Tetrahedron Letters, Vol.32, No.27, pp 3225-3228, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

HIGHLY EFFICIENT NITROALDOL REACTION PROMOTED BY TRIALKYLSILYL CHLORIDES

Rosario Fernández, Consolación Gasch, Antonio Gómez-Sánchez* and José Eduardo Vílchez

Departamento de Química Orgánica "Profesor García González", Universidad de Sevilla, and Instituto de la Grasa y sus Derivados, CSIC, Apartado de Correos No. 553, E-41071 Seville, Spain

Abstract: β-Nitroalcohols can be readily obtained in high yields by the one-pot reaction of aldehydes with nitrocompounds in the presence of Et_3N, $Bu_4NF{\cdot}3H_2O$ and $^tBuMe_2SiCl$. Model experiments indicated that trialkylsilyl nitronic esters are not reaction intermediates.

β-Nitroalcohols are useful synthetic intermediates usually obtained by the nitroaldol (Henry) reaction,[1] the base-catalyzed condensation of a carbonyl compound with a nitroalkane. This procedure has the inconvenience of the low yields sometimes obtained, the usually long reaction times, the reversion of the reaction on attempted purification or further transformation of the product, and the difficulty to extend the reaction to high and functionalized nitroalkanes. Improvements have been introduced, sacrificing simplicity. Thus, the reaction of silyl nitronates with carbonyl compounds catalyzed by anhydrous Bu_4NF,[2] the addition of doubly metallated nitroalkanes to aldehydes,[3] or the reaction of lithium nitronates with aldehydes in the presence of isopropoxytitanium trichloride,[4] often afford the β-nitroalcohol (or an inmediate precursor) in high yield and, using the appropriate conditions, with high stereoselectivity. However, these step-wise procedures require stringent conditions and are technically too cumbersome, particularly when applied to large scale preparations.

We describe herein a one-step and simple variation of the Henry reaction, apparently related to the Seebach's silyl nitronate procedure, but that seems to proceed by a different mechanistic pathway. In this method, the nitrocompound (1 mol), the aldehyde (1 mol), Et_3N (1 mol), and $^tBuMe_2SiCl$ (1.5 mol) are sequentially added, *in this order*, to a solution cooled at 0ºC of $Bu_4NF{\cdot}3H_2O$ (0.25 mol) in THF (conditions *A*). The reaction is allowed to proceed at room temperature without any need of an inert atmosphere, and is complete in a short time. The product is the β-nitroalcohol which is formed in some cases almost quantitatively and can be isolated in good yields. Yields can be improved, at the expenses of stereoselectivity, by raising the proportions of the nitrocompound (1.5 mol) and $Bu_4NF{\cdot}3H_2O$ (0.38 mol) (conditions *B*). Table 1 lists several examples of condensation of simple and functionalized nitrocompounds

TABLE 1

R^1-CHO + $R^2R^3CHNO_2$ ⟶ R^1-CHOH-CR^2R^3-NO_2

1 2 3

Compound	R^1	R^2	R^3	Conditions (time)	Yield %[a] (Conversion %)[b]	Erythro/threo	Lit. yield %
3a	n-C_5H_{11}	Me	H	*A* (5 min)	92 (100)	67/33	47[c] 52[d] 71[e]
				B (5 min)	96 (100)	60/40	
3b	n-C_6H_{13}	Et	H	*A* (2 h)	84 (95)	60/40	13[f] 28[f]
				B (5 min)	92 (100)	55/45	
3c	n-C_6H_{13}	Me	Me	*A* (2 h)	63 (75)	-	9[g]
				B (5 min)	91 (100)		
3d	Ph	Me	H	*A* (2 h)	80 (85)	60/40	27[h]
				B (5 min)	95 (100)	53/47	
3e	Ph	Et	H	*A* (2 h)	75 (85)	35/65	26[d] 41[f] 58[c]
				B (5 min)	90 (100)	44/56	61[f] 65[e] 78[e]
3f	Ph	Me	Me	*A* (2 h)	58 (70)	-	8[g]
				B (2 h)	70 (85)		
3g	Ph	$CH(OEt)_2$	H	*A* (2 h)	41 (66)	30/70	-
				B (2 h)	51 (75)	38/62	

