

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

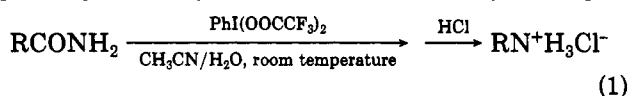
I. Mark Lazbin and Gerald F. Koser\*

*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 ( $\text{RCONH}_2$ , 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 ( $\text{RN}^+\text{H}_3^-\text{OTs}$ ) 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  $\alpha$ -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.<sup>1</sup> Much more recently, Loudon and his co-workers have developed a procedure for effecting the Hofmann reaction under mildly acidic conditions.<sup>2-4</sup> 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).



The range of substrates that respond to **1** includes acylamino amides and peptide amides,<sup>2,3,5,6</sup> and **1** has been employed in the sequential degradation of carboxyl terminal peptides.<sup>5</sup> Several precautionary measures for the effective use of **1** as a Hofmann reagent have been advised.<sup>3</sup> 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).

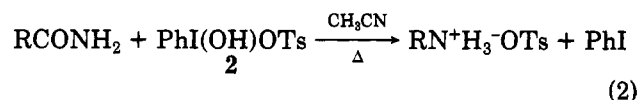
[Hydroxy(tosyloxy)iodo]benzene (**2**) is a readily available and stable crystalline compound which can be handled under ambient conditions with no ill effects.<sup>7-9</sup> It has

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

RCONH <sub>2</sub> , R	vol MeCN, mL	time at reflux	yield of RN <sup>+</sup> H <sub>3</sub> <sup>-</sup> OTs, %
CH <sub>3</sub>	45	15 h	93
CH <sub>3</sub> CH <sub>2</sub>	50	40 min	90
(CH <sub>3</sub> ) <sub>2</sub> CH	45	40 min	71
(CH <sub>3</sub> ) <sub>3</sub> C	50	40 min	91
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> CH <sub>2</sub>	45	45 min	94
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> CH <sub>2</sub>	50	1.5 h	93
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub> CH <sub>2</sub>	50	40 min	57
CH <sub>2</sub> =CHCH <sub>2</sub>	45	15 min	59
PhCH <sub>2</sub>	50	1.5 h	89
cyclobutyl	50	75 min	88
cyclohexyl	55	30 min	90

proven to be a useful reagent for the tosyloxylation of ketones<sup>10</sup> and alkenes<sup>11,12</sup> and in the synthesis of iodonium salts from alkynes,<sup>13-15</sup> thiophenes,<sup>16</sup> (trimethylsilyl)furans,<sup>17</sup> and (trimethylsilyl)arenes.<sup>18</sup> 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.

[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).



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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.<sup>21</sup> 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.<sup>19</sup> 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-(toxyloxy)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 ( $Me_2SO-d_6$ )  $\delta$  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  $\alpha$ -Phenylacetamide with 2 in Ethanol.** A solution of  $\alpha$ -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  $H_2O$  ( $2 \times 30$  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.<sup>22</sup> 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;  $CH_3(C-H)_2CH_2CONH_2$ , 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;  $H_3CNH_2 \cdot HOTs$ , 2840-20-2;  $H_3CCH_2NH_2 \cdot HOTs$ , 102520-37-6;  $(CH_3)_2CHNH_2 \cdot HOTs$ , 63458-89-9;  $(CH_3)_3CNH_2 \cdot HOTs$ , 63458-91-3;  $H_3C(CH_2)_5CH_2NH_2 \cdot HOTs$ , 102520-38-7;  $H_3C(CH_2)_9CH_2NH_2 \cdot HOTs$ , 102520-39-8;  $H_3C(CH_2)_9CH_2NH_2 \cdot HOTs$ , 102520-40-1;  $CH_2=CHCH_2NH_2 \cdot HOTs$ , 102520-41-2;  $PhCH_2NH_2 \cdot HOTs$ , 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,<sup>1</sup> Université Pierre et Marie Curie, Bâtiment F, 75232 Paris Cedex 05, and the Laboratoire de Recherches Organiques<sup>2</sup> de l'École 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.<sup>3,4</sup> In this field, the use of imines,<sup>5</sup> 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  $\alpha$  carbon,<sup>6</sup> 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  $\alpha,\alpha$ -disubstituted chiral cyclanones has been proposed.<sup>7</sup> 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 ( $\sim 90\%$ ) 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.<sup>8</sup> in which a model of the

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\*Laboratoire de Chimie Organique Théorique.

†Laboratoire de Recherches Organiques.