Nicotinium Dichromate (= 3-Carboxypyridinium Dichromate; NDC) as an Efficient Reagent for the Oxidative Deamination of Amines and Aminophosphonates

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A new method for the efficient synthesis of aldehydes, ketones, and oxophosphonates from various types of amines (primary and secondary) and aminophosphonates *via* oxidative deamination by nicotinium dichromate (= 3-carboxypyridinium dichromate; NDC) is described.

Introduction. – Nicotinium dichromate (= 3-carboxypyridinium dichromate; $(C_5H_5N–COOH)_2Cr_2O_7$; NDC) is easily prepared by the reaction of nicotinic acid (= pyridine-3-carboxylic acid) with CrO_3 in H_2O [1]. It is a stable, cheap, and easily handled compound. In conjunction with our interest in the development of new oxidation methods for the synthesis of carbonyl compounds from readily available precursors, we recently have reported NDC as an efficient oxidizing agent for the oxidation of hydroxyphosphonates to oxophosphonates [2]. In this connection, we wish to introduce herein a simple, new, and efficient protocol for the selective oxidation of amines and aminophosphonates to the corresponding aldehydes, ketones, and oxophosphonates by NDC.

Results and Discussion. – At first, the oxidation reaction of benzylamine (= benzenemethanamine) to benzaldehyde by NDC at room temperature was investigated. Solvent screening revealed that MeCN was the best solvent for this oxidative deamination without formation of any by-product (*Table 1*, *Entry 6*). No benzaldehyde was obtained when the reaction was carried out in solvents such as H_2O

Table 1. *Oxidation of Benzylamine by NDC in Different Solvents at Room Temperature*

Entry	Solvent	Time [h]	Yield[a]) [%]
1	H_2O	24	0
2	EtOH	24	0
3	Hexane	24	15
4	Toluene	24	12
5	CH_2Cl_2	24	52
6	MeCN	–[b])	98
7	–	24	54

[a]) Yield of isolated benzaldehyde. [b]) Reaction occurred immediately.

or EtOH (*Table 1*, *Entries 1* and *2*). Similar reactions in hexane, toluene, and CH_2Cl_2 or in the absence of solvent led to the formation of the desired product in low yield (*Table 1*, *Entries 2–5* and *7*).

Then, the applicability of this oxidative deamination to the synthesis of aldehydes and ketones from a variety of amines with NDC in MeCN was investigated. As shown in *Table 2*, substituted benzaldehydes were obtained selectively in high yields by oxidative deamination of benzylamines containing electron-donating and electron-withdrawing groups (*Entries 1–3*). The procedure was suitable for the high yielding preparation of terephthaldehyde (= benzene-1,4-dicarboxaldehyde) from benzene-1,4-dimethanamine as an example of a difunctional amine (*Entry 4*). By this method, benzaldehyde and benzeneacetaldehyde could be produced from amines *N*-protected with a 4-methoxyphenyl or benzyl group, respectively (*Entries 5* and *6*). In these reactions, the protecting groups were released as benzoquinone (= cyclohexa-2,5-diene-1,4-dione) and benzaldehyde, respectively. Aliphatic aldehydes were synthesized in excellent yields by the oxidation of secondary amines including dialkylamines (*Entries 7–9*). The applicability of this method for the synthesis of ketones from primary amines was also examined. The results showed that the oxidation reaction worked well, and the expected products were obtained in 95–97% yields (*Entries 10–13*). No by-product was formed in any of these transformations, and aldehydes and ketones were cleanly and selectively produced by the oxidative deamination reaction.

