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Captodative Formyl- and Acyl(amino)alkenes Containing a Terminal Double Bond or a Weakly Basic Tertiary Amino Group

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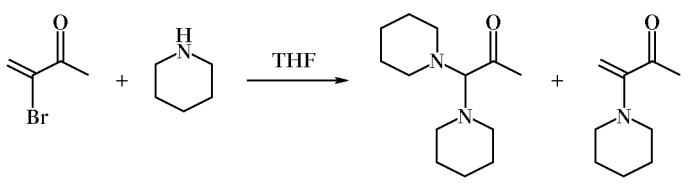
Abstract—Piperidine reacts with 3-bromo-3-buten-2-one to give a mixture of 3,4-dipiperidinobutan-2-one and 3-piperidino-3-buten-2-one. The latter is also formed by the action of a strong base (Et_3N in THF or MeONa in MeOH) on the dipiperidino derivative. Analogous reaction of 2-bromo-3-phenylpropenal with *N*-methylaniline affords 2-[methyl(phenyl)amino]-3-phenylpropenal which is the first captodative formyl-(amino)alkene having a weakly basic tertiary amino group.

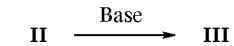
Until recently, captodative carbonyl-containing aminoalkenes remained *terra incognita*. However, they now attract increasing attention and constitute a specific group of organic compounds [1]. We previously developed a procedure for the synthesis of 1-formyl-1-aminoalkenes on the basis of reaction of the corresponding haloalkenes with highly basic secondary amines [2, 3]. Numerous examples of the synthesis of captodative acyl(amino)alkenes by nucleophilic substitution of the halogen atom in geminal acyl(halo)alkenes have been reported [4]. However, it is considerably more difficult to obtain in this way captodative formyl- or acyl(amino)alkenes having a terminal double bond or a weakly basic tertiary amino group. It is known that the predominant pathway of the reaction of 2-chloropropenal with secondary amines is formation of 1,3-diamino-2-chloropropene [3]. Methyl 2-piperidinoacrylate is formed in a poor yield (5–10%) by the action of piperidine on methyl 2-chloroacrylate in benzene, whereas the major product is methyl-2,3-dipiperidinopropionate [5].

We have found that the reaction of 3-bromo-3-buten-2-one (**I**) with piperidine leads to a mixture of di- and monopiperidino derivatives **II** and **III**. The product ratio depends on the presence of another base in the reaction mixture. In the reaction of piperidine with bromoalkene **I** at a ratio of 2:1 in THF at room temperature, a mixture of 3,4-dipiperidinobutan-2-one (**II**) and 3-piperidino-3-buten-2-one (**III**) at a ratio of 4:1 was obtained. When the reaction was carried out with equimolar amounts of the reactants in the presence of 2 equiv of triethylamine, the fraction of monopiperidino derivative **III** increased to 45%

Scheme 1.



I **II** **III**



II → **III**

Base = Et_3N or MeONa/MeOH.

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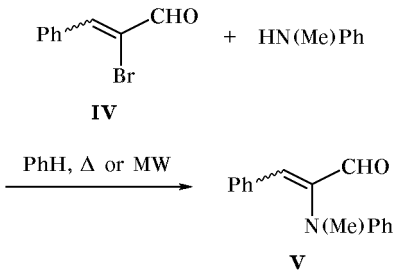
(Scheme 1). These results led us to presume that the basicity of the deaminating agent (in the above case, tertiary amine) should be increased to successfully complete the process. This presumption was confirmed when triethylamine was replaced, e.g., by an alcoholic solution of alkali metal alkoxide. In fact, by the action of sodium methoxide in methanol, diaminoketone **II** loses piperidine at room temperature, affording captodative acetyl(amino)alkene **III**. Aminoenone **III** was also obtained by one-pot procedure including successive treatment of bromoalkene **I** with 2 equiv of piperidine and a solution of sodium methoxide in methanol.

We previously reported on unsuccessful attempts to involve weakly basic secondary amines in reactions with geminal formyl(halo)alkenes [3]. However, it was recently showed that Michael addition of primary and secondary amines to α,β-unsaturated carbonyl compounds can be accelerated by microwave radiation [6] or by applying a high pressure [7–9]. Taking this into account, we turned again to the synthesis of captodative aminoalkenes having a weakly basic amino group. We have found that the reaction of 2-bromo-3-phenylpropenal (**IV**) with *N*-methylaniline (which is 4 to 7 orders of magnitude less basic than the secondary amines used so far) proceeds at a low rate but with excellent selectivity. According to the GC–MS data, heating of a mixture of aldehyde **IV** and *N*-methylaniline in an ampule for 30 h at 90°C gave aminoalkenal **V** as the only product (Scheme 2). In the microwave-activated reaction, the conversion of substrate **IV** was 15% in 15 min.

Scheme 2.



IV **V**

The formation of aminoalkenal **V** in a good yield is the first example pf successful synthesis of geminal formyl(amino)alkenes having a weakly basic tertiary amino group.

