Elemental analysis: Anal. Calculated for C_3H_7N: (M_w = 57.095g/mol); C-63.158%, H-12.281%, N-24.561%; found: C-62.987%, H-12.269%, N-24.492%.

2-propionimine methyl ester (methyl ester of 2-iminopropionic acid): Yield: 90.95g (90%). Rf-0.822 (system E), Rf-0.706 (system F), Rf-0.456 (system G), Rf-0.373 (system H). **^{1}H NMR (600 MHz, DMSO-d6, 25°C):** δ =1.463(s, 3H, 3-CH_3), 3.623(s, 3H, OCH_3), 8.983(s, broad, 1H, C=NH). **^{13}C NMR (150 MHz, DMSO-d6, 25°C):** δ=21.33(3-CH_3), 38.98(2-C), 52.55(OCH_3), 175.32(1-C, $COOCH_3$). Elemental analysis: Anal. Calculated for $C_4H_7NO_2$: (M_w = 101.055g/mol); C-45.542%, H-6.932%, N-13.86%; found: C-45.467%, H-6.856%, N-13.802%.

RESULTS AND DISCUSSION

To verify and to prove our predicted and proposed statements we carried out model reaction with model substrates, using our originally developed procedure, whose representative from each class of compounds exists. In the case of examination of the possibility of oxidation of primary alcohols we investigated our methodology, using ethyl and benzyl alcohol, whereas when we tried to obtain 5'-oxo nucleoside by oxidation of primary carbon atom at the 5'-position of nucleoside as a model reaction for preparation of nucleoside analogues – we used 2',3'-O-isopropylidene-N^6-(p-nitrobenzoyl)-Adenosine (2',3'-O-isopropylidene-N^6-[Bz(NO_2)]-adenosine) as a starting substrate.



X = O or NH

R^1 = COOH or H or alkyl residue

R^2 = amino acid residue or H or alkyl residue

Fig.5. Reaction scheme for oxidation of primary and secondary alcohols and amines, as well as amino acids, using TBTU, dimethyl sulfoxide and triethylamine as reagents, whereas dichloromethane was used as a reaction media.

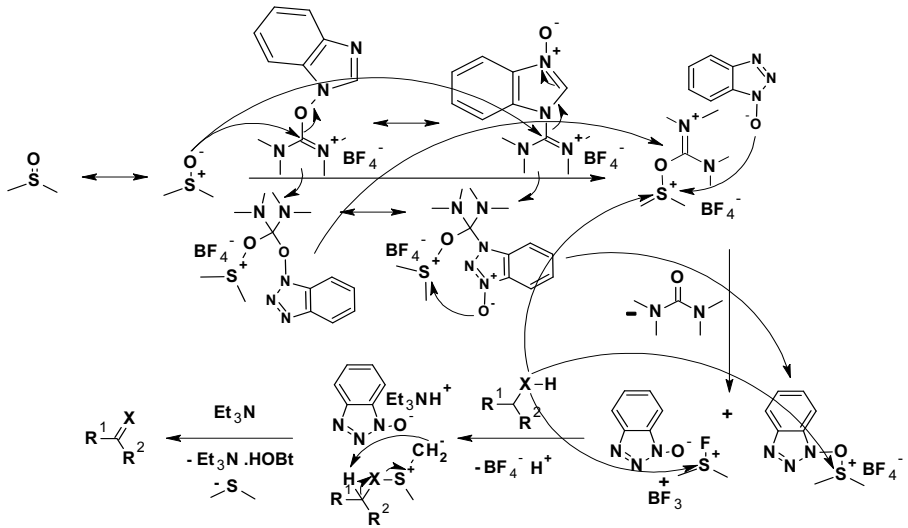


Fig.6. A proposed reaction mechanism for oxidation of primary and secondary alcohols and amines as well as amino acids, using TBTU, dimethyl sulfoxide and triethylamine as reagents, whereas dichloromethane was used as a reaction media.

As a model substrate for reaction of oxidation of secondary alcohols (for preparation of ketones) we used isopropanol, to obtain acetone as a reaction product. For preparation of aldimines and ketimines, as well as for the preparation of alfa-imines of natural amino acids we used ethylamine, benzylamine, isopropyl amine (for the preparation of imines) and natural alfa-amino acid as its ester: L-alanine methyl ester – for the preparation of alfa-imines of methyl esters of natural amino acids. The reaction products: acetaldehyde and acetone - were avoided from reaction mixture only by distillation, and thus they were obtained in pure form. Acetaldimine, benzaldimine, acetonimine, methyl ester of 2-iminopropionic acid were obtained in pure appearance by washing of the organic phase 2-3 times with 0,2 N HCl or diluted solution of $NaHSO_4$, and then – by alkalization of the combined water phases and extraction with organic solvent, which was dried over Na_2SO_4 or $MgSO_4$ and evaporated in vacuo. In another cases the mixture was worked up by dilution with CH_2Cl_2 and by washing of organic phase 3 times with 0,5 N HCl, 3 times with saturated solution of $NaHCO_3$ (10% $NaHCO_3$) and brine. The organic phase was dried over Na_2SO_4 or $MgSO_4$ and evaporated under vacuo. In the case of amine or amino acid oxidation - the reaction media was washed by the same manner except the rinse of the mixture with diluted acid. Thus the reaction products were obtained in pure form, good yields and without additionally purification. The yields of reaction products were good to excellent (65-90%). They may be used as structural elements for carbohydrate and oligonucleotide synthesis (standard and modified) as well as for the synthesis of modified peptides and peptidomimetics.

CONCLUSION

1. A new mild and selective method for oxidation of primary and secondary alcohols and amines, as well as amino acids, using a modification of Swern, Pfitzner–Moffatt and Corey–Kim, was discovered and developed.

2. It allows the efficient, elegant and low-cost preparation of imines and carbonyl compounds at 0^0C at the beginning of the reaction, which increases to a room temperature with the time course, and which is an advantage over the standard Swern procedure.

3. The methodology can be employed for a large-scale sugar-, nucleoside- and nucleotide- aldehydes and ketones preparation, to be used as structural units for linkers, as well as for carbohydrate and oligonucleotide synthesis. Moreover the prepared alfa-imines of natural amino acids may be used as structural fragments (monomers) for the synthesis of modified peptides and peptidomimetics.

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ABOUT THE AUTHOR

Assist. Prof. Dr. Stanislav G. Bayryamov, Department of “Repairing, Reliability and Chemical Technologies”, Agrarian and Industrial Faculty, University of Ruse “Angel Kanchev”, Phone: 082-888 228, 082-888 459, email: sbayryamov@uni-ruse.bg

Докладът е рецензиран.