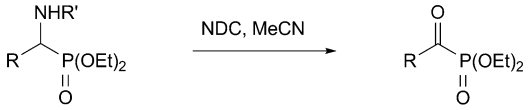
Table 2. *Synthesis of Aldehydes and Ketones from Amines* via *Oxidative Deamination by NDC*

Entry	Amine	Product	Time [min]	Yield[a]) [%]
1	$PhCH_2NH_2$	PhCHO	–[b])	98
2	2-Cl–$C_6H_4CH_2NH_2$	2-Cl–C_6H_4CHO	–[b])	93
3	2-MeO–$C_6H_4CH_2NH_2$	2-MeO–C_6H_4CHO	–[b])	94
4	1,4-$C_6H_4(CH_2NH_2)_2$	1,4-$C_6H_4(CHO)_2$	–[b])[c])	92
5	4-MeO–$C_6H_4NHCH_2Ph$	PhCHO	–[b])	85
6	$Ph(CH_2)_2NHCH_2Ph$	$PhCH_2CHO$	10	95
7	Bu_2NH	$Me(CH_2)_2CHO$	5	94
8	Piperidine	$OHC(CH_2)_3CHO$	5	97
9	4-Methylpiperidine	$OHCCH_2CH(Me)CH_2CHO$	–[b])	93
10	Butan-2-amine	Butan-2-one	10	96
11	Heptan-2-amine	Heptan-2-one	–[b])	96
12	4-Phenylpentan-2-amine	4-Phenylpentan-2-one	5	95
13	Cyclooctanamine	Cyclooctanone	15	97

[a]) Yield of pure isolated product characterized by comparison of its spectroscopic data with those of an authentic sample. Conditions: NDC (1 equiv., except for *Entry 4*), MeCN, r.t. [b]) Reaction occurred immediately. [c]) Conditions: NDC (2 equiv.).

In addition to ordinary amines, some aminophosphonates were also screened to examine their oxidation by NDC. As depicted in *Table 3*, this method worked well for the oxidative deamination of [amino(aryl)methyl]phosphonates bearing both electron-releasing and electron-withdrawing groups at the phenyl moiety and produced the corresponding oxophosphonates **1**–**6** in 85–91% yields (*Entries 1–6*). Benzoyl-

Table 3. *Synthesis of Oxophosphonates from Aminophosphonates* via *Oxidative Deamination by NDC*



1 – 9

Entry	R	R′	Time [h]	Product	Yield[a]) [%]
1	Ph	H	2.5	**1**	91
2	4-MeO–C_6H_5	H	1	**2**	75
3	4-Me–C_6H_5	H	1.5	**3**	86
4	4-Br–C_6H_5	H	1.5	**4**	95
5	4-Cl–C_6H_5	H	1	**5**	85
6	3-Cl–C_6H_5	H	1.5	**6**	86
7	Ph	4-MeO–C_6H_5	5 min	**1**	92
8	Naphthalen-2-yl	H	1	**7**	97
9	Hexyl	H	2	**8**	87
10	i-Pr	H	2	**9**	92

[a]) Yields refer to those of pure isolated products characterized by comparison of their spectroscopic data with those of authentic samples [2–5]. Conditions: NDC (2 equiv.), MeCN, under reflux conditions.

phosphonate **1** was also prepared by the oxidation of {[(4-methoxyphenyl)amino]-(phenyl)methyl}phosphonate as an example of a protected amine (*Entry 7*). The oxidation of [amino(naphthalen-2-yl)methyl]phosphonate as an example of a poly-aromatic phosphonate derivative proceeded well to afford the desired product **7** in 97% yield (*Entry 8*). (1-Aminoalkyl)phosphonates were also oxidized selectively to the corresponding (1-oxoalkyl)phosphonates **8** and **9** under these reaction conditions (*Entries 9* and *10*). It is worth to note that the C(O)–P bonds in oxophosphonates are known to be sensitive towards hydrolysis and acidic conditions [6]. In the present protocol, the resulting chromium(III) residue (green) accompanied by nicotinic acid was isolated from the reaction mixture by a simple filtration without requiring acidic workup. Evaporation of the solvent produced the desired oxophosphonates as the only products without any cleavage of the sensitive C(O)–P bond.

The merit of the present protocol in comparison with other reagents used for the oxidative deamination is shown by some results obtained in the oxidative deamination of benzylamine (*Table 4*), indicating well the superior activity of NDC over other reagents in terms of conversion rate and yield of the producted benzaldehyde.

Conclusions. – In conclusion, we found that nicotinium dichromate can be used as a new and efficient reagent for the facile preparation of a variety of aldehydes, ketones, and oxophosphonates by oxidative deamination of various types of amines (primary and secondary) and aminophosphonates as viable substrates. Short reaction times, good to high yields, lack of by-products, simple workup, and excellent selectivity for the formation of carbonyl compounds make this method an attractive and useful contribution to the already available methodologies.

