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Sulfamidation of 2-Arylaldehydes and Ketones with Chloramine-T

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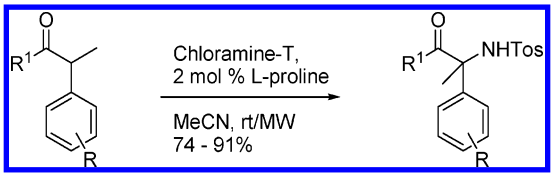
ABSTRACT



A series of aliphatic and aromatic carbonyl compounds has been transformed into the corresponding sulfamidated products by means of amine-catalyzed nitrene transfer of chloramine-T. Depending on the residues R, either α-sulfamidation in the case of aromatic aldehydes and acetone derivatives or direct sulfamidation at the carbonyl functionality of aliphatic aldehydes has been observed. Applying microwave conditions, good to excellent yields under significantly reduced reaction times could be obtained, thus providing a facile access to α,α-disubstituted amino acids.

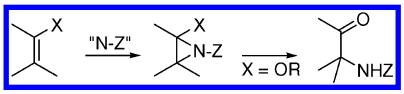
A key issue in current chemical transformations is the development of mild yet highly selective reaction conditions. This includes the realization of environmental benignity as well as high atom economy. Since most organic compounds carry nitrogen functional groups, the carbon−nitrogen formation plays an important role in organic synthesis. An elegant way of introducing a nitrogen atom into a molecule is by means of aziridination, in which a nitrene or nitrenoid species is transferred onto an olefin.[1a,b] Because of their high reactivity, aziridines undergo various regio- and stereoselective nucleophilic ring-opening reactions and thus serve as valuable building blocks for the synthesis of nitrogen-containing compounds.[2] Following the aziridination of enol derivatives (X = OR, Scheme 1), ring-opening of the aziridine intermediate produces the corresponding α-amino carbonyl compound. Most of the methods reported to date use *N*-arylsulfonyliminophenyliodinanes as the nitrenoid source, which inevitably produces a stoichiometric amount of iodobenzene as a waste coproduct.[3]

Our interest in nitrene transfer sulfamidation using azides[4] led us to investigate cheap, commercially available chloramine-T hydrate as a nitrene-transfer agent.[5] In fact, Komatsu has recently demonstrated an interesting chloramine-T/CuCl-catalyzed aziridination process but with a limited substrate scope.[6] Furthermore, chloramine-T has been shown by Sharpless to aziridinate a wide range of olefin classes with phenyl trimethylammonium tribromide PTAB as a necessary bromine source.[7]

However, as far as we are aware, no catalytic α-amination of carbonyl compounds with chloramine-T as the nitrenoid species have been reported. Herein we describe an efficient α-sulfamidation process of in-situ formed enolates with chloramine-T under L-proline catalysis.

At the outset of our study we examined the reaction of 2-phenylpropionaldehyde **1a** with chloramine-T, using pyrrolidine and PTAB as catalysts. After stirring at room temperature for 12 h, the racemic α-sulfamidated product **2a** could be isolated in good yields (Scheme 2). The only

Scheme 1. Aziridination of Olefins (X = R or Ar) and Enol Derivatives (X = OR)



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(2) For a recent review, see Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.

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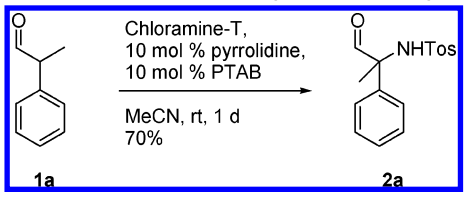
Scheme 2. α-Sulfamidation of 2-Phenylpropionaldehyde **1a** with Chloramine-T under Pyrrolidine Catalysis



byproduct that was found turned out to be toluenesulfonamide, which was formed from chloramine-T in very low quantity (less than 5%). This observation seemed to confirm our assumption of an in-situ generated enamine whose double bond is most likely halogenated by tribromide. The formed bromonium species will then be attacked by the nucleophilic chloramine-T to yield the aziridine intermediate. This theory is further supported by the observation that aldehydes without α-protons such as pivaldehyde do not react at all under these conditions, thus verifying the required formation of an enamine intermediate.

On the basis of this pathway for olefins proposed by Sharpless, substitution of the achiral pyrrolidine with L-proline or its derivatives should result in scalemic α-sulfamidated products. Thus, the proline-catalyzed aziridination of 2-phenylpropionaldehyde with chloramine-T and PTAB was carried out using standard conditions. Unfortunately, no level of stereoselectivity could be observed, indicating the formation of enolates rather than enamines, and therefore no control over the side of attack. Other proline derivatives were less efficiant in terms of yields. Again, trisubstituted aldehydes were found to be not reactive under these conditions.

A screening of different protic and aprotic solvents revealed acetonitril[8] to provide the best results in terms of yield and reaction time, but in all cases only racemic products were obtained. In most apolar solvents such as ether or THF, only traces of the desired products could be found, together with an increasing amount of toluenesulfonamide. This was obviously due to the poor solubility of the catalysts L-proline and PTAB.

