Vinylogous Formylation of Aromatics with 3-Trifloxypropeneiminium Triflates

Gerhard Maas,*,† Rainer Rahm,† Michael Schletz,† and Ernst-Ulrich Würthwein‡

Fachbereich Chemie, Universität Kaiserslautern, D-67663 Kaiserslautern, Germany, and Organisch-Chemisches Institut, Universität Münster, Corrensstrasse 40, D-48149 Münster, Germany

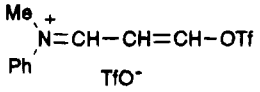
Received June 13, 1994

By analogy with the formylation of sufficiently electron-rich aromatic and heteroaromatic compounds by DMF/$POCl_3$ (the Vilsmeier–Haack reagent), the vinylogous formylation can be achieved with the 3-chloropropeneiminium salt obtained from $POCl_3$ and 3-(*N*,*N*-dimethylamino)acrolein or 3-(*N*-methyl-*N*-phenylamino)acrolein (NMPA), respectively.[1,2] This vinylformylation is confined to electron-rich aromatics such as 1,3-dimethoxybenzene, *N*,*N*-dimethylaniline, pyrroles, and indoles, whereas anisole is obviously not sufficiently electron-rich to react with NMPA/$POCl_3$.[3]

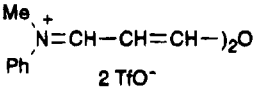
It has recently been reported that less nucleophilic aromatics can be formylated when the classical Vilsmeier–Haack reagent is replaced by DMF/triflic anhydride. The iminium salt so formed, (trifloxymethylene)-dimethyliminium triflate, reacts even with naphthalene and mesitylene.[4,5] With these findings in mind, we reasoned that the scope of vinylformylation reactions could be expanded if 3-trifloxypropeneiminium salts, readily prepared from enaminones and triflic anhydride,[6] rather than 3-chloropropeneiminium salts were utilized.

Surprisingly, the synthesis of 3-(2,4-dimethoxyphenyl)-propenal from 1,3-dimethoxybenzene and NMPA proceeded both more slowly and in lower yield when the enamino aldehyde was activated with triflic anhydride (Tf_2O) rather than with $POCl_3$ (Scheme 1). Furthermore, less electrophilic aromatics such as anisole, toluene, and naphthalene did not react with NMPA/triflic anhydride even at 130 °C.

The seemingly low efficiency of Tf_2O in this specific case is due to the competitive formation of the desired 3-trifloxypropeneiminium salt **1** and the unwanted, since it is the less reactive dication, ether salt **2**. In an independent experiment, a stoichiometric amount of NMPA

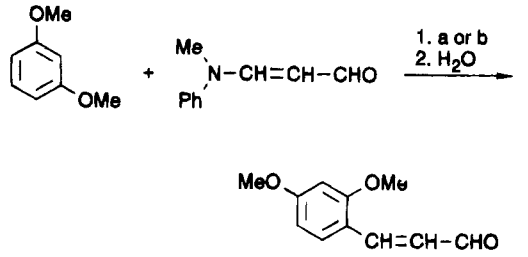


1



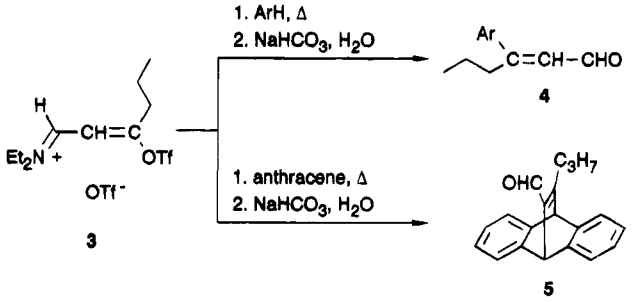
2

Scheme 1[a]



[a] Conditions: (a) $POCl_3$ (1 equiv), solvent $CHCl_3$, 0 °C, then 35 °C/1 h; 90% yield;[3] (b) $(CF_3SO_2)_2O$ (1 equiv), solvent CH_2Cl_2, 0 °C, then 20 °C/72 h; 70% yield.