Despite obvious similarity, there are considerable differences in the structures of compounds **III** and **V**. Acetyl(piperidino)ethene **III** has an *s-trans* conformation, while its formyl analog **V** is an *s-cis* conformer. This follows, e.g., from the intensities of IR absorption bands belonging to stretching vibrations of the carbonyl group and double bond. In addition, NOE analysis of the structure of aminoalkene **V** confirmed the *Z-s-trans* conformation of its major isomer.

A fundamental problem in the chemistry of captodative olefins is estimation of the donor and acceptor effects of geminal substituents on the degree of p,π and π,π conjugation in such systems. In the first approximation, these effects can be estimated from the difference in the chemical shifts of the neighboring olefinic carbon atoms. As a rule, the C_β atom in captodative carbonyl-containing aminoalkenes resonates in a stronger field than the α-carbon atom [1, 10]. The difference $\Delta(\delta C_\beta - \delta C_\alpha)$ reaches –25 to –45 ppm and is comparable with that observed for unsubstituted enamines. In the ^{13}C NMR spectrum of aminoenone **III**, the β- and α-sp^2-carbon signals appear at δ_C 98.52 and 157.34 ppm, respectively. These data indicate a strong polarization of the double bond and predominant contribution of the enamine structure to the ground state of the molecule. By contrast, the difference $\delta(C_\beta) - \delta(C_\alpha)$ for aminoalkene **V** having a formyl group ranges from –1.2 to 10.7 ppm, which is the result of reduced donor power of the disubstituted amino group.

Analysis of the two-dimensional (COSY, HMBC, and NOESY) NMR spectra of 2-[methyl(phenyl)amino]-3-phenylpropenal (**V**) allowed us to assign unambiguously all its ^1H and ^{13}C signals. Our results put in doubt the assignment of signals from the sp^2-carbon atoms in the previously described acyl analog of aminoalkene **V**, 3-(*N*-methylanilino)-3-hexen-2-one. The authors [11] assigned the signals at δ_C 116.9 and 142.0 ppm to the olefinic and aromatic carbon atoms, respectively; we believe it more reasonable to interchange them. In this case, the disagreement between the spectral data for *N*-methylanilinoalkenes activated by alkoxycarbonyl, acyl, or formyl group is eliminated [1].

The synthesis of captodative formyl- and acyl(amino)alkenes having a terminal double bond or a weakly basic tertiary amino group extends the scope of application of the method based on nucleophilic vinyl substitution of halogen in activated haloalkenes. Undoubtedly, captodative aminoalkenes possessing double bonds with considerably different polarities attract specific interest; they will be the subject of our further studies.

EXPERIMENTAL

The IR spectra were recorded on a Specord 75IR spectrophotometer from samples prepared as thin films. The ^1H and ^{13}C NMR spectra were obtained

on a Bruker DPX-400 instrument (400 and 100 MHz, respectively) from solutions in $CDCl_3$ at room temperature. The ^{13}C signals were assigned using the DEPT sequence. GC–MS data were acquired on a Hewlett–Packard HP 5971A mass selective-detector coupled with an HP-5890 chromatograph (energy of ionizing electrons 70 eV; Ultra-2 column, 5% of phenylmethylsilicone).

α-Bromocinnamaldehyde (**IV**) was prepared by successive bromination and dehydrobromination of cinnamaldehyde [12]. 3-Bromo-3-buten-2-one (**I**) was synthesized by a procedure analogous to that reported in [13].

3-Bromo-3-buten-2-one (I). A solution of 16 g (10 mmol) of bromine in 15 ml of $CHCl_3$ was added over a period of 0.5 h at 0°C to a solution of 7.0 g (10 mmol) of methyl vinyl ketone in 20 ml of $CHCl_3$. When the addition of bromine was complete, the mixture was allowed to warm up to room temperature and was left to stand for 3 h. The solution was evaporated, the residue was dissolved in 20 ml of diethyl ether, the solution was cooled to 10°C, a solution of 12.1 g (10 mmol) of *N*,*N*′-dimethylaniline in 20 ml of Et_2O was added, and the mixture was left to stand for 12 h at room temperature. The mixture was treated with water and extracted with ether (2 × 50 ml), the extracts were dried over $MgSO_4$, the solvent was distilled off, and the residue was distilled under reduced pressure. Yield 6.0 g (40%), bp 55–56°C (20 mm) (cf. [14]). IR spectrum, ν, cm^{-1}: 1609 (C=C), 1697 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.43 s (3H); 6.38 d (1H, *J* = 2.4), 6.76 d (2H, *J* = 2.4). ^{13}C NMR spectrum, δ_C, ppm: 26.03 (CH_3), 129.53 (=CH_2), 131.96 (=CBr), 191.88 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 150, 148 (45, M^+); 107, 105 (27); 143 (100). Found, %: C 32.11; H 3.68; Br 53.66. C_4H_5BrO. Calculated, %: C 32.25; H 3.38; Br 53.63.