Table 4. *Comparison of NDC with Other Reagents Used for the Oxidative Deamination of Benzylamine*

Entry	Reagents or catalyst	Time	Yield [%]	Ref.
1	NDC, MeCN, r.t.	–[a])	98	–[b])
2	Riboflavin tetraacetate (10 mol-%), air, D_2O/(D_6)DMSO 24 : 1, LED 440 nm	10 min	79	[7a]
3	5% Pd/C, *PEG-400*, microwave, 170°	3 h	68	[7b]
4	Ascorbic acid, Cu^I-3-methylsalicylate, DMA[c]), 50°	2 h	82	[7c]
5	30% aq. H_2O_2 soln. (5 equiv.), toluene, 60°	2–3 h	69	[7d]
6	$KMnO_4$ (1.25 equiv.), H_2O, *t*BuOH	10 min	61	[7e]

[a]) Reaction occurred immediately. [b]) Present work. [c]) *N,N*-Dimethylacetamide.

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Experimental Part

Oxidation of Amines to Aldehydes and Ketones: General Procedure. NDC (1 mmol) was added to the soln. of amine (1 mmol) in MeCN (2 ml) and stirred for the appropriate time at r.t. (*Table 2*). The resulting heterogeneous mixture was then filtered, and the filter cake was washed with Et_2O (2 × 10 ml). In most cases, evaporation of the filtrate yielded the desired pure product. If further purification was required, the crude product was purified by column chromatography (silica gel, hexane/AcOEt 3 : 1).

Oxidation of Aminophosphonates: General Procedure. A mixture of aminophosphonate (5 mmol) and NDC (10 mmol) in MeCN (10 ml) was stirred under reflux conditions for the time given in *Table 3*. The resulting heterogeneous reaction mixture was cooled and filtered. The filter cake was washed with Et_2O (2 × 10 ml). The solvent was evaporated to give the crude product. The pure product was obtained by vacuum distillation in 85–97% yield (*Table 3*).

Diethyl P-*Benzoylphosphonate* (**1**): IR (neat): 1660 (C=O), 1250 (P=O). ^{1}H-NMR ($CDCl_3$): 1.39 (*t*, ^3J(H,H) = 7.1, 2 *Me*CH_2O); 4.22 (*qt*, ^3J(P,H) = ^3J(H,H) = 7.1, 2 Me*C*H_2O); 7.28–7.6 (*m*, 3 arom. H); 8.23 (*d*, ^3J(H,H) = 7.7, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 16.6 (*d*, ^3J(C,P) = 5.7, *Me*CH_2O); 64.3 (*d*, ^2J(C,P) = 7.5, Me*C*H_2O); 129.1, 130.1, 135.0, 136.3 (Ph); 199.1 (*d*, ^1J(C,P) = 177.5, C=O). MS (70 eV): 242 (M^+), 105 ([M – P(O)$(OEt)_2$]$^+$).

Diethyl P-*(4-Methoxybenzoyl)phosphonate* (**2**): IR (neat): 1655 (C=O), 1265 (P=O). ^{1}H-NMR ($CDCl_3$): 1.20 (*t*, ^3J(H,H) = 7.1, 2 *Me*CH_2O); 3.80 (*s*, MeO); 4.00 (*qt*, ^2J(P,H) = ^3J(H,H) = 7.1, 2 Me*C*H_2O); 6.84–6.90 (*m*, 2 H); 7.42–7.50 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$): 16.7 (*d*, ^3J(C,P) = 5.7, *Me*CH_2O); 55.6 (MeO); 63.5 (*d*, ^2J(C,P) = 7.5, Me*C*H_2O); 114.0, 128.8, 129.2, 159.8 (C_6H_4); 198.01 (*d*, ^1J(C,P) = 176.2, C=O). MS (70 eV) : 272 (M^+), 135 ([M – P(O)$(OEt)_2$]$^+$).

