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Regioselective cationic reduction of 2-aryl-1-*N*-(ethoxycarbonyl)enamines to 2-arylethylamine carbamates

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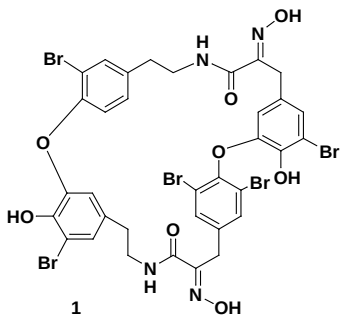
Abstract—2-Aryl-1-*N*-carboalkoxyenamines (enamides) are selectively reduced to the corresponding 2-arylethylamine carbamates by Et_3SiH in the presence of CF_3COOH in excellent yields. The reduction proceeds by addition of hydride at C-1 and the rate-limiting step involves proton transfer from CF_3COOH. This reduction is useful for preparation of isotopically labeled arylethylamines. © 2001 Elsevier Science Ltd. All rights reserved.

2-Arylethylamines, especially derivatives of dopamine, serotonin and analogous neuroactive phenethylamines, occupy a special place in medicinal chemistry.[1,2] Many methods have been described for synthesis of phenethylamines and their *N*-acyl derivatives including reduction of β-nitrostyrenes,[3] alkylation of acetonitriles by benzyl halides followed by reduction,[4] and Curtius rearrangement of cinnamic acid-derived acyl azides followed by reduction of the resulting enamide C=C double bond.[5]

In our synthesis of novel analogs of bastadin-5 (**1**),[6] an agonist of the RyR1 Ca^{2+} channel, we required a general preparation of arylethylamines by reduction of enamides which would be a tolerant substitution on the aryl ring by halogen and other functional groups sensitive to reduction. Furthermore, we required regiospecific delivery of a hydride equivalent to the vinyl group in anticipation of preparation of several ^3H-labeled analogs.



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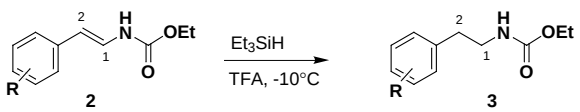
Unfortunately, most of the above-mentioned syntheses of phenethylamines methods require conditions for reduction that are relatively harsh or would result in loss or scrambling of ^3H-label. We report here that cationic reduction of 1-*N*-(ethoxycarbonyl)enamines (referred to, herein, as enamides, Scheme 1) with Et_3SiH in the presence of trifluoroacetic acid (TFA) proceeds smoothly to give 2-aryl-1-ethylamine carbamate derivatives in excellent yields. Kinetic studies and isotopic labeling show that the mechanism of reduction proceeds by exclusive delivery of hydride to the carbon α- to the nitrogen.

Starting material enamides **2a**–**f** were prepared from the corresponding cinnamic acids in three sequential steps: conversion to the acyl azides (EtOCOCl, *i*-Pr_2EtN, −10°C, 2 h, acetone, then NaN_3, aq., 0°C 5 h), Curtius rearrangement[7] (toluene, 110°C) and capture of the intermediate isocyanate with EtOH (80°C, overall yields for three steps, 70–83%). Optimization of the cationic reduction was performed by surveying various conditions with the substrate **2a**. The most efficient method was found to be addition of TFA to a rapidly stirred mixture of Et_3SiH (1.6–10 equiv.) and **2a** (final conc. ~70 mM) at −10°C, and stirring for 30 min at −10°C followed by quenching the reaction with $NaHCO_3$ aq. and extractive workup.[8] The yield of product **3** was



2 **3**

Scheme 1.

