A New Formylation Reagent: *N,N*-Diformylacetamide

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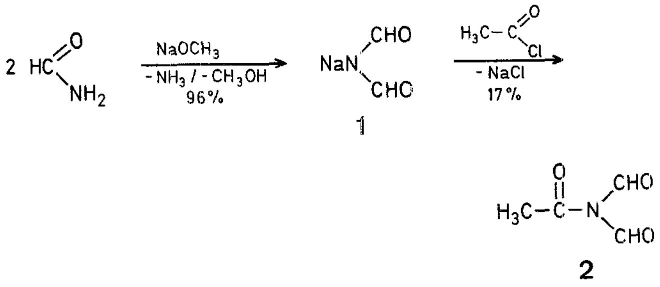
In recent years, a number of methods have been reported which allow the formylation of alcohols[1], amines[2,3], imines[4,5,6], enamides[7], and indoles[8]. These methods often use very specific and not always accessible formylating agents[3], and the yields of formylated products are not satisfactory. The direct formylation of compounds such as amides, lactams, and imides cannot be realized by means of these reagents. The reported syntheses of *N*-formylamides are not direct and are generally not efficient. Thus, 1-formyl-2-pyrrolidone has been prepared in 15% yield by ozonolysis of 1-vinyl-2 pyrrolidone[9]; a better yield was obtained[10] by carrying out the C—C cleavage with potassium permanganate according to Ref.[11]. *N*-Formyl-2-piperidone has been obtained in low yield by oxidation of 1-formylpiperidine with peroxoic acids[12] and cyclic amines have been *N*-formylated and oxidized to *N*-formyllactams with oxygen under irradiation in the presence of benzophenone as sensitizer[13].

We report here the use of *N,N*-diformylacetamide (**2**) as formylating agent. This reagent has already been used to prepare *N,N*-diformylformamide ("triformamide") from *N*-formylformamide ("diformamide")[14]. We prepare reagent **2** according to Ref.[14] by treatment of formamide with sodium methoxide and reaction of the resultant sodium diformylamide (**1**) with acetyl chloride.



The low yield (17%) in the second step of this sequence results from partial decomposition of **2** during distillation. It is necessary to perform the preparation of **2** under strictly anhydrous conditions.

N,N-Diformylacetamide (**2**) can be used for the *N*-formylation of strongly nucleophilic NH compounds (**3**→**6**) and for the *O*-formylation of secondary and tertiary alcohols (**4**→**7**). It was also applied to the *C*-formylation of 2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizine (**5**→**8**).

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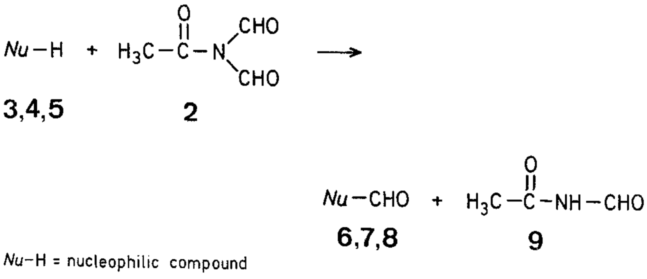


N,*N*-Diformylacetamide (2):

Sodium Diformylamide (**1**): A mixture of formamide (90 g, 2 mol) and sodium methoxide (54 g, 1 mol) is stirred at room temperature for 2.5 h under a dry atmosphere (drying tubes). The flask is then evacuated and the temperature of the mixture gradually raised to 80 °C within 1.5 h. Stirring is continued at 80 °C for 1.5 h and the mixture then allowed to cool. The precipitated product **1** is isolated by suction and washed with tetrahydrofuran; yield: 91 g (96%).

N,N-*Diformylacetamide* (**2**): A solution of compound **1** (47.5 g, 0.5 mol) and acetyl chloride (48.6 g, 0.61 mol) in ether (120 ml) is stirred at room temperature for 93 h under a dry atmosphere (drying tubes filled with potassium hydroxide and phosphorus pentoxide, respectively). The sodium chloride is then filtered off and washed with ether. The clear combined filtrate is evaporated and the residual yellow liquid distilled in vacuo to give **2**; yield: 10 g (17%); b.p. 73 °C/14 torr.

I.R. (film): $\nu = 1600\ \text{cm}^{-1}$.

^{1}H-N.M.R. ($CDCl_3$/TMS): $\delta = 2.6$ (s, 3 H); 9.45 ppm (s, 2 H).

Formylation of Nucleophilic Compounds (3, 4, 5); General Procedure: A solution of the nucleophilic compound (1 equiv) and *N*,*N*-diformylacetamide (**2**; 1 equiv) in dry benzene is heated to reflux under ni-

Table. Formylation of Nucleophilic Compounds with *N*,*N*-Diformylacetamide (**2**)

