Direct Conversion of Aliphatic Carboxamides to Alkylammonium Tosylates with [Hydroxy(tosyloxy)iodo]benzene

I. Mark Lazbin and Gerald F. Koser*

Department of Chemistry, The University of Akron, Akron, Ohio 44325

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The utility of [hydroxy(tosyloxy)iodo]benzene (2) as a "Hofmann reagent" has been explored. Treatment of various primary, aliphatic carboxamides ($RCONH_2$, R = methyl, ethyl, isopropyl, *tert*-butyl, *n*-pentyl, *n*-heptyl, undecyl, allyl, benzyl, cyclobutyl, cyclohexyl) with 2 in acetonitrile at reflux gave the corresponding alkylammonium tosylates ($RN^+H_3^-OTs$) in yields ranging from 57% to 94%. The alkylammonium tosylates separated directly from the solvent when the reaction mixtures were kept at room temperature or below. When α-phenylacetamide was allowed to react with 2 in ethanol, ethyl benzylcarbamate (4) was obtained in 50% yield, a result consistent with the intermediate existence of benzyl isocyanate in this reaction. A mechanism for the conversion of carboxamides by 2 to alkylammonium tosylates, involving the initial formation of *N*-phenyl iodonio amides and their collapse to iodobenzene and alkyl isocyanates, is proposed. The reaction of malonamide with 2 in acetonitrile followed a divergent course: 2-(tosyloxy)malonamide (3) was obtained in ca. 81% yield (crude).

The conversion of primary carboxamides to amines possessing one less carbon atom by the action of chlorine or bromine in aqueous alkali was first described by Hofmann over a century ago.[1] Much more recently, Loudon and his co-workers have developed a procedure for effecting the Hofmann reaction under mildly acidic conditions.[2-4] Treatment of an aliphatic, primary carboxamide with [bis(trifluoroacetoxy)iodo]benzene (1) in 1:1 v/v aqueous acetonitrile (pH 1–3) followed by the introduction of HCl (aqueous), extraction of the mixture with ether, and concentration of the aqueous layer delivers the corresponding amine hydrochloride in excellent yield (eq 1).

$$RCONH_2 \xrightarrow[CH_3CN/H_2O,\ \text{room temperature}]{PhI(OOCCF_3)_2} \xrightarrow{HCl} RN^+H_3Cl^- \quad (1)$$

The range of substrates that respond to 1 includes acylamino amides and peptide amides,[2,3,5,6] and 1 has been employed in the sequential degradation of carboxyl terminal peptides.[5] Several precautionary measures for the effective use of 1 as a Hofmann reagent have been advised.[3] These include careful control of the proportions of (diacetoxyiodo)benzene and trifluoroacetic acid used in its preparation, protection of 1 from light and its storage under nitrogen, the use of glass-distilled water in the reaction medium, and the exclusion of chloride ions from the starting amide (i.e., if the amide is prepared from an acyl chloride).

[Hydroxy(tosyloxy)iodo]benzene (2) is a readily available and stable crystalline compound which can be handled under ambient conditions with no ill effects.[7-9] It has proven to be a useful reagent for the tosyloxylation of ketones[10] and alkenes[11,12] and in the synthesis of iodonium salts from alkynes,[13-15] thiophenes,[16] (trimethylsilyl)furans,[17] and (trimethylsilyl)arenes.[18] We were prompted by the investigations of Loudon to explore the utility of 2 as a Hofmann reagent, and we report herein the results of that study.