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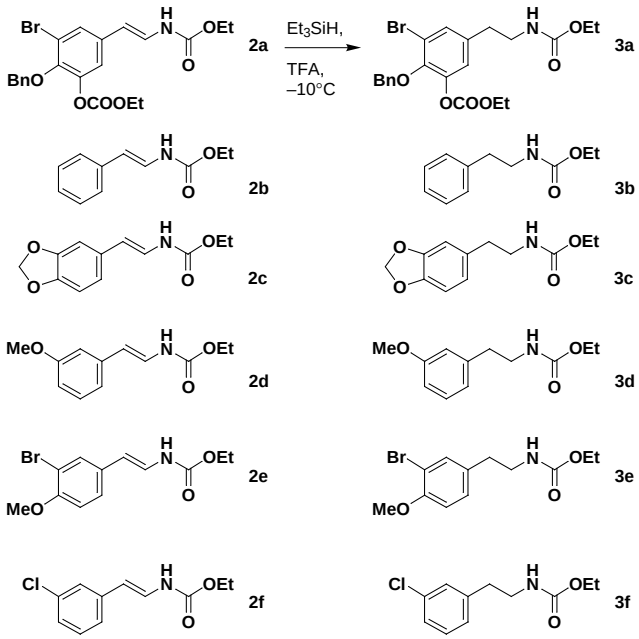
Table 1. Cationic reduction of enamides **2** using Et_3SiH (10 equiv.) in TFA (−10°C)[a]

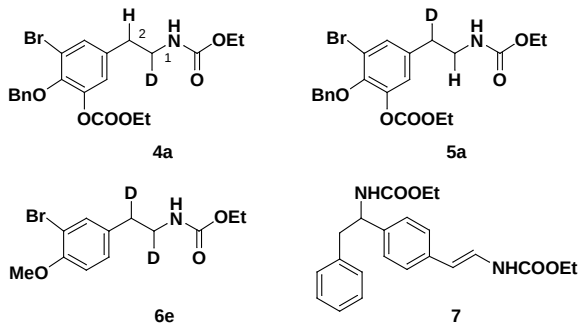
Entry	Reductant (10 equiv.)	Solvent	Substrate	Product	Reaction time (h)	Yield (%)
1	Et_3SiH	TFA	**2a**	**3a**	0.5	94
2	Et_3SiH	TFA	**2b**	**3b**	0.5	92
3	Et_3SiH	TFA	**2c**	**3c**	0.5	97
4	Et_3SiH	TFA	**2d**	**3d**	0.5	99
5	Et_3SiH	TFA	**2e**	**3e**	0.5	99
6	Et_3SiH	TFA	**2f**	**3f**	0.5	94
7	Et_3SiD	TFA	**2a**	**4a**	0.5	63[b]
8	Et_3SiH	TFA-d_1	**2a**	**5a**	6.0	77[b]
9	Et_3SiD	TFA-d_1	**2e**	**6e**	7.0	98

[a] Substrate concentraion, 60–90 mM. The reactions were conducted with vigorous stirring (two-phase system) and quenched by pouring the mixture into cold $NaHCO_3$ aq. followed by extractive workup (CH_2Cl_2) in the usual manner.
[b] Unoptimized yields.

excellent in every case studied (92–99%) and the conditions mild enough to preserve other functional groups sensitive to reduction or prone to solvolysis. Neither aryl halides nor *O*-Bn groups were reduced (entries 1, 5 and 6) and catechol acetals and carbonate esters (entries 1 and 3) were preserved. Enamides containing highly functionalized aryl rings were efficiently reduced without side reaction. For example, conversion of the enamide **2a** to **3a** (entry 1, 94%) proceeded smoothly and preserved the ethyl carbonate ester, the *O*-benzyl protecting group and the aryl Br group (the latter two would be readily cleaved by catalytic hydrogenation). Reduction of **2a** with $NaBH_4$ in TFA (−10°C) also resulted in high yields of **3a** (>90%) although, workup was less convenient.



The mechanism of the reaction was briefly explored by measuring and comparing the reaction rates in the presence of deuterated and non-deuterated reagents. Reduction of **2a** using Et_3SiD in place of Et_3SiH, but otherwise employing the same conditions as for other entries in Table 1, resulted in high conversion to deuterium-labeled arylethylamine d_1-**4a** in about the same time (30 min).