Scheme 2



was slowly added at −40 °C to a solution of Tf_2O in CH_2Cl_2, and after 1 h, the composition of the mixture was checked by ^{19}F NMR at ambient temperature. Signals were found at δ (relative to C_6F_6) = 90.7 (unconsumed Tf_2O), 89.8 (covalent triflate in **1**[6]), and 84.0 (anionic triflate). From the signal intensities, a molar ratio **2/1** = 3.6 was calculated. When Tf_2O and NMPA were allowed to react at −70 °C, a **2/1** ratio of 2.5 resulted; thus, the formation of **2** by reaction of **1** with excess enamino aldehyde can only partly be suppressed at low temperature, in contrast to some other cases.[6] The presence of the two salts could also be confirmed by ^1H NMR spectroscopy; in this case, the reaction was carried out in $CDCl_3$ at −40 °C, and after 1 h, CD_3CN was added as a cosolvent. The olefinic signals of **1** were observed at δ = 7.01 (t), 8.48 (d), and 8.80 (d) ppm and those of **2** at δ = 6.91, 8.59, and 8.73 ppm. Attempts to isolate **1** failed. When ether was added to the reaction solution, a mixture of salts was precipitated that showed the expected ^1H NMR signals of **2**; instead of the signals of **1**, however, a new set of signals was present which was also obtained when NMPA and triflic acid were combined and is attributed to the O-protonated enamino aldehyde. These observations show that salt **1** is extremely sensitive to hydrolysis. Nevertheless, this mixture of salts also allowed vinylogous formylation of 1,3-dimethoxybenzene under similar conditions and in similar yield as with the in-situ procedure described in Scheme 1.

In contrast to **1**, salt **3** can be prepared cleanly from the corresponding enamino ketone and Tf_2O.[6] Reaction of **3** with anisole, 1,3-dimethoxybenzene, or mesitylene at 100 °C provided the expected 3-aryl-2-hexenals **4** after hydrolysis of the initially formed vinylogous iminium salts (Scheme 2 and Table 1). In all cases, mixtures of (*E*)- and (*Z*)-isomers were obtained. Stereochemical assignments for **4a,c,d** obtained from ^1H NMR NOE experiments (irradiation at the allylic CH_2 resonance and observation of the signal for the aldehyde proton) are consistent with the predictions based on the γ-effect (i.e.,

† University of Kaiserslautern.
‡ University of Münster.

(1) Simchen, G. In *Methoden der organischen Chemie (Houben-Weyl)*; Thieme: Stuttgart, 1983; Vol. E3, p 86. Jutz, C. In *Iminium Salts in Organic Chemistry*; Böhme, H., Viehe, H., Eds.; Wiley: New York, 1976; Part 1, p 330.
(2) Lee, G. T.; Amedio, J. C., Jr.; Underwood, R.; Prasad, K.; Repic, O. *J. Org.Chem.* **1992**, *57*, 3250.
(3) Jutz, C. *Chem. Ber.* **1958**, *91*, 850.
(4) García Martínez, A.; Martínez Alvarez, R.; Osío Barcina, J.; de la Moya Cerero, S.; Teso Vilar, E.; Garcia Fraile, A.; Hanack, M.; Subramanian, L. R. *J. Chem. Soc., Chem. Commun.* **1990**, 1571.
(5) Another considerable improvement of the Vilsmeier formylation is achieved when DMF is activated with pyrophosphoryl chloride: Downie, I. M.; Earle, M. J.; Heaney, H.; Shuhaibar, K. F. *Tetrahedron* **1993**, *49*, 4015.
(6) Singer, B.; Maas, G. *Chem. Ber.* **1987**, *120*, 485.

