The Generation and Use of a Masked α-Acyl Cation in Aromatic Substitution Reactions; Ag$^+$ induced Reactions of 3-(Bromomethyl)-5,6-dihydro-1,4,2-dioxazine Derivatives

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