Reaction of 3-bromo-3-buten-2-one (I) with piperidine. A solution of 2.8 g (18 mmol) of 3-bromo-3-buten-2-one in 30 ml of anhydrous THF was added with stirring to a solution of 3.4 g (40 mmol) of piperidine in 40 ml of anhydrous THF. The mixture was kept for 24 h at room temperature, the precipitate of piperidine hydrobromide was filtered off, and the filtrate was evaporated. A solution of sodium methoxide in methanol (prepared from 0.2 g of sodium and 20 ml of methanol) was added to the residue, and the mixture was left to stand for 24 h at room temperature. The mixture was treated with water (10 ml) and extracted with ether (5 × 50 ml), the extracts were dried over $MgSO_4$ and evaporated, and the residue was distilled under reduced pressure to obtain 0.6 g (22%) of 3-piperidino-3-buten-2-one (**III**), bp 43–44°C (1 mm). IR spectrum, ν, cm^{-1}: 1585 (C=C), 1698 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.45–1.70 m (6H, β,γ-CH_2, piperidine), 2.30 s (3H, CH_3CO), 2.70–2.75 m (4H, α-CH_2, piperidine), 4.47 d (1H, =CH_2, *J* = 0.9), 4.87 d (1H, =CH_2, *J* = 0.9). ^{13}C NMR spectrum, δ_C, ppm: 24.16, 25.68 (β,γ-CH_2, piperidine); 27.69 (CH_3), 50.66 (NCH_2); 98.52 (=CH_2); 157.34 (=C–N); 200.54 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 153 (41, M^+), 152 (34), 110 (100), 54 (44), 43 (42). Found, %: C 70.00; H 10.00; N 8.87. $C_9H_{15}NO$. Calculated, %: C 70.55; H 9.87; N 9.14.

3,4-Dipiperidinobutan-2-one (II) was identified by the ^1H and ^{13}C NMR spectra, as well as by the GC–MS data [in a mixture with 3-piperidino-3-buten-2-one (**III**)]. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.30–1.55 m (12H, β,γ-CH_2, piperidine), 2.14 s (3H, CH_3CO), 2.30–2.50 m (10H, NCH_2), 3.08 d.d (1H, CHN, *J* = 9.1, 5.1). ^{13}C NMR spectrum, δ_C, ppm: 24.46, 24.61, 26.20, 26.52 (β, γ-CH_2, piperidine); 28.27 (CH_3); 52.01, 55.27 (NCH_2); 210.22 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 238 (< 1, M^+), 195 (1), 98 (100), 41 (13).

(*Z*,*E*)-2-[Methyl(phenyl)amino]-3-phenylpropenal (V). *a*. A mixture of 1.1 g (10 mmol) of *N*-methylaniline, 1.1 g (5 mmol) of α-bromocinnamaldehyde (**IV**), and 0.6 g (5.5 mmol) of triethylamine in 2 ml of anhydrous THF was heated for 30 min at 90°C in a sealed ampule. The precipitate of triethylamine hydrobromide was filtered off, and the filtrate was evaporated. The residue was subjected to column chromatography on silica gel using hexane–ether (1 : 1) as eluent to isolate 0.6 g (51%) of (*E*,*Z*)-2-[methyl(phenyl)amino]-3-phenylpropenal (**V**) as a colorless oil. Both isomers were isolated by column chromatography. IR spectrum, ν, cm^{-1}: 1592 (C=C), 1684 (C=O). ^1H NMR spectrum, δ, ppm: *Z* isomer: 3.03 s (3H, NMe); 7.28 s (1H, CH=); 6.65–7.55 m (10H, C_6H_5); 9.50 s (1H, CHO); *E* isomer: 3.24 s (3H, NMe); 6.90–7.50 m (11H, CH=, C_6H_5); 9.81 s (1H, CHO). ^{13}C NMR spectrum, δ, ppm: *Z* isomer: 37.81 (NMe); 113.78, 118.87, 129.05, 129.47, 130.28, 139.77, 133.40, 146.79 (C_6H_5); 142.36 (CH=); 143.54 (=C–N); 192.39 (CHO); *E* isomer: 40.52 (NMe); 119.00, 121.23, 128.33, 128.49, 128.78, 129.66, 134.18, 148.42 (C_6H_5); 135.41 (CH=); 146.10 (=C–N); 189.57 (CHO). Mass spectrum, *m*/*z* (I_{rel}, %): 237 (37, M^+), 208 (56), 193 (100), 165 (44), 77 (60). Found, %: C 80.27; H 6.56; N 5.86. $C_{16}H_{15}NO$. Calculated, %: C 80.98; H 6.37; N 5.90.

b. The reaction mixture (prepared as described above in *a*) was kept for 15 min in a sealed ampule placed in a microwave oven at a power of 700 W.

According to the GC–MS data, the conversion of initial bromoaldehyde **IV** was ~15%.

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