0022-3263/94/1959-6862$04.50/0

Table 1. 3-Aryl-2-hexenals 4 Obtained from Arenes and 3-Trifloxypropeneiminium Salt 3

arene	product 4 Ar	yield, %	(*E*)-**4**/(*Z*)-**4**
anisole	C_6H_4-4-OMe (**4a**[a])	55	1.33
	C_6H_4-2-OMe (**4b**[a])	6	1.00
1,3-dimethoxybenzene	C_6H_3-2,4-$(OMe)_2$ (**4c**)	49	0.19
mesitylene	C_6H_2-2,4,6-Me_3 (**4d**)	60	0.10

[a] The ratio **4a**:**4b** before chromatographic workup and distillation was 6.8:1.

Table 2. Heats of Formation ΔH_f, Relative Energies E_{rel}, and Torsion Angles between the Aryl and Olefinic Planes in 4a,c,d As Obtained from AM1 Calculations

compd	H_f, kcal/mol	E_{rel}, kcal/mol	torsion angle, deg
(*Z*)-**4a**	−50.02	0.00	58.4
(*E*)-**4a**	−49.96	0.06	48.0
(*Z*)-**4c**	−85.72	0.00	68.3
(*E*)-**4c**	−85.60	0.12	51.8
(*Z*)-**4d**	−31.90	0.00	83.0
(*E*)-**4d**	−31.48	0.42	82.1

the ^{13}C NMR resonance of the allylic CH_2 as well as of the aromatic ipso carbon[7] appears at higher field when it is *cis* to CHO). Furthermore, the observation that the CHO resonance appears at higher field in the (*Z*)-isomer is readily explained by the magnetic anisotropy of the aryl ring, provided that the latter is approximately orthogonal to the olefinic σ-plane and that the formyl group is attached in the s-trans conformation.

The decrease in the *E*/*Z* ratio in the sequence **4a** > **4b** > **4c** > **4d** appears at first glance surprising. This trend is reflected, however, by the heats of formation obtained from geometry-optimized AM1 semiempirical calculations at an elevated level of precision (GNORM = 0.01) (Table 2). Although the calculated energy differences are small, it can clearly be seen that in the series **4a**,**c**,**d** the (*E*)-isomer is increasingly disfavored with respect to the (*Z*)-isomer. While the tilting of the aryl ring against the olefinic plane (hereafter called torsion angle α) results from a compromise between π-conjugation and steric factors, increasing ortho-substitution of the aryl ring causes the latter to predominate. Thus, the tendency for a perpendicular arrangement increases in the series **4a** < **4c** < **4d**, and it is higher for the respective (*Z*)-isomer. Obviously, the perpendicularly arranged aryl ring maintains smaller steric interactions with the formyl group than the propyl substituent. The value of α calculated for (*E*)-**4a** (48°) may at first glance appear rather large, since the phenyl ring does not carry an ortho substituent. Theory and experiment show, however, that this is a consequence of α-alkyl substitution. Thus, our AM1 calculations predict α = 39.9° for α-methylstyrene, and crystal structure analyses[8] revealed α = 33 and 47° for the ketazine derived from (*E*)-3-phenyl-2-butenal, but α = 0° for the azine derived from (*E*)-3-(4-bromophenyl)-propenal. With α ≈ 40°, the formyl group (s-trans conformation) can be accommodated in a cis-relationship with the phenyl ring without much additional steric strain. In fact, our AM1 calculations provide α values of 15.7 and 43.8° for (*E*)- and (*Z*)-3-phenylpropenal, respectively.[9]

Both stereoisomers of **4a** have been prepared before, en route to potential platelet-activating factor antagonists, by Meyers' method[10] from the aromatic ketone (4-$MeOC_6H_4COC_3H_7$) and a (lithioenamino)phosphonate.[11] In contrast, the examples given in Table 1 represent the first syntheses of such substituted cinnamic aldehydes by direct introduction of a 1-substituted 2-formylvinyl moiety onto an aromatic nucleus. Furthermore, entry 1 reports the first successful vinylformylation of anisole. Note also that the reactions with **3** occur at a temperature that is probably detrimental to the thermally rather labile[1] 3-chloropropeneiminium salt generated from NMPA and $POCl_3$.

