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Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/uopp20

EFFICIENCY OF THE VILSMEIER-HAACK METHOD IN THE SYNTHESIS OF p-AMINOBENZALDEHYDES

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Version of record first published: 09 Feb 2009

To cite this article: Ryszard Gawinecki, Sylwia Andrzejak & Agnieszka Puchala (1998): EFFICIENCY OF THE VILSMEIER-HAACK METHOD IN THE SYNTHESIS OF p-AMINOBENZALDEHYDES, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 30:4, 455-460

To link to this article: <u>http://dx.doi.org/10.1080/00304949809355310</u>

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EFFICIENCY OF THE VILSMEIER-HAACK METHOD IN THE SYNTHESIS OF *p*-AMINOBENZALDEHYDES

Submitted by (09/29/97)

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Aromatic aldehydes¹ and their oximes² are important synthetic intermediates. In addition, p-aminobenzaldoximes show interesting chemical and biological activities.³ It is known that only thermodynamically more stable *E*-oximes are formed by direct oximation of aromatic aldehydes,⁴ thus, the product of reaction of p-(N,N-dimethylamino)benzaldehyde with hydroxylamine⁵ is E-p-(N,N-dimethylamino)benzaldoxime⁶ and it is noteworthy that *Z*-isomers of p-aminobenzal-doximes are not known.

Various methods are used to synthesize *p*-aminobenzaldehydes. The unstable parent *p*-aminobenzaldehyde has been obtained by the McFadyen-Stevens reaction of N'-benzenesulfonyl*p*-amino-benzhydrazide,⁷ by reduction of *p*-nitrobenzaldehyde⁸ or from *p*-nitrotoluene.⁹ N-Alkyl substituted *p*-formylanilines have been prepared by amination-dehalogenation of *p*-(formyl)halobenzenes,¹⁰⁻¹² by formylation of anilines,¹³⁻¹⁵ from the reaction of formaldehyde with 4,4'-di(alkylamino)-N-benzylideneanilines¹⁶ or *p*-(alkylamino)phenylmagnesium halide with alkyl formates.¹⁷ A literature search for preparative procedures shows that the Vilsmeier-Haack and Duff¹⁸ methods were most commonly used. The present paper describes the efficiency of formylation of various anilines by the

		R⁴ N— R ³	R ⁵	R ⁶ R ¹		R ⁴ N R ³	R ⁵ R ²	R ⁶ COR ⁷		R' Ri	\mathbb{R}^{5}		-c ,	₹ ⁷ ЮН	
			1				2					3			
	\mathbb{R}^1	R ²	\mathbb{R}^3	R ⁴	R ⁵	R ⁶	R ⁷		\mathbb{R}^1	\mathbb{R}^2	R ³	R ⁴	R ⁵	R ⁶	R ⁷
a	Н	Н	Н	Н	Н	Н	Н	1	Η	Н	(CH ₂) ₆	(CH ₂) ₆	Η	Н	Н
b	Н	Н	Me	Н	Н	Н	Н	m	Н	(CH ₂)	(CH ₂) ₂	Me	Н	Н	Н
c	h	Н	Me	Me	Н	Н	Н	n	Н	(CH ₂)	(CH ₂) ₃	H	Н	Н	Н
d	Н	Н	Et	Me	Н	Н	Н	0	Н	(CH ₂)	(CH ₂) ₃	Me	Н	Н	Н
e	Н	Н	Et	Et	Н	Н	Н	р	Н	(CH ₂)	4(CH ₂)4	Me	Н	Н	Н
f	Me	Н	Me	Me	Н	Н	Н	q	H	(CH ₂)	$_{2}(CH_{2})_{3}$	(CH ₂) ₂ ((CH ₂)	3 H	Н
g	Me	Н	Me	Me	Н	Me	Н	r	Н	(CH ₂)	$_{2}(CH_{2})_{3}$	(CH ₂) ₃	(CH ₂)	, Н	Н
h	Н	Me	Me	Me	Н	Н	Н	S	Н	Н	Н	Η	Η	Н	Me
i	Н	Me	Me	Me	Me	Н	Н	t	Н	Н	Me	Me	Н	Н	Me
j	Н	Н	(CH ₂) ₄	(CH ₂) ₄	Н	Н	Н	u	Н	Н	(CH ₂) ₅	(CH ₂) ₅	Н	Н	Me
k	Н	Н	(CH,),	(CH ₂),	н	Н	Н								

Vilsmeier-Haack method (reaction $1 \rightarrow 2$). The *p*-aminobenzaldehydes obtained were subsequently transformed into respective oximes (reaction $2 \rightarrow 3$), many of which being new compounds.