The catalyst loading of L-proline could be lowered down to 2 mol % without significant loss of conversion and yield, respectively. Surprisingly, absence of the brominating agent PTAB did not influence the formation of the product whatsoever, but identical yield and reaction time were observed. Therefore the following set of reaction conditions was established for further experimentation: addition of 1 equiv of the aldehyde to a solution of 2 mol % of L-proline and a slight excess of chloramine-T in acetonitrile until GC or TLC indicated complete consumption of the aldehyde. This was followed by subsequent isolation of the product by removal of the solvent, and flash chromatography of the residue.

The effect of temperature was examined in acetonitrile with L-proline as the catalyst. While no reaction had occurred after 4 days at 0 °C, an acceleration could be observed at elevated temperature. At 70 °C, the reaction time was reduced to 5 h with significantly better yield (85%) compared to room-temperature yields. This influence was further tested by employing microwave conditions which benefit from faster heating rates (Table 1). Variation of temperature, maximum power, and reaction time led to the highest yield of 90%, which was isolated after 30 min at 60 °C and 200 W. To further evaluate the effect of microwave irridation and to determine its real impact on the reaction conditions, comparative studies were performed using conventional heating. As seen before, higher temperatures resulted in faster reaction rates, with an optimum conversion at 60 °C. The only noticeable difference observed to the microwave experiments was the required reaction time, which had to be extened to achieve comparable conversions and yields. Thus, the observed rate enhancement is obviously a result of the very fast heating rates when irridated in a microwave field and most likely not attributed to a specific microwave effect.[9]

Once the optimum reaction conditions had been established, the scope and limitation of this catalytic sulfamidation, with respect to the substrates, were tested. Different para substituted 2-phenylpropionaldehydes **1a**−**i** were used to

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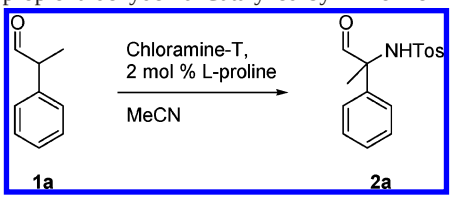
Table 1. Microwave-Assisted α-Sulfamidation of 2-Phenyl-propionaldehyde **1a** Catalyzed by L-Proline[a]

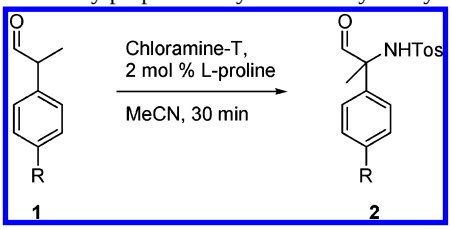


entry	power[b] [W]	temp[c] [°C]	time [min]	yield[d] [%]
1	100	90	30	50
2	200	70	30	68
3	200	60	20	76
4	200	60	30	90
5	200	60	30	80
6	150	50	30	66
7	200	50	40	90

[a] Reaction conditions: 1 equiv of aldehyde, 2 mol % of L-proline, 1.5 equiv of chloramine-T. [b] Application of constant microwave power. [c] For cooling, compressed air with a constant pressure of 0.7 bar (10 psi) was used during the entire experiment. [d] Isolated yields; see Supporting Information for details.

evaluate their electronic influence. Remarkably higher yields could be observed for electron-withdrawing groups such as nitro, fluoro, and cyano substituents, which probably stabilize the negatively charged benzylic position. On the other hand, electron-donating groups, like the methyl substituent, lowered both conversion and yield, most likely as a result of halogenation of the electron-rich aromatic ring system (Table 2).

Table 2. Microwave-Assisted α-Sulfamidation of Para-Substituted 2-Phenylpropionaldehydes **1** Catalyzed by L-Proline[a]

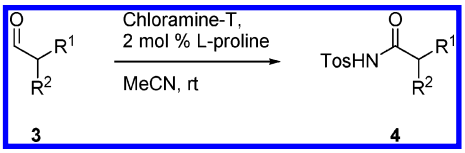


aldehyde	R	power[b] [W]	temp[c] [°C]	yield[d] [%]
1a	H	200	60	90
1b	F	200	60	85
1c	CF_3	200	60	79
1d	NO_2	200	60	89
1e	CN	200	60	86
1f	Me	200	60	73
1g	e	200	60	91
1h	f	200	60	88
1i	g	200	60	83[h]

[a] Reaction conditions: 1 equiv of aldehyde, 2 mol % of L-proline, 1.5 equiv of chloramine-T. [b] Application of constant microwave power. [c] For cooling, compressed air with a constant pressure of 0.7 bar (10 psi) was used during the entire experiment. [d] Isolated yields; see Supporting Information for details. [e] 2-Naphthylpropionaldehyde served as a starting material. [f] Diphenylacetaldehyde served as a starting material. [g] 3-(4-^{i}Propylphenyl)-2-methylpropionaldehyde served as a starting material. [h] Reaction was performed at rt for 1 d.