Comparison of the ^1H NMR signals for the α-CH_2 and β-CH_2 groups (δ 3.38, dt, $J=5.6$, 6.8 Hz and 2.74, t, $J=6.8$ Hz) with those of d_1-**4a** showed simplified ^1H NMR multiplet patterns due to substitution by ^2H and significant ^1H–^2H coupling. Integration of the respective signals in d_1-**4a** gave a ratio of ~2:1 indicating substitution of the α-position with one ^2H atom. This was confirmed by analysis of the MS spectrum of 1-d_1-**4a** which revealed almost complete mono-deuteriation (d_1 ~95 atom%). EIMS spectra **3a** and d_1-**4a** did not give useful fragmentation patterns, but ^{13}C NMR confirmed the location of the deuterium exclusively at the α-carbon (δ 41.7, CH_2, C-1). Conversely, when the reduction was carried out with Et_3SiH and TFA-d_1 as solvent the reaction was much slower (6 h, see below) and gave a high yield of an isomeric d_1 product, 2-d_1-**5a** (77%) in which deuterium was located entirely at the β-position (δ 35.2, CH_2, C-2, d_1 ~80 atom%).[9] Finally, doubly-deuterated **6e** was prepared by reduction of **2e** in the presence of both deuterated silane and TFA (entry 9, 98%).

The relative rates of reduction of **2a** in the presence of deuteriated and non-deuteriated reagents (Table 2) in excess (10-fold excess of Et_3SiH/D or ~12 M CF_3COOH/D) were measured by monitoring the ^1H NMR spectrum of aliquots of the reaction mixture. Suprisingly, the rate of reaction (intergration of ^1H NMR signals) was found to follow zero-order kinetics with respect to **2a** (rate $=7.12\times10^{-5}$ mol dm^{-3} s^{-1}, Table 2, entry 1). When Et_3SiD was used as reductant the rate of formation of **4a** was essentially the same as that of **3a** (7.10×10^{-5} mol dm^{-3} s^{-1}), however, substitution of TFA by TFA-d_1 diminished the rate of formation of **5a** by an order of magnitude (6.8×10^{-6} mol dm^{-3} s^{-1}).

Table 2. Apparent zero-order rates for cationic triethylsilane reductions of enamide **2a** (initial $c = 70$–90 mM, $T = -10$°C) in TFA

Reagents[a]	Rate (mol dm^{-3} s^{-1})
Et_3SiH–TFA	7.12×10^{-5}
Et_3SiD–TFA	7.10×10^{-5}
Et_3SiH–TFA-d_1	6.80×10^{-6}

[a] Initial concentrations. $CF_3COOH(D)$; ~12 M; $Et_3SiH(D)$ ~1 M

The lack of dependence of the rate of reduction on enamide concentration suggests that the rate-limiting step does not involve the protonation of enamide, nor hydride transfer from silane.[10] While more detailed analysis of this kinetic isotope effect on the reduction is beyond the scope of this communication, the kinetic isotope effect is highly suggestive that the rate-limiting step possibly involves dissociation of TFA prior to proton transfer to the enamide (Fig. 1, path a).

Another possible explanation for both the rate and kinetic isotope effect is protonation followed by a slow, rate-limiting C-2→C-1 migration of hydride, then fast Et_3SiH reduction of the incipient cation (*ii*, Fig. 1, *path b*), however, the expected isotope effects for 1,2-^{2}H migration should be much smaller than those observed. Alternatively, since the reaction is two-phase, we cannot discount the possibility that rate-limiting physical processes occur at the liquid–liquid interface.

Classical cationic silane reductions of vinyl compounds,[11] even *N*-enelactams,[12] usually proceed slowly (12–50 h) or require elevated temperatures (≥ 50°C). Conversely, we find that reduction of the *N*-(alkoxycarbonyl)enamines, **2**, are efficient at −10°C. The ease of reduction of these *N*-vinyl *carbamate*s is clearly related to the high electrophilicity of *N*-acyliminium ion, *i* (Fig. 1), a property that manifested itself in other ways.