a) Of isolated pure product. b) By ^{1}H-NMR monitoring. c) As the TBDMSi-ether of 3 by the Bu_4NF-catalyzed addition of the TBDMSi-nitronate of 2 to 1; yield from 2 (two steps); ref. 3. d) Catalyzed by NaOH; ref. 3. e) Through the doubly metallated nitroalkane; ref. 3. f) Through the lithium nitronate of 2, in the presence of $TiCl_3(OPr^i)$; ref. 4. g) Bu_4NF-catalyzed addition of the TBDMSi-nitronate of 2 to 1; yield from 2 (two steps); ref. 2. h) As the TMSi-ether of 3 by the Et_3N-catalyzed addition of the TMSi-nitronate of 2 to 1; yield from 2 (two steps); ref. 5.

with aliphatic and aromatic aldehydes, and comparison of the yields obtained with those reported in the literature using other procedures. As an illustration, the preparation of 2-nitro-1-phenyl-1-butanol (**3e**) is described below.

To a stirred solution of $Bu_4NF{\cdot}3H_2O$ (2.4 g, 7.5 mmol) in THF (20 mL), cooled at 0º, are sequentially added 1-nitropropane (2.7 mL, 30 mmol), benzaldehyde (2 mL, 20 mmol), Et_3N (2.8 mL, 20 mmol), and a solution of ^{t}BuMe$_2$SiCl (4.5 g, 30 mmol) in THF (20 mL). After 5 min (100% conversion by ^{1}H-NMR monitoring), the suspension is filtered, the filtrate is poured into a 1:3 ether-hexane mixture (500 mL), and washed with water (2x40 mL). After drying ($MgSO_4$), the solvent is evaporated, and the residue bulb-to-bulb distilled to yield **3e** (3.5 g, 90%), b.p. 115ºC/1 mbar.

Substitution of Me_3SiCl for $^tBuMe_2SiCl$ decreases the yields. From the data of Table 1, it appears that 1,1-diethoxy-2-nitroethane (**2g**) is rather unreactive. In order to test comparatively the efficiency of the new and other previously reported procedures, we chose, as model system, the reaction of **2g** [or its trimethyl- (**4**) or *t*-butyldimethyl-silyl (**5**) nitronic ester] with benzaldehyde, to give 3,3-diethoxy-2-nitro-1-phenyl-1-propanol (**3g**) [or its trimethyl- (**6**) or *t*-butyldimethyl-silyl (**7**) ethers].[6] The results we obtained using the different procedures have been collected in Table 2. It can be seen that the yields by the method here reported are far superior, and that the stereoselectivity attained is not much different from the best observed. The new procedure has the added advantage of not requiring the silylation of the starting nitrocompound and the desilylation of the product.

TABLE 2

Entry	Compound	Reaction time	Conditions	Product	Yield % (Conversion %)	Erythro/ threo
1	**2g**	2 h	This work, *A*	**3g**	41 (66)	30/70
2	**2g**	2 h	This work, *B*	**3g**	51 (75)	38/62
3	**4**	36 h	Et_3N, 40ºC[a]	**6**	30[b]	38/62
4	**5**	24 h	Bu_4NF, 0ºC[c]	**7**	21[b]	42/58
5	**2g**	24 h	Al_2O_3[d]	**3g**	15 (21)	30/70
6	**2g**	48 h	SiO_2, 0ºC → r.t.	**3g**	(<5)	-
7	**2g**	7 days	Et_3N, 0ºC → r.t.	**3g**	6 (17)	30/70
8	**2g**	7 days	$Bu_4NF \cdot 3H_2O$[e]	**3g**	9 (24)	30/70
9	**2g**	4 days	KF/Bu_4NI[f]	**3g**	(<5)	-
10	**2g**	3 days	NaOH[g]	**3g**	8 (14)	37/63

a) Optimization of Torssell's conditions; ref 5. b) Overall yields from 2g. c) Optimization of Seebach's conditions; ref 2. d) Ref. 7. e) Ref. 8. f) Ref. 9. g) Ref. 3.