Benzene, toluene, and naphthalene did not react with **3** even at 130 °C. On the other hand, a reaction with pyrrole and indole, respectively, already at −40 to 0 °C was indicated by a color change to deep-red, but no product could be isolated.

From the reaction of anthracene with **1**, the dibenzobarrelene carbaldehyde **5** is obtained in low yield after hydrolysis (Scheme 2). The formation of this product may proceed in one of two ways, (a) by electrophilic addition of salt **3** to anthracene, followed by HOTf elimination and cyclization, or (b) by thermal β-elimination of triflic acid from **3** and [2 + 4]-cycloaddition of the propyneiminium salt so formed to anthracene. While the two steps of the latter pathway, i.e., generation and Diels–Alder reactions of propyneiminium salts, have been realized in several other cases,[12] our efforts to convert **3** into the corresponding propyneiminium triflate by vacuum thermolysis at ca. 160 °C/0.005 mbar[13] resulted only in unspecific decomposition reactions. Nevertheless, it is still possible that this propyneiminium salt has been trapped *in situ* in the presence of anthracene.

It is expected that other 3-trifloxypropeneiminium salts can also be utilized for the vinylformylation of aromatic compounds, thus providing ready access to ring-substituted cinnamaldehydes bearing additional substituents in the α- and/or β-position. However, reaction conditions or substrates that promote the base-induced[12,14] or thermal[13] β-elimination of such 3-trifloxypropeneiminium salts must be avoided.

Experimental Section

General. NMR spectra (^1H NMR: 200.1 and 400.1 MHz; ^{13}C NMR: 100.6 MHz) were measured in $CDCl_3$ with TMS as internal standard. Column chromatography was performed on silica gel, grain size 0.05–0.2 mm.

General Procedure for the Preparation of 4a–d. A solution of salt **3**[6] (3–7 mmol) and an arene (3–10 mL) in 1,2-dichloroethane (3 mL) was heated for 10–12 h at 100 °C in a Schlenk pressure tube. After cooling, the mixture was diluted with CH_2Cl_2 (20 mL), a saturated aqueous solution of $NaHCO_3$ (10 mL) was added, and the two-phase system was refluxed for

(7) Compare the assignment of the two aromatic ipso carbon atoms in 3,3-diphenylpropenal by an INAPT experiment: Bernstein, M. A. *Magn. Reson. Chem.* **1989**, *27*, 659.

(8) Elguero, J.; Marzin, C.; Berthou, J. *Bull. Soc. Chim. Fr.* **1973**, 3303.

(9) The torsion angle obtained for (*Z*)-cinnamaldehyde is in good agreement with the values obtained by earlier LCAO-MO calculations (α = 50°) and estimated from spectroscopic data (α = 46°): Remko, M.; Polcin, J. *Z. Phys. Chem. (Leipzig)* **1977**, *258*, 1187.

(10) Meyers, A.; Tamioka, K.; Fleming, M. *J. Org. Chem.* **1978**, *43*, 3789.

(11) Guthrie, R. W.; Kaplan, G. L.; Mennona, F. A.; Tilley, J. W.; Kierstead, R. W.; Mullin, J. G.; LeMahieu, R. A.; Zawoiski, S.; O'Donnell, M.; Crowley, H.; Yaremko, B.; Welton, A. F. *J. Med. Chem.* **1989**, *32*, 1820. Guthrie, R. W.; Kierstead, R. W.; Tilley, J. W. U. S. Patent US 4,788,206, 29 Nov 1988.

(12) Maas, G.; Singer, B.; Wald, P.; Gimmy, M. *Chem. Ber.* **1988**, *121*, 1847.

(13) Rahm, G.; Maas, G. *Synthesis* **1994**, 295.