The data in Table 1 shows that most aldehydes 2 can be easily obtained from arylamines by the Vilsmeier-Haack method. The yield decreased when the number of substituents on the amine nitrogen is lower, ranging from 43-91% for tertiary amines (1c-1m and 1o-1r) to 24 and 14% for secondary amines 1b and 1n, respectively; formylation of aniline itself by N.N-dimethylformamide and phosphorus oxychloride failed completely. 1-Formyl-1,2,3,4-tetrahydroquinoline is a self-formylating compound and its rearrangement in presence of phosphorus oxychloride gave 2n in 21% yield. The twisted dimethylamino groups of **1h** and **1i** are weak electron-donors and this fact explains why 2.N.N-trimethyl- and 2.6.N.N-tetramethylanilines are resistant to such formylation and the less efficient Duff method has to be utilized to obtain 2h and 2i.

Oximes 3 were obtained by oximation of aldehydes and ketones 2 in a medium to high yield (no attempt was made to improve the reaction efficiency). The NMR spectra of all oximes obtained show there is only one isomer present.²⁹ Since the p-(N,N-dimethylamino)benzaldoxime obtained reveals the same physical data as that of E-p-(N,N-dimethylamino)benzaldoxime,⁶ other oximes 3 have the same E configuration.

EXPERIMENTAL SECTION

Aldehydes 2c and 2e and ketones 2s and 2u are commercial products. p-(N,N-Dimethylamino)acetophenone (2t) was as a gift from Dr. Tomasz Bak (Pedagogical University, Kielce). Alde-

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hydes **2b**, **2d**, **2f-k** and **2m-r** were obtained by the Vilsmeier-Haack¹³ or Duff reaction^{14,15} (see Table 1) and purified by vacuum distillation or crystallization from aqueous ethanol.

		Aldehydes 2			Oximes 3
Cmpd	Reagent ^a (%, Yield)	bp. (°C/mm Hg)	mp. (°C)	Yield (%)	mp. (°C)
a	A (0)			41	126-130 (127-128) ³
b	B (24) ^b	151-154/5 (127-130/0.04) ¹⁹	55-56 (54) ¹⁹	55	96.5-99
с	—		— —	80	147-148 (145-147) ²⁰
d	A (52)		42-44 (44)14	77	117-121
e				81	89-91 (93) ¹⁴
f	A (68)		65-67 (67) ¹⁴	78	105-109 (107-109) ²⁰
g	A (58)		81-83 (83) ²¹	36	134-135
h	C (63) ^c	138-141/8 (130-134/3) ²⁰		61	97-98 (97-98) ²⁰
i	C (24) ^c	150-165/1 (64-66/0.09) ²⁰		21	75-85 ^d
j	A (91)		83-85 (84.5-85.5) ²²	76	190-192
k	A (61)		59-62 (61-62) ²²	79	161-163
l	e (72)	193-196/1	<u> </u>	82	110-114
m	A (84)		38-40 (40.1) ²³	41	97-99
n	B (14)	165-175/4	93-95 ^r (95-96) ²⁴	35	147-151
0	A (90)	180-195/4 (219-221/15) ²⁵	27-30 (30.6) ²⁴	51	87-88
р	A (43)	202-206/19		91	107-109
q	A (67)	165-167/4	36-38	82	104-106.5
r	A (80)		79-81 (83) ²⁶	85	126-128 (127-128) ²⁶

TABLE 1. Yields and Physical Constants of Aldehydes 2 and Oximes 3

a) A: N,N-Dimethylformamide, phosphorus oxychloride; B: N-methylformanilide, phosphorus oxychloride; C: hexamethylenetetramine, paraformaldehyde, acetic acid (Duff). b) No aldehyde obtained when N,N-dimethyl-formamide was used. c) Starting materials were recovered when the Vilsmeier-Haack method was used. d) Crude oxime was first distilled (bp. 165-80°/1 mm Hg) and then recrystallized from aqueous ethanol. e) For reaction conditions see Experimental Section. f) This compound was also obtained in 21% yield by rearrangement of 1-formyl-1,2,3,4-tetrahydro-quinoline in presence of phosphorus oxychloride.²⁴