Diethyl P-*(4-Methylbenzoyl)phosphonate* (**3**): IR (neat): 1650 (C=O), 1261 (P=O). ^{1}H-NMR ($CDCl_3$): 1.32 (*t*, ^3J(H,H) = 7.1, 2 *Me*CH_2O); 2.35 (*s*, Me); 4.14 (*qt*, ^2J(P,H) = ^3J(H,H) = 7.1, 2 Me*C*H_2O); 7.12–7.21 (*m*, 2 arom. H); 8.04–8.07 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 16.7 (*d*, ^3J(C,P) = 5.7, *Me*CH_2O); 22.2 (Me); 64.2 (*d*, ^2J(C,P) = 7.5, Me*C*H_2O); 127.3, 129.9, 130.3, 146.4 (C_6H_4); 198.5 (*d*, ^1J(C,P) = 176.6, C=O). MS: 256 (M^+), 119 ([M – P(O)$(OEt)_2$]$^+$).

Diethyl P-*(4-Chlorobenzoyl)phosphonate* (**5**): IR (neat): 1650 (C=O), 1260 (P=O). ^{1}H-NMR ($CDCl_3$): 1.39 (*t*, ^3J(H,H) = 7.1, 2 *Me*CH_2O); 4.28 (*qt*, ^2J(P,H) = ^3J(H,H) = 7.1, 2 Me*C*H_2O); 7.49 (*d*, ^3J(H,H) = 7.8, 2 H); 8.23 (*d*, ^3J(H,H) = 8.0, 2 H). ^{13}C-NMR ($CDCl_3$): 16.7 (*d*, ^3J(C,P) = 5.7, *Me*CH_2O); 64.5 (*d*, ^2J(C,P) = 7.5, Me*C*H_2O); 129.6, 131.6, 133.7, 141.8 (C_6H_4); 198.1 (*d*, ^1J(C,P) = 180.0, C=O). MS (70 eV): 277 (M^+), 279 ([M + 2]$^+$), 139 ([M – P(O)$(OEt)_2$]$^+$).

Diethyl P-*(3-Chlorobenzoyl)phosphonate* (**6**): IR (neat): 1650 (C=O), 1267 (P=O). ^{1}H-NMR ($CDCl_3$): 1.28–1.34 (*m*, 2 *Me*CH_2O); 4.22 (*qt*, ^2J(P,H) = ^3J(H,H) = 6.9, 2 Me*C*H_2O); 7.22–7.53 (*m*, 3 H); 7.96 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 18.4 (*d*, ^3J(C,P) = 5.7, *Me*CH_2O); 66.4 (*d*, ^2J(C,P) = 7.4, Me*C*H_2O);

130.3, 131.3, 131.4, 132.3, 135.1, 136.5 (C_6H_4); 201.5 (*d*, ^1J(C,P) = 182.0, C=O). MS (70 eV): 276 (M^+), 279 ($[M+2]^+$), 139 ($[M-P(O)(OEt)_2]^+$).

Diethyl P-*(Naphthalen-2-ylcarbonyl)phosphonate* (**7**): IR (neat): 1655 (C=O), 1260 (P=O). ^{1}H-NMR ($CDCl_3$): 1.33–1.44 (*m*, 2 *Me*CH_2O); 4.33 (*m*, ^2J(P,H) = ^3J(H,H) = 7.1, 2 MeCH_2O); 7.60 (*t*, ^3J(H,H) = 8.4, 2 H); 7.89 (*t*, ^3J(H,H) = 8.3, 2 H); 8.05 (*d*, ^3J(H,H) = 7.7, 1 H); 8.12 (*d*, ^3J(H,H) = 8.5, 1 H); 9.08 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 16.8 (*d*, ^3J(C,P) = 5.7, *Me*CH_2O); 64.5 (*d*, ^2J(C,P) = 7.3, Me*C*H_2O); 123.7, 126.9, 127.4, 128.4, 129.2, 129.3, 129.9, 132.8, 133.9, 136.6 ($C_{10}H_7$); 199.1 (*d*, ^1J(C,P) = 174.9, C=O). MS (70 eV) : 292 (M^+), 155 ($[M-P(O)(OEt)_2]^+$).

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