(14) Singer, B.; Maas, G. *Chem. Ber.* **1987**, *120*, 1683.

3 h. The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was prepurified by column chromatography on silica gel (20 g, eluant ether–petroleum ether (1:1)) and then subjected to Kugelrohr distillation.

3-(4-Methoxyphenyl)-2-hexenal (4a) and 3-(2-Methoxyphenyl)-2-hexenal (4b). Kugelrohr distillation at 150 °C/0.05 mbar afforded a mixture of **4a** and **4b**, yield 61%, (*E*)-**4a**:(*Z*)-**4a**:(*E*)-**4b**:(*Z*)-**4b** = 10.5:7.9:1:1 according to ^{1}H NMR. Partial separation of **4a** and **4b** was achieved by bulb-to-bulb distillation at 130 °C/0.05 mbar, which left pure **4a** (*E*/*Z* = 2.2) behind, yield 31%: ^{1}H NMR (**4a**) δ 0.92 (t, CH_3, *Z*), 0.96 (t, CH_3, *E*), 1.39–1.62 (m, CH_2CH_3), 2.55 (dt, J = 7.3, 1.1 Hz, $=CCH_2$, *Z*), 3.0 (t, $=CCH_2$, *E*), 3.84 (s, OMe), 6.08 (d, J = 8.1 Hz, 2-H, *Z*) 6.30 (d, J = 8.1 Hz, =CH, *E*), 6.91–7.51 (several m), 9.48 (d, J = 8.1 Hz, CHO, *Z*), 10.12 (d, J = 8.1 Hz, CHO, *E*); (**4b**, mixture with **4a**) δ 3.78 (s, OMe), 5.16 (d, J = 7.9 Hz, 2-H, *E*), 6.11 (d, J = 8.2 Hz, 2-H, *Z*), 9.33 (d, J = 8.2 Hz, CHO, *Z*), 9.80 (d, J = 7.9 Hz, CHO, *E*); ^{13}C NMR ((*E*)-**4a**) δ 13.4 (q), 23.0 (t), 31.1 ($=CCH_2$), 55.0 (q), 113.9 (d, C-2), 127.8 (d), 129.8 (d), 131.2 ($C_{arom}C=C$), 160.9 (s), 161.9 (s), 190.5 (CHO); ((*Z*)-**4a**) δ 13.2 (q), 20.6 (t), 41.1 ($=CCH_2$), 55.0 (q), 113.5 (d, C-2), 126.0 (d), 127.8 (d), 129.5 ($C_{arom}C=C$), 160.1 (s), 165.6 (s), 193.2 (CHO). Anal. Calcd for $C_{13}H_{16}O_2$ (204.3): C, 76.44; H, 7.90. Found: C, 76.6; H, 7.8.

3-(2,4-Dimethoxyphenyl)-2-hexenal (4c). Kugelrohr distillation at 130 °C/0.01 mbar gave an oil, yield 49%, *E*/*Z* ratio = 0.19 (^{1}H NMR): IR (film) 1655, 1605 cm^{-1}; ^{1}H NMR ((*Z*)-**4c**) δ 0.91 (t, 3 H), 1.42 (m_c, 2 H), 2.52 (t, $=CCH_2$), 3.78 (s, 3 H), 3.83 (s, 3 H), 6.08 (d, J = 8.1, 2-H), 6.48–6.50 (m, 2 H), 7.00 (d, 1 H), 9.35 (d, J = 8.1 Hz, CHO); ((*E*)-**4c**) δ 2.99 (t, =C-CH_2), 6.10 (partly covered by major isomer), 7.08 (d, 1 H), 10.13 (d, J = 8.2 Hz, CHO), remaining signals covered by those of the major isomer; ^{13}C NMR ((*Z*)-**4c**) δ 13.5 (q), 20.6 (t), 40.9 (t, C-4), 55.2 (q), 55.3 (q), 98.5 (d), 104.2 (d), 119.3 (s, $C_{arom}C=$), 128.9 (d, C-2), 131.0 (d), 157.5 (s), 161.3 (s), 164.1 (s), 193.7 (d, CHO); ((*E*)-**4c**) 13.6 (q), 22.7 (t), 32.8 (t, C-4), 98.6 (d), 104.5 (d), 123.0 (s, $C_{arom}C=$), 157.7 (s), 161.6 (s), 163.9 (s), 190.4 (d, CHO), remaining signals coincide with those of the major isomer. Anal. Calcd for $C_{14}H_{18}O_3$ (234.3): C, 71.8; H, 7.7. Found: C, 71.6; H, 7.6.