For example, when **2b** was left to stand in $CDCl_3$ solution at room temperature, spontaneous dimerization to **7** (purified yield, ~23%) and other products was observed. This electrophilic aromatic substitution, which was also observed for **2c** and **2d** but not **2f**, was

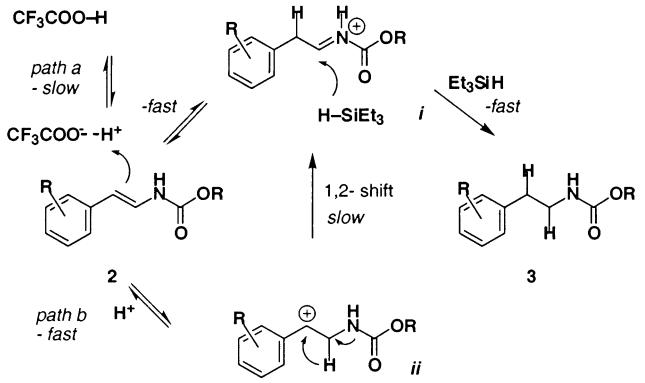


Figure 1. Two possible mechanisms of cationic enamide reduction in the presence of CF_3COOH and Et_3SiH.

presumed to be catalyzed by trace acid in the NMR solvent and proceeded at a rate that was observed to be dependent upon the initial concentration of starting material. Under the same conditions, spontaneous dimerization was not seen in the electron-poor enamide **2f** suggesting that suitably electron-rich arenes are required as electrophilic acceptors in this reaction.

In summary, we have described a new preparation of phenethylamine carbamates by mild cationic reduction of the corresponding enamide. This reaction should find utility in preparation of biologically active phenethylamines. The facile nature of the reaction is a consequence of the high electrophilicity of *N*-(alkoxycarbonyl)enamines.

Acknowledgements

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8. Representative preparation of **3a**: A mixture of triethylsilane (170 μL, 1.07 mmol) and **2a** (32 mg, 0.069 mmol) was cooled to −10°C in an ice-salt bath, under N_2, and treated with pre-cooled TFA (1.0 mL) in one portion. The two-phase mixture was *rapidly* stirred at −10°C for 0.5 h, poured into ice-cold satd. aq. $NaHCO_3$, worked up by extraction with CH_2Cl_2, dried (Na_2SO_4) and concentrated to give essentially pure **3a** (30 mg, 94%). ^{1}H NMR ($CDCl_3$) 1.22 (t, $J=7.2$ Hz, 3H, Me), 1.29 (t, $J=7.2$ Hz, 3H, Me), 2.74 (t, $J=6.8$ Hz, 2H, CH_2, C-2), 3.38 (dt, $J=5.6$, 6.8 Hz, 2H, CH_2, C-1), 4.10 (q, $J=7.2$ Hz, 2H, CH_2), 4.21 (q, $J=7.2$ Hz, 2H, CH_2), 4.74 (bt, $J=5.6$ Hz, 1H, NH), 4.99 (s, 2H, $PhCH_2O$), 6.96 (d, $J=2.0$ Hz, 1H, Ar), 7.29 (d, $J=2.0$ Hz, 1H, 7.3–7.5 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$) 14.1 (CH_3), 14.6 (CH_3.), 35.2 (CH_2, C-2), 41.7 (CH_2, C-1), 60.8 (CH_2) 65.2 (CH_2), 75.5 (CH_2), 118.1 (C), 122.6 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 131.1 (CH), 136.4 (C), 136.6 (C), 145.1 (C), 146.8 (C), 152.9 (C=O), 156.5 (C=O), HRMS (CI), m/z 466.0864, $C_{21}H_{25}BrNO_6$ $[MH]^+$, calcd. 466.0865
9. The slightly lower *d*-content of **5a** is explained by dilution of the isotopic content of TFA-d_1 by rapid exchange of the NH group.
10. This contrasts with ionic silane hydrogenations of unactivated alkenes where hydride addition is the rate-limiting step (see Ref. 11)
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