Interestingly, α,α-disubstituted aliphatic aldehydes **3** were not found to be sulfamidated at the α-position but were instead attacked directly at the carbonyl carbon center. This resulted in protected carboxylic acid amides **4** in moderate to good yields (Table 3). This is obviously due to an alternative mechanism which involves formal oxidation of the aldehydes. Thus, the presence of an aromatic ring seems to be mandatory for this reaction type (see Table 2, entry 9).

Table 3. α-Sulfamidation of 2-Alkylpropionaldehydes **3** with Chloramine-T under L-Proline Catalysis[a]

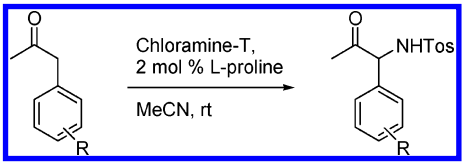


aldehyde	R^1	R^2	time [d]	yield[b] [%]
3a	Me	Me	1	83
3b	Me	Et	1	81
3c	Et	Et	1	78
3d	H	^{i}Pr	1	86
3e	H	Hex	2	76
3f	Et	Hex	2	72
3g	$(CH_2)_5$		2	86

[a] Reaction conditions: 1 equiv of aldehyde, 2 mol % of L-proline, 1.5 equiv of chloramine-T. [b] Isolated yields; see Supporting Information for details.

To further test the regioselectivity of this process, phenylacetone **5a** was reacted with chloramine-T under standard room temperature conditions (Table 4). The only product **6a** that could be found and isolated was sulfamidated at the benzylic α-position, again indicating the necessity of this

Table 4. α-Sulfamidation of Substituted Phenylacetone **5** Catalyzed by L-Proline[a]



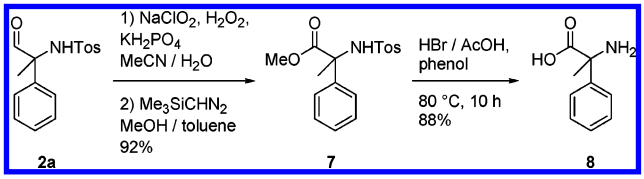
ketone	R	time [d]	yield[b] [%]
5a	H	1	83
5b	4-OMe	1	71
5c	3-OMe	1	74
5d	4-F	2	82
5e	3-CF_3	2	83

[a] Reaction conditions: 1 equiv of ketone, 2 mol % of L-proline, 1.5 equiv of chloramine-T. [b] Isolated yields; see Supporting Information for details.

reactive site. No attack at the methyl group occurred, which underlined the formation of a conjugated enolate. The scope was extended to aryl-substituted propanone derivatives which showed similar results to the *para*-substituted 2-phenylpropionaldehydes. Electron-withdrawing groups gave consistently better yields as a consequence of the stabilized benzylic position. In contrast, the more electron-rich aromatic systems were halogenated as a side reaction and thus gave slightly lower yields.

Since α-amino aldehydes can serve as valuable precursors for the synthesis of α-amino acids, the conversion into the corresponding nonproteogenic disubstituted amino acids was demonstrated on aldehyde **2a** (Scheme 3). Mild oxidation

Scheme 3. Synthesis of α-Methyl Phenylgycine **8**



using sodium chlorite/hydrogen peroxide[10] and subsequent esterification with trimethylsilyldiazomethane delivered the fully protected α-amino acid **7** in almost quantitative yield. Removal of the tosyl group was achieved under acidic conditions: Hydrogen bromide was used in acetic acid,[11] furnishing the free α-methylphenylglycine derivative **8** in 88% yield.

In summary, an easy[12] and efficient route for α,α-disubstituted amino aldehydes and their corresponding amino acids is presented. By using commercially available chloramine-T, the α-sulfamidation reaction delivered the aminated products in good to excellent yields, to date as racemic mixtures. This is probably due to the formation of enolates rather than enamines and therefore no control of the side of attack. Promising first experiments with chiral phase-transfer catalysts show the formation of enantiomerically enriched α-sulfamidated products and will be part of future work in our research group.

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Supporting Information Available: Full experimental details, characterization of all new compounds, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Sharpless, K. B.; Li, G.; Chang, H.-T., PCT Int. Appl. 1997, 77 pp.

(12) **General Procedure for the Proline-Catalyzed α-Sulfamidation under Microwave Irradiation.** Preparation of *2-Phenyl-2-(4′-toluene-)-sulfonylamino-propionaldehyde* **2a** as a detailed representative example. In a 10 mL vessel was placed 2-phenylpropionaldehyde **1a** (0.134 g, 1.0 mmol, 1.0 equiv), L-proline (2.30 mg, 0.02 mmol, 2 mol %), chloramine-T (0.423 g, 1.5 mmol, 1.5 equiv), acetonitrile (5 mL), and a magnetic stir bar. The vessel was sealed with a septum, placed into the microwave (MW) cavity, and locked with the pressure device. Constant MW irradiation of 200 W as well as simultaneous air-cooling (0.7 bar, 10 psi) were used during the entire reaction time (30 min). After cooling to room temperature, the solvent was removed under reduced pressure, and the product was purified by column chromatography (silica gel, diethyl ether/pentane, 1: 2) to afford the α-sulfamidated aldehyde **2a** as a white solid (0.273 g, 90%).