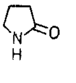
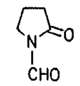
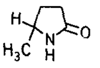
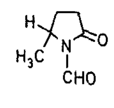
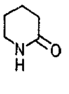
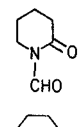
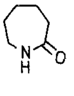
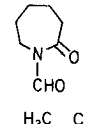
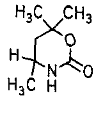
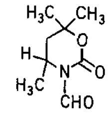
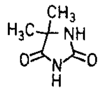
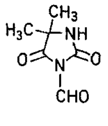
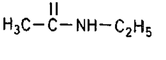
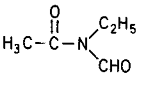
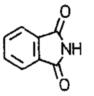
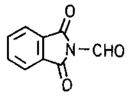
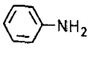
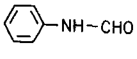
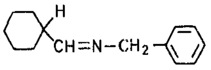
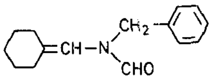
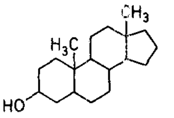
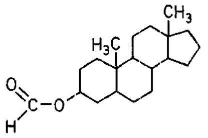
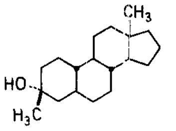
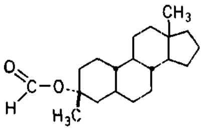
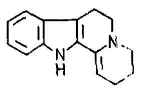
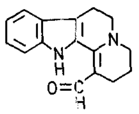
Nucleophile		Product		Yield [%]	m.p. or b.p./torr [°C]	Molecular formula[a] or Lit. data [°C]	I.R. (film) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
	3 a		6 a	75	b.p. 224°/760	b.p. 98.3°/7.5[9]	1750, 1690	2.2 (m, 2H); 2.6 (m, 2H); 3.7 (t, 2H); 9.1 (s, 1H)
	3 b		6 b	69	b.p. 235°/760	$C_6H_9NO_2$ (127.1)	1740, 1690	1.35 (d, 3H); 1.7-2.3 (m, 4H); 4.3 (m, 1H); 9.1 (s, 1H)
	3 c		6 c	52	b.p. 110°/14	b.p. 80-82°/3[12]	1720, 1690	1.9 (m, 4H); 2.6 (m, 2H); 3.6 (m, 2H); 10.4 (s, 1H)
	3 d		6 d	64	b.p. 214°/760	$C_7H_{11}NO_2$ (141.2)	1720, 1640	1.25 (m, 6H); 2.7 (m, 2H); 3.9 (m, 2H); 9.5 (s, 1H)
	3 e		6 e	67	m.p. 126-127°	$C_8H_{13}NO_3$ (171.2)	1720, 1690 ($CHCl_3$)	1.4 (d, 3H, $J = 6$ Hz); 1.5 (s, 6H); 2.1 (m, 2H); 4.2 (m, 1H); 9.3 (s, 1H)
	3 f		6 f	80	m.p. 142°	$C_6H_8N_2O_3$ (156.1)	1795, 1750, 1710	1.7 (s, 6H); 9.1 (s, 1H); 9.25 (s, 1H, exchangeable with D_2O)
	3 g		6 g	30	b.p. 210°/760	b.p. 212°/760[16]	1750, 1695	1.1 (t, 3H); 2.4 (s, 3H); 3.7 (q, 2H); 9.2 (s, 1H)
	3 h		6 h	60	m.p. 150°	$C_9H_5NO_3$ (175.1)	1800, 1765, 1750	7.9 (m, 4H); 9.3 (s, 1H)
	3 i		6 i	86	m.p. 46-47°	m.p. 46.5-47.5°[15]	1720 (CCl_4)	7.5 (m, 6H with 1H exchangeable with D_2O); 9.1 (s, 1H)

Table. (Continued)

Nucleophile		Product		Yield [%]	m.p. or b.p./torr [° C]	Molecular formula[a] or Lit. data [° C]	I.R. (film) ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$/TMS) δ [ppm]
	3j		6j	80	dec.	M$^{+\bullet}$=229.1463[b]	1700	1.5 (m, 6H); 2.1 (m, 4H); 4.6 (s, 2H); 5.7 (s, 1H); 7.4 (s, 5H); 8.1 (s, 1H)
	4a		7a	84	m.p. 90–91°	$C_{20}H_{32}O_2$ (304.5)	1730	0.7 (s, 3H); 0.9 (s, 3H); 8.1 (s, 1H)
	4b		7b	70	m.p. 70°	$C_{20}H_{32}O_2$ (304.5)	1730 (CCl$_4$)	0.7 (s, 3H); 1.5 (s, 3H); 8.2 (s, 1H)
	5		8	22	m.p. 226°	M$^{+\bullet}$=252[c]	1600, 1550, 1510 (CHCl$_3$)	—[d]

[a] The microanalyses were in good agreement with the calculated values: C, ±0.15; H, ±0.18; N, ±0.16.

[b] High-resolution mass spectrum. M$^{+\bullet}$ in agreement with $C_{15}H_{19}NO$; calc. 229.1466.

[c] The mass spectrum service of Institut de Chimie des Substances Naturelles CNRS of Gif s/ Yvette is gratefully acknowledged for the determination of the mass spectrum of this compound; calc. 252.3.

[d] ^{13}C-N.M.R. (DMSO/TMS): δ=20.08 (t); 21.02 (t); 21.28 (t); 49.43 (t); 50.74 (t); 106.14 (s); 112.30 (d); 114.98 (s); 119.18 (s); 119.57 (s); 123.48 (d); 124.79 (s); 126.94 (s); 137.69 (s); 152.02 (s); 184.16 ppm (s).

trogen until the nucleophilic compound can no longer be detected in the reaction mixture by T.L.C. (Merck Kieselgel 60 F 254 plates) analysis. The solvent is then evaporated and the formylation product separated from *N*-formylacetamide (**9**) by column chromatography on Merck Kieselgel 60 using hexane/ethyl acetate (1/1) as solvent.

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