Formamides undergo in-plane bimolecular nucleophilic vinylic substitutions (S_N2) by the reaction with (*E*)-alkenyl(phenyl)iodonium tetrafluoroborates: stereoselective synthesis of (*Z*)-vinyl formates

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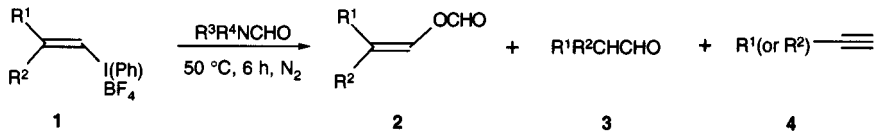
Reported for the first time is the stereoselective synthesis of (*Z*)-vinyl formates, which involves in-plane bimolecular nucleophilic vinylic substitutions of (*E*)-β-alkylvinyl-(phenyl)iodonium tetrafluoroborates with formamides.

The chemistry of vinyl formates is relatively unexplored, mostly due to the lack of an efficient method for their syntheses. Baeyer–Villiger rearrangement of conjugated enals with H_2O_2 activated with selenium catalysts, *i.e.* SeO_2 and bis(2-nitrophenyl)diselenide, affords vinyl formates.[1] Ring opening of α,β-epoxysilanes with anhydrous formic acid, followed by *anti* β-elimination of silanol, was utilized to create the vinyl formate functionality of *Latia* luciferin.[2] A method for stereoselective synthesis of (*Z*)-vinyl formates is not available. We report herein, for the first time, stereoselective synthesis of (*Z*)-vinyl formates, which involves in-plane biomolecular nucleophilic vinylic substitutions of (*E*)-β-alkylvinyl(phenyl)iodonium tetrafluoroborates **1a**–**c** with formamides (Scheme 1).[3]

The vinyl S_N2 reaction has been considered to be a high-energy pathway and neglected for a long time.[4,5] However, we reported recently that use of aryliodonio groups as a leaving group with very high leaving ability makes possible the vinylic S_N2 pathway; thus, (*E*)-(β-alkylvinyl)iodonium salts **1a**–**c** on exposure to Bu_4NX (X = Cl, Br and I) at room temperature afford the corresponding (*Z*)-vinyl halides stereoselectively with exclusive inversion of configuration in high yields.[6,7] All of the kinetic results, secondary isotope effects, substituent effects of the leaving groups, the solvent effects, the pressure effects as well as stereochemistry of the substitutions firmly establish the in-plane S_N2 mechanism. Interestingly, we found reaction of (*E*)-(β-alkylvinyl)iodonium salts **1a**–**c** with *N*,*N*-disubstituted formamides gives (*Z*)-vinyl formates **2** stereoselectively with inversion of configuration: thus, heating of a solution of (*E*)-dec-1-enyl(phenyl)iodonium tetarfluoroborate **1a** in DMF at 50 °C for 6 h under nitrogen afforded the (*Z*)-vinyl formate **2a**† in a high yield (83%) (Table 1, entry 1). The



1 **2** **3** **4**

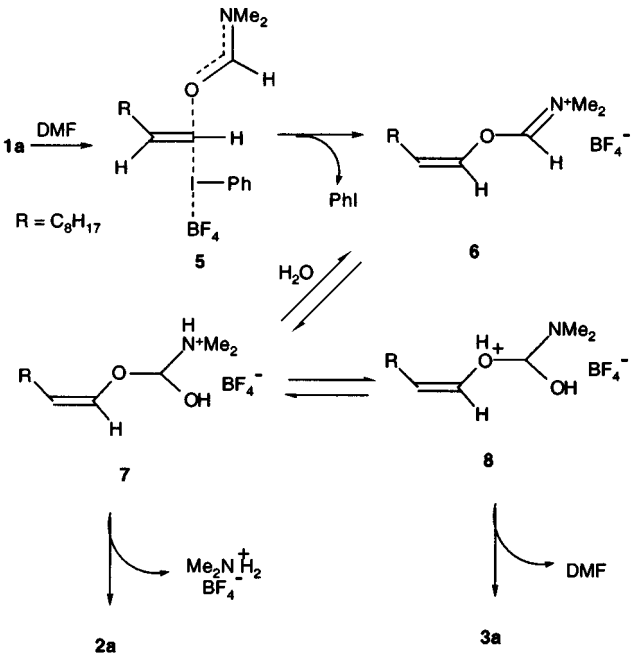
a $R^1 = C_8H_{17}$, R^2 = H, **b** $R^1 = Me_2CH(CH_2)_2$, R^2 = H, **c** $R^1 = Ph(CH_2)_3$, R^2 = H,
d $R^1 = Bu^t$, R^2 = H, **e** R^1 = Ph, R^2 = H, **f** R^1 = H, $R^2 = C_8H_{17}$, **g** $R^1 = Ph(CH_2)_3$, R^2 = Me