It seemed at first that reaction might proceed through the intermediacy of the trialkylsilyl nitronic ester. In order to test this, experiments were perfomed using *i*) the nitronic ester **5** (instead of **2g**) in the absence of $^tBuMe_2SiCl$, and *ii*) 0.7 mol of **5** (*i.e.*, the equivalent to the amount of **3g** formed, instead of **2g**) and 0.8 mol of $^tBuMe_2SiCl$, all the other conditions being the same. ^1H-NMR monitoring indicated in *i*) desilylation of **5** and little reaction, and in *ii*) desilylation of **5** that further reacted to yield the product **3g**.

These results indicated that **5** is not an intermediate. Other observations, in addition to the order in which the reagents have to be added, significant to the reaction pathway are: a) omitting, or using less than 1 mol of the trialkylsilyl chloride, decreases the yield; b) the use of anhydrous Bu_4NF instead of the tri-hydrate also causes a yield drop, c) Et_3N is not critical to the process, but its presence increases the yields in *ca.* 15%, and d) careful NMR-monitoring of the reaction course showed doubling of the methylene proton signals of **2g** in the presence of $Bu_4NF \cdot 3H_2O$ and failed to detect the β-nitroalcohol *O*-trialkylsilyl ether **7** in the product, even when anhydrous Bu_4NF was used. All these results suggest that the nitrocompound is activated by the Bu_4NF,[10] and the aldehyde by the trialkylsilyl chloride,[11] and that the two activated species merge in a complex intermediate, the hydrolysis of which gives rise to the β-nitroalcohol and regenerates Bu_4NF. However, Bu_4NF cannot act catalytically because of the comcomitant splitting of the intermediate producing R_3SiF which can be detected (NMR), together with $(R_3Si)_2O$ and/or R_3SiOH, among the reaction products.

Acknowledgments. We wish to thank the 'Comisión Interministerial de Ciencia y Tecnología (CICYT)' (Project PB87-0454) and the 'Junta de Andalucía' for generous financial assistance.

References and Notes

1. L. Henry, *Bull. Soc. Chim. France*, **1895**, *13*, 999.
2. E.W. Colvin, A.K. Beck and D. Seebach, *Helv. Chim. Acta*, **1981**, *64*, 2264.
3. D. Seebach, A.K. Beck, T. Mukhopadhyay and E. Thomas, *Helv. Chim. Acta*, **1982**, *65*, 1101.
4. A.G.M. Barrett, C. Robyr and C.D. Spilling, *J. Org. Chem.*, **1989**, *54*, 1233.
5. K. Torssell and O. Zeuthen, *Acta Chem. Scand.*, **1978**, *B32*, 118.
6. New compounds **3g**, **4**, **5**, **6** and **7** were characterized by high resolution mass and/or NMR spectral analysis.
7. G. Rosini, R. Ballini and S. Sorrenti, *Synthesis*, **1983**, 1014.
8. R. Öhrlein and V. Jäger, *Tetrahedron Lett.*, **1988**, *29*, 6083.
9. O. Sakanaka, T. Ohmori, S. Kozaki, T. Suami, T. Ishi, S. Ohba and Y. Saito, *Bull. Chem. Soc. Jpn.*, **1986**, *59*, 1753.
10. J.H. Clark, J.M. Miller and K.-H. So, *J. Chem. Soc., Perkin Transactions I*, **1978**, 940.
11. H. Oshino, E. Nakamura, I. Kuwajima, *J. Org. Chem.*, **1985**, *50*, 2804; T.V. RajanBabu, *J. Org. Chem.*, **1984**, *49*, 2083.

(Received in UK 26 February 1991)