3-(2,4,6-Trimethylphenyl)-2-hexenal (4d). Kugelrohr distillation at 150 °C/0.01 mbar afforded an oil, yield 60%, *E*/*Z* ratio = 0.10 (^{1}H NMR): IR (film) 1665, 1605 cm^{-1}; ^{1}H NMR ((*Z*)-**4d**) δ 0.99 (t, 3 H), 1.60 (m_c, 2 H), 2.16 (s, 6 H), 2.28 (s, 3 H), 2.37 (dt, J = 8.1, 1.5 Hz, $=CCH_2$), 6.17 (dt, J = 8.3, 1.5 Hz, 2-H), 6.89 (s, 2 H), 9.20 (d, J = 8.3 Hz, CHO); ((*E*)-**4d**) δ 6.51 (dt, J = 8.3, 1.65 Hz, 2-H), 9.43 (d, J = 8.3 Hz, CHO), remaining signals covered by those of the major isomer; ^{13}C NMR ((*Z*)-**4d**) δ 13.8 (q), 19.7 (q), 19.8 (q), 20.8 (t), 40.9 (C-4), 128.1 (d), 128.4 (d, 2 C), 134.2 (s, 2 C), 134.8 (s), 137.2 (s), 167.4 (s, C-3), 193.5 (d, CHO). Anal. Calcd for $C_{15}H_{20}O$ (216.3): C, 83.3; H, 9.3. Found: C, 83.0, H, 9.2.

9,10-Dihydro-12-propyl-9,10-ethenoanthracene-11-carbaldehyde (5). A solution of salt **3**[6] (2.31 g, 5.11 mmol) and anthracene (0.91 g, 5.11 mmol) in 1,2-dichloroethane (1 mL) was kept for 17 h at 130 °C in a Schlenk pressure tube. After cooling, CH_2Cl_2 (50 mL) and a saturated aqueous solution of $NaHCO_3$ (30 mL) were added, and the mixture was refluxed for 3 h. Usual workup of the organic phase and column chromatography on silica gel (eluent petroleum ether–ether (5:1)) afforded colorless crystals of **5** (0.30 g, 21% yield): mp 140 °C; IR (KBr) 1640 cm^{-1}; ^{1}H NMR δ 0.75 (t, 3 H), 1.61 (m_c, 2 H), 2.70 (t, 2 H, $=CCH_2$), 5.08 (s, 1 H), 5.79 (s, 1 H), 6.93–7.01 (m, 4 H), 7.29–7.34 (m, 4 H), 9.84 (s, CHO); ^{13}C NMR δ 13.4 (q), 20.9 (t), 32.0 (t), 47.0 (d, J = 145.0 Hz), 57.2 (d, J = 142.0 Hz), 123.2, 123.4, 124.8, 125.4 (all d), 143.7, 144.4, 145.0, 170.3 (all s), 185.1 (CHO).

Computational Procedure. The semiempirical molecular orbital calculations were carried out using the AM1 method[15] as implemented in the MOPAC 6.0 program.[16] Energy-minimized geometries were determined by the EF (Eigenvector following) routine (GNORM = 0.01).

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. R.R. thanks the Land Rheinland-Pfalz for a postgraduate fellowship. The BASF AG (Ludwigshafen/Rhein) has provided us with some chemicals.

(15) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
(16) Stewart, J. J. P. QCPE no. 455.