Scheme 1

Table 1 Nucleophilic vinylic substitution of alkenyl(phenyl)iodonium tetrafluoroborates **1** with formamides[a]

		Formamide		Product [yield (%)][b]				
Entry	**1**	R^3	R^4	**2**	**3**	Ratio[c]	**4**	Ratio[d]
1	**1a**	Me	Me	**2a** (83)	**3a** (12)	88:12	**4a** (5)	95:5
2	**1a**	Et	Et	**2a** (62)	**3a** (27)	69:31	**4a** (4)	95:5
3	**1a**	$(CH_2)_4$		**2a** (48)	**3a** (24)	67:33	**4a** (4)	94:6
4	**1a**	$(CH_2)_5$		**2a** (72)	**3a** (24)	75:25	**4a** (5)	95:5
5	**1a**	$(CH_2)_2O(CH_2)_2$		**2a** (77)	**3a** (23)	77:23	**4a** (6)	95:5
6	**1a**	Pr^i	Pr^i	**2a** (32)	**3a** (16)	67:33	**4a** (52)	48:52
7	**1a**	*c*-C_6H_{11}	*c*-C_6H_{11}[e]	**2a** (0)	**3a** (0)	—	**4a** (62)	0:100
8	**1a**	Ph	Me	**2a** (80)	**3a** (1)	99:1	**4a** (3)	97:3
9	**1a**	*p*-$MeOC_6H_4$	Me	**2a** (42)	**3a** (0)	100:0	**4a** (5)	89:11
10	**1a**	*p*-ClC_6H_4	Me	**2a** (59)	**3a** (0)	100:0	**4a** (2)	96:4
11	**1b**	Me	Me	**2b** (76)	**3b** (17)	81:19	**4b** (4)	96:4
12	**1b**	Pr^i	Pr^i	**2b** (42)	**3b** (26)	62:38	**4b** (18)	79:21
13	**1b**	Ph	Me	**2b** (47)	**3b** (1)	97:3	**4b** (0)	100:0
14	**1c**	Me	Me	**2c** (72)	**3c** (19)	79:21	**4c** (3)	97:3
15	**1c**	Pr^i	Pr^i	**2c** (0)	**3c** (0)	—	**4c** (52)	0:100
16	**1c**	Ph	Me	**2c** (31)	**3c** (1)	96:4	**4c** (1)	98:2
17	**1d**	Me	Me	**2d** (0)	**3d** (0)	—	**4d** (—)[f]	—
18	**1e**	Me	Me	**2e** (0)	**3e** (0)	—	**4e** (2)	—
19	**1f**[g]	Me	Me	**2f** (0)	**3f** (0)	—	**4a** (80)	0:100

[a] Reactions were carried out at 50 °C under N_2 for 6 h. [b] Yields were determined by GC. [c] Ratios of **2**:**3**. [d] Ratios of (**2** + **3**):**4**. [e] Reaction was carried out in a solution of $(c\text{-}C_6H_{11})_2NCHO$–DMF (3:1) at 82 °C. [f] Not determined. [g] **1f**: (*Z*)-dec-1-enyl(phenyl)iodonium perchlorate.



Scheme 2

reaction is highly stereoselective and no formation of the (*E*)-vinyl formate **2f** was detected by GC and 400 MHz ^{1}H NMR. The saturated aldehyde **3a** and the terminal alkyne **4a** were obtained as minor products in 12 and 5% yields.

N,*N*-Diethylformamide and *N*-formyl cyclic amines, *i.e. N*-formyl-pyrrolidine, -piperidine and -morpholine, similarly gave the (*Z*)-vinyl formate **2a** as a major product but with an increased amount of the aldehyde **3a** (entries 2–5). It is noted that the use of aromatic formamides such as *N*-formyl-*N*-methylanilines resulted in reactions almost free of the byproduct **3a** (entries 8–10). In contrast, the reaction course was dramatically changed when sterically demanding *N*,*N*-diisopropylformamide was used and a large amount of dec-1-yne **4a** (52%) was produced *via* elimination. With *N*,*N*-dicylohexylformamide, this elimination is the sole detectable pathway. Acetamides also act as good nucleophiles in this reaction; for instance, treatment of **1a** with *N*,*N*-dimethylacetamide at 50 °C for 6 h afforded stereoselectively (*Z*)-dec-1-enyl acetate in 62% yield, along with formation of **3a** (26%) and **4a** (7%).