Cmpd		Elemen		δ_{CHO} or $\delta_{CH=NOH}$			
	(2	H	ł	Ν	1	(ppm) ^a
21	76.81	(76.65)	8.43	(8.59)	6.89	(6.97)	9.62 ^b
2p	76.15	(76.05)	7.99	(7.86)	7.40	(7.45)	9.77°
2q	76.97	(77.12)	7.00	(6.94)	7.48	(7.54)	9.59 ^d
3b	63.98	(64.17)	6.71	(6.66)	18.66	(18.47)	7.96
3d	67.38	(67.20)	7.92	(8.03)	15.72	(15.54)	7.99
3g	68.71	(68.90)	8.39	(8.22)	14.57	(14.39)	8.34
3i	68.71	(68.60)	8.39	(8.21)	14.57	(14.69)	8.01
3j	69.44	(69.55)	7.42	(7.56)	14.73	(14.81)	7.97
3k	70.55	(70.39)	7.90	(8.01)	13.72	(13.61)	8.00
31	71.85	(71.65)	7.89	(7.76)	12.90	(13.01)	7.96
3m	68.15	(68.02)	6.87	(6.69)	15.90	(16.01)	7.98
3n	68.15	(68.26)	6.87	(6.99)	15.90	(15.99)	7.90
30	69.44	(69.32)	7.42	(7.58)	14.73	(14.60)	7.93
3p	70.55	(70.39)	7.90	(7.99)	13.72	(13.59)	8.03
3q	71.26	(71.45)	6.98	(6.79)	13.85	(13.61)	7.93
3t	67.38	(67.18)	7.92	(7.96)	15.72	(15.82)	_
3u	71.52	(71.46)	8.31	(8.41)	12.84	(12.97)	_

TABLE 2. Elemental Analyses and Chemical Shifts of α -Protons of New Compounds

a) In DMSO- d_6 . All signals are the singlets (1H). Complete ¹H and ¹³C NMR spectral data of oximes obtained is the subject of another paper.²⁹ b) Other ¹H NMR signals (δ , ppm): 7.63d (2H, H2 and H6); 6.63d (2H, H3 and H5); 3.47t (4H, NCH₂); 1.73m (4H, NCH₂CH₂); 1.48m (4H, NCH₂CH₂CH₂). IR (KBr): 1676 cm⁻¹ (C=O). c) Other ¹H NMR signals (δ , ppm): 7.61d (1H, H6); 7.56s (1H, H2); 6.83d (1H, H5); 3.20t (2H, NCH₂); 2.95s (3H, NCH₃); 2.83m (2H, NCH₂CH₂CH₂CH₂); 1.76m (4H, NCH₂CH₂ and CH₂CH₂CH₂). IR (KBr): 1678 cm⁻¹ (C=O). d) Other ¹H NMR signals (δ , ppm): 7.39s and 7.29s (1H + 1H, H2 and H6); 3.51t (2H, NCH₂CH₂CH₂CH₂); 3.14t (2H, NCH₂CH₂); 2.97t and 2.66t (2H + 2H, NCH₂CH₂CH₂ and NCH₂CH₂CH₂); 2.02m (2H, NCH₂CH₂CH₂). IR (KBr): 1664 cm⁻¹ (C=O).

Synthesis of Aldehyde 21.- A solution of *p*-fluorobenzaldehyde (6.21 g, 5.26 mL, 0.05 mol) and hexamethyleneimine (14.88 g, 16.91 mL, 0.15 mol) in DMSO (90 mL) was stirred for 24 h at 95°. It was then poured into water (1.75 L) and extracted with ether. Evaporation of the solvent and distillation of the residue gives 21.

Preparation of Oximes 3.- *p*-Aminobenzaldoxime, **3a**, was obtained in 47% yield by reduction of *p*nitrobenzaldoxime, according to the procedure used in synthesis of *p*-aminoacetophenone oxime.²⁸ The product was purified by crystallization from aqueous ethanol. Aldoximes **3b-r** were obtained by refluxing (2h) the reaction mixture consisting of a saturated aqueous solution of hydroxylamine hydrochloride (6 g, 0.086 mol), potassium carbonate (5 g) and aldehyde (0.07 mol) in 96% ethanol (100 mL), followed by the addition of water. The precipitated products were recrystallized from aqueous ethanol. To obtain ketoximes **3s-u**, a mixture of appropriate acetophenone (0.08 mol), hydroxylamine hydrochloride (11.1 g, 0.16 mol), 96% aqueous ethanol (60 mL) and few drops of conc. hydrochloric acid was refluxed for 1.5 h. The reaction mixture was then diluted with water (150 mL) and extracted with ether. Evaporation of the solvent and crystallization of the residue from 96% ethanol gave **3s** (yield 51%, mp. 150-152°, lit.²⁷ mp. 155-156°), **3t** (yield 69%, mp. 218-222°) and **3u** (yield 65%, mp. 163-166°). The yields and physical data of other oximes **3** are collected in Table 1.

Acknowledgements. This work was supported by the Polish State Committee for Scientific Research (KBN), grant number 3 T09A 147 09.

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IMPROVED PREPARATION OF SURFACTANTS DERIVED FROM SUCROSE WITH ULTRASOUND

Submitted by Jacques Besson, Catherine Fayet, J. Gelas^{*} and Christelle Lamazzi (10/09/97)

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Sugars can constitute the hydrophilic part of a detergent, as they possess a number of hydroxy groups. For this purpose, they must be associated with a lipophilic tail, generally a linear alkyl chain. Such saccharide-derived materials have become a focus of great interest ¹ because (i) they