Table I. Alkylammonium Tosylates from Primary Carboxamides and [Hydroxy(tosyloxy)iodo]benzene in Acetonitrile

$RCONH_2$, R	vol MeCN, mL	time at reflux	yield of $RN^+H_3^-OTs$, %
CH_3	45	15 h	93
CH_3CH_2	50	40 min	90
$(CH_3)_2CH$	45	40 min	71
$(CH_3)_3C$	50	40 min	91
$CH_3(CH_2)_3CH_2$	45	45 min	94
$CH_3(CH_2)_5CH_2$	50	1.5 h	93
$CH_3(CH_2)_9CH_2$	50	40 min	57
$CH_2{=}CHCH_2$	45	15 min	59
$PhCH_2$	50	1.5 h	89
cyclobutyl	50	75 min	88
cyclohexyl	55	30 min	90

[Hydroxy(tosyloxy)iodo]benzene is largely insoluble in acetonitrile at room temperature but dissolves at reflux to give yellow solutions. When 2 was mixed with various aliphatic primary carboxamides in acetonitrile (reagent grade, *no water added*) and the mixtures were heated at reflux, the yellow solutions usually decolorized. When they were then cooled at room temperature or below, the corresponding alkylammonium tosylates separated (eq 2).

$$RCONH_2 + \underset{2}{PhI(OH)OTs} \xrightarrow[\Delta]{CH_3CN} RN^+H_3^-OTs + PhI \quad (2)$$

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Thus, [hydroxy(tosyloxy)iodo]benzene not only promotes the Hofmann reaction in acetonitrile alone but also functions as an in situ source of *p*-toluenesulfonic acid and gives ammonium salts having relatively low solubilities in the cold solvent.

For example, a mixture of isobutyramide (10 mmol) and **2** (10 mmol) in acetonitrile (45 mL) was heated under reflux for 40 min. The resulting colorless solution was then kept at ca. −20 °C, whereupon isopropylammonium tosylate separated and was isolated in 71% yield. The conditions and yields for the reactions of ten other aliphatic amides with **2** are summarized in Table I. The method is not without limitations; attempts by us to obtain anilinium tosylate from benzamide and aliphatic ammonium tosylates from cyclopropanecarboxamide, chloroacetamide, and 2-cyclopenteneacetamide were unsuccessful.

The reaction of **2** with malonamide in acetonitrile followed a different course; 2-(tosyloxy)malonamide (**3**) was obtained in ca. 81% yield (crude). This result parallels the reactions of **2** with ketones and β-diketones wherein α-tosyloxylation occurs.[10]

$$\underset{\mathbf{3}}{TsOCH(CONH_2)_2} \qquad \underset{\mathbf{4}}{PhCH_2NHCOOEt}$$

The formation of intermediate alkyl isocyanates in the reactions of **2** with carboxamides, as in the reactions of carboxamides with **1** in aqueous acetonitrile and in the classical Hofmann reaction, seems likely and was tested with a selected amide. When a solution of phenylacetamide and **2** in ethanol was heated under reflux, ethyl benzylcarbamate (**4**) was formed and isolated in 50% yield after workup.

A plausible mechanism for the conversion of aliphatic amides to alkylammonium tosylates by **2** is given in Scheme I. The initial formation of an *N*-phenyl iodonio amide and its collapse to an alkyl isocyanate seems likely and is consistent with the intermediacy of *N*-halo amides in the classical Hofmann reaction. Hydration of the isocyanate, decarboxylation of the resulting carbamic acid, and protonation of the amine thus produced are all well-documented processes. The water for the hydration step may either originate in the first step or be present as adventitious moisture in the solvent which was not dried prior to use.

Scheme I

$$RCONH_2 + PhI^+(OH)^-OTs \rightarrow RCONHI^+Ph^-OTs + H_2O$$

$$RCONHI^+Ph^-OTs \rightarrow RN{=}C{=}O + p\text{-}TsOH + PhI$$

$$RN{=}C{=}O \xrightarrow{H_2O} RNHCOOH \rightarrow RNH_2 + CO_2$$

$$RNH_2 + p\text{-}TsOH \rightarrow RN^+H_3{}^-OTs$$

Experimental Section

General. ^1H NMR spectra were recorded on a Varian EM-360 spectrometer. Elemental analyses were performed by Galbraith Laboratories in Knoxville, TN. Melting points are uncorrected. Some of the starting amides (R = Me, Et, *i*-Pr, *t*-Bu, cyclobutyl, cyclohexyl, undecyl) were purchased. Others were prepared from the corresponding acid chlorides and liquid ammonia. Malonamide was prepared from diethyl malonate and aqueous ammonia. A number of reaction mixtures were cooled in the freezer compartment of a refrigerator to induce the separation of alkylammonium tosylates from acetonitrile. The storage temperature in the experimental procedures is given as ca. −20 °C but may actually have varied between ca. −10 and −31 °C.

Alkylammonium Tosylates from Carboxamides with [Hydroxy(tosyloxy)iodo]benzene. In general, mixtures of **2** (10.0 mmol) and the carboxamides (10 mmol) in acetonitrile were stirred and heated under reflux for the time periods given in Table I. The resulting solutions, upon cooling at room temperature or below, yielded the corresponding alkylammonium tosylates, $RN^+H_3{}^-OTs$. In all cases except two (i.e., R = $CH_2{=}CHCH_2$, *n*-pentyl), the alkylammonium tosylates were identified by melting point and ^1H NMR spectral comparisons with reference compounds prepared from the corresponding amines with *p*-$TsOH{\cdot}H_2O$ in acetonitrile. Some of the ammonium tosylates (R = Me, Et, *i*-Pr, $PhCH_2$, c-C_6H_{11}) are known. Those which were not found in the literature (R = *t*-Bu, *n*-C_5H_{11}, *n*-C_7H_{15}, *n*-$C_{11}H_{23}$, $CH_2{=}CHCH_2$, c-C_4H_7) were sent for elemental (C,H) analysis. One detailed procedure is given below and is followed by workup summaries for the remaining amides.

2,2-Dimethylpropanamide with 2. A hot solution of 2,2-dimethylpropanamide (1.01 g, 10.0 mmol) in CH_3CN (30 mL) was added to a stirred mixture of **2** (3.92 g, 10.0 mmol) and CH_3CN (20 mL). The reaction mixture was heated and maintained under reflux for 40 min. The colorless solution that resulted was then allowed to stand at room temperature, whereupon *tert*-butylammonium tosylate separated and was isolated by vacuum filtration: yield, 2.22 g (90%); mp 219–221 °C; reference compound, mp 221–222.5 °C; ^1H NMR (Me_2SO-d_6) δ 1.27 (s, 9 H), 2.31 (s, 3 H), 7.38 and 7.84 (AA'BB' and br "s", 7 H).

Anal. Calcd for $C_{11}H_{19}NO_3S$: C, 53.85; H, 7.81. Found: C, 53.77; H, 7.83.

Acetamide with 2. The light brown solution was allowed to stand at room temperature, whereupon methylammonium tosylate separated: yield, 1.89 g, (93%); mp 145.5–147 °C (lit.[19] mp 146–147 °C); reference compound, mp 145.5–146.5 °C.

Propanamide with 2. The colorless solution was kept for 2 h at ca. −20 °C, whereupon ethylammonium tosylate separated: yield, 1.96 g (90%); mp 118–119 °C (lit.[20] mp 118 °C); reference compound, mp 118–119.5 °C.

Isobutyramide with 2. The colorless solution was kept for 1 h at ca. −20 °C, whereupon isopropylammonium tosylate separated: yield, 1.65 g (71%); mp 126.5–127.5 °C (lit.[20] mp 128 °C); reference compound, mp 127–128.5 °C.

Hexanamide with 2. The colorless solution was kept for a time at room temperature and then overnight at ca. −20 °C, whereupon *n*-pentylammonium tosylate separated: yield, 2.44 g (94%); mp 119–120 °C.

Anal. Calcd for $C_{12}H_{21}NO_3S$: C, 55.57; H, 8.16. Found: C, 55.18; H, 8.12.

Octanamide with 2. The colorless, cloudy solution was kept first at room temperature and then in an ice/H_2O bath, whereupon *n*-heptylammonium tosylate separated: yield, 2.66 g (93%); mp 131.5–133.5 °C; reference compound, mp 131.5–133 °C.

Anal. Calcd for $C_{14}H_{25}NO_3S$: C, 58.50; H, 8.77. Found: C, 58.06, 58.51, 58.39; H, 8.76.

Dodecanamide with 2. The pale yellow solution was allowed to stand at room temperature, whereupon undecylammonium tosylate separated: yield, 1.95 g (57%); mp 102–130 °C; reference compound, mp 117–132 °C, after three recrystallizations from acetonitrile.

Anal. Calcd for $C_{18}H_{33}NO_3S$: C, 62.93; H, 9.68. Found: C, 63.80, 64.01; H, 9.59.

3-Butenamide with 2. The colorless solution was allowed to stand at room temperature, whereupon allylammonium tosylate separated: yield, 1.19 g; mp 90–93 °C. Concentration of the filtrate to ca. one-fifth of the original volume and treatment with Et_2O (20 mL) gave additional product: yield, 0.17 g; mp 87–93 °C; combined yield, 1.36 g (59%). Recrystallization of the first fraction from CH_3CN returned 1.00 g (mp 95.5–97 °C).

Anal. Calcd for $C_{10}H_{15}NO_3S$: C, 52.38; H, 6.59. Found: C, 52.09; H, 6.59.

α-Phenylacetamide with 2. The purple solution was allowed to stand at room temperature, whereupon benzylammonium tosylate separated: yield, 2.49 g (89%); mp 183–185 °C (lit.[21] mp 185.5 °C); reference compound, mp 184.5–185.5 °C.

Cyclobutanecarboxamide with 2. The colorless solution was kept for 2 h at ca. −20 °C, whereupon cyclobutylammonium tosylate separated: yield, 2.10 g (88%); mp 152.5–153.5 °C;

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reference compound, mp 152–153 °C.

Anal. Calcd for $C_{11}H_{17}NO_3S$: C, 54.30; H, 7.04. Found: C, 54.28; H, 7.14.

Cyclohexanecarboxamide with 2. The yellow solution was kept overnight at room temperature, whereupon cyclohexylammonium tosylate separated: yield, 2.44 g (90%); mp 181–183 °C (lit.[21] mp 184 °C); reference compound, mp 183–184.5 °C.

Reaction of Malonamide with 2. A mixture of malonamide (1.02 g, 10.0 mmol), **2** (3.92 g, 10.0 mmol), and CH_3CN (40 mL) was heated for 1 h under reflux. The pale yellow mixture that resulted was filtered to give 0.19 g of a solid (mp 338–341 °C dec) presumed to be ammonium tosylate (lit.[19] mp 345–346 °C). The filtrate was concentrated on a rotary evaporator, and the residual material was triturated with Et_2O (50 mL) to give crude 2-(tosyloxy)malonamide as a yellow, crystalline solid: yield, 2.20 g (81%); mp 162–172 °C dec. Treatment of 0.5 g of the crude product with H_2O (20 mL) returned 0.33 g of product as a white powder; mp 183.5–185.5 °C; ^1H NMR (Me_2SO-d_6) δ 2.43 (s, 3 H), 5.07 (s, 1 H), 7.2–8.1 and 7.57 (overlapping AA'BB' m and br s, 8 H), 2.06 and 3.37 (weak s, impurities).

Anal. Calcd for $C_{10}H_{12}N_2O_5S$: C, 44.11; H, 4.44. Found: C, 44.13; H, 4.29.

(The NMR spectrum and elemental composition were obtained for the product from another run).

Reaction of α-Phenylacetamide with 2 in Ethanol. A solution of α-phenylacetamide (1.35 g, 10.0 mmol) and **2** (3.92 g, 10.0 mmol) in ethanol (35 mL) was heated for 30 min under reflux. The resulting colorless solution was passed through anhydrous $MgSO_4$ and concentrated on a rotary evaporator to an oil mixed with some crystalline material. The mixture was then taken up in CH_2Cl_2 (30 mL), and the solution was washed with H_2O (2 × 30 mL), dried ($MgSO_4$), and concentrated to a yellow oil. The oil was kept open to the atmosphere for 14 h (to ensure the removal of PhI) and subsequently crystallized from ligroin to give 0.74 g of ethyl benzylcarbamate, mp 44–46.5 °C (lit.[22] mp 44 °C). The filtrate, upon cooling at ca. −20 °C, gave 0.15 g more of product, mp 45–47.5 °C; combined yield, 0.89 g (50%).

Registry No. H_3CCONH_2, 60-35-5; $H_3CCH_2CONH_2$, 79-05-0; $(CH_3)_2CHCONH_2$, 563-83-7; $(CH_3)_3CCONH_2$, 754-10-9; $CH_3(CH_2)_3CH_2CONH_2$, 628-02-4; $CH_3(CH_2)_5CH_2CONH_2$, 629-01-6; $CH_3(CH_2)_9CH_2CONH_2$, 1120-16-7; $CH_2{=}CHCH_2CONH_2$, 28446-58-4; $PhCH_2CONH_2$, 103-81-1; H_3CNH_2·HOTs, 2840-20-2; $H_3CCH_2NH_2$·HOTs, 102520-37-6; $(CH_3)_2CHNH_2$·HOTs, 63458-89-9; $(CH_3)_3CNH_2$·HOTs, 63458-91-3; $H_3C(CH_2)_3CH_2NH_2$·HOTs, 102520-38-7; $H_3C(CH_2)_5CH_2NH_2$·HOTs, 102520-39-8; $H_3C(CH_2e_6CH_2NH_2$·HOTs, 102520-40-1; $CH_2{=}CHCH_2NH_2$·HOTs, 102520-41-2; $PhCH_2NH_2$·HOTs, 14613-34-4; PhI(OTs)OH, 27126-76-7; $H_2NCOCH_2CONH_2$, 108-13-4; $H_2NCOCH(OTs)CONH_2$, 102520-43-4; $PhCH_2NHCO_2CH_2CH_3$, 2621-78-5; cyclobutanecarboxamide, 1503-98-6; cyclohexanecarboxamide, 1122-56-1; cyclobutylamine 4-methylbenzene sulfonate, 102520-42-3; cyclohexylamine 4-methylbenzene sulfonate, 53050-53-6.

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Toward a Transition-State Model in the Asymmetric Alkylation of Chiral Ketone Secondary Enamines by Electron-Deficient Alkenes. A Theoretical MO Study

Alain Sevin,*† Jeanine Tortajada,† and Michel Pfau‡

Laboratoire de Chimie Organique Théorique,[1] Université Pierre et Marie Curie, Bâtiment F, 75232 Paris Cedex 05, and the Laboratoire de Recherches Organiques[2] de l'Ecole Supérieure de Physique et Chimie Industrielles, 75231 Paris Cedex 05, France

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The processes involved in the asymmetric alkylation of chiral ketone secondary enamines, by electron-deficient alkenes, are theoretically simulated by ab initio SCF calculations, using ethyleneamine and propenal as prototype structures. It is shown that a compact activated complex might compensate to a large extent the steric hindrance by attractive MO interactions, arising from frontier orbitals. The corresponding structure of lowest energy, compatible with asymmetric induction, is the chair-like intermediate, with an s-cis conformation for the propenal moiety.

The alkylation of carbonyl compounds, through their tertiary enamine derivatives, by electron-deficient alkenes, is widely used in synthesis chemistry and constitutes the so-called Stork's first method.[3,4] In this field, the use of imines,[5] the reaction of which occurs via their tautomeric secondary enamines, provides an extension of the aforementioned method. It is worth noting that the imine method gives alkylations on the more substituted α carbon,[6] contrary to the case of tertiary enamines. This characteristic has recently been exploited for synthesizing compounds bearing a quaternary carbon center. A general method using imines arising from a chiral amine and yielding α,α-disubstituted chiral cyclanones has been proposed.[7] Both chemical and optical high yields are obtained, according to the sequence of reactions depicted in Scheme I. The high diastereofacial selectivity which is actually observed (~90%) remains to be rationalized on the grounds of simple molecular models.

A previous approach related to analogous situations has been made by Seebach et al.[8] in which a model of the

† Laboratoire de Chimie Organique Théorique.
‡ Laboratoire de Recherches Organiques.

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