The concerted vinylic S_N2 pathways are highly sensitive to the nature of β-substituents of the vinyliodonium salts and are inhibited or retarded when (*E*)-β-*tert*-butylvinyl- **1d** and (*E*)-β-phenylvinyliodonium salt **1e** were used in the reaction with halides.[6,8] This tendency was also kept in the reaction of iodonium salts **1d** and **1e** with DMF at 50 °C, which afforded no S_N2 products **2d** and **2e** (entries 17 and 18). Reaction of the (*Z*)-isomer with DMF resulted in extensive *anti* β-elimination to give **4a** in 80% yield, as reported previously.[6]

Scheme 2 illustrates a possible mechanism for formation of the (*Z*)-vinyl formate **2a** and the aldehyde **3a** from (*E*)-vinyliodonium salt **1a** by the reaction with DMF. Formamide on treatment with alkyl tosylates undergoes exclusive *O*-alkylation with no *N*-alkylation;[9] therefore, it seems reasonable to assume that the oxygen atom of DMF selectively attacks the (*E*)-vinyliodonium salt **1a** to produce the inverted (*Z*)-*O*-vinylimidonium salt **6** (Vilsmeier–Haack salt) *via* the vinylic S_N2 transition state **5**, which was stabilized by delocalization of the nitrogen lone-pair electrons. The hyper-leaving group ability of the phenyliodonio group would be responsible for the vinylic S_N2 reaction.[7] Subsequent attack of water will produce *N*-protonated tetrahedral species **7**, which collapses to **2a** with the ammonio group being released, or *O*-protonated tetrahedral species **8**, which collapses to **3a** with DMF being released.

The formate **2a** and the aldehyde **3a** seem to be kinetic products, since neither isomerization of the double bond of **2a** yielding **2f** nor hydrolysis of **2a** to the saturated aldehyde **3a** was observed under the conditions used. We believe that the ratios of the (*Z*)-vinyl formate **2a** to the saturated aldehyde **3a** might depend on the leaving ability of the ammonio groups, which will increase in the order $HN^+Pr^i_2$ < HN^+Et_2 < HN^+Me_2 < HN^+(Me)Ar. These hypotheses are in a good agreement with the observed ratios shown in Table 1.

Base-induced α-eliminations generating free alkylidene carbenes are a feasible process for β-alkylvinyliodonium salts.[10,11] The α-elimination pathway to yield the alkyne **4a**, which was established by analysis of the deuterium content (88%) of [1-^{2}H]dec-1-yne obtained by the reaction of β-deuterated **1a** with *N*,*N*-diisopropylformamide at 50 °C, would compete with the vinylic S_N2 reaction leading to the formation of **2** and **3**. The ratios of the vinylic S_N2 reaction *versus* the α-elimination shown in Table 1 clearly indicate that sterically demanding *N*,*N*-diisopropylformamide and *N*,*N*-dicyclohexylformamide will lead to steric retardation of the S_N2 pathway, which, in turn, results in formation of a large amounts of the alkyne **4**.

In general, bimolecular nucleophilic substitutions are favoured when a good nucleophile is present; however, formamides with rather low nucleophilicity undergo the vinylic S_N2 reaction under mild conditions. The origin of this unusual reaction is attributable to the hyper-leaving group ability of the phenyliodonio group.

Notes and references

† *Selected data* for **2a**: δ_H(400 MHz, $CDCl_3$) 0.88 (t, *J* 6.3, 3H), 1.2–1.44 (m, 12H), 2.16 (q, *J* 6.9, 2H), 4.99 (dt, *J* 7.5 and 6.9, 1H), 7.07 (d, *J* 7.5, 1H), 8.08 (s, 1H); δ_C(100 MHz, $CDCl_3$) 14.1, 22.7, 24.5, 29.1, 29.2, 29.3, 29.4, 31.9, 116.1, 132.7, 158.0; ν_{max}($CHCl_3$)/cm^{-1} 2920, 2850, 1725, 1665, 1460, 1380, 1170, 910; *m/z* (EI) 184 (M^+, 1%), 138 (4), 110 (8), 96 (19), 82 (38), 68 (32), 57 (100); HRMS calc. for $C_{11}H_{20}O_2$ (M^+), 184.1463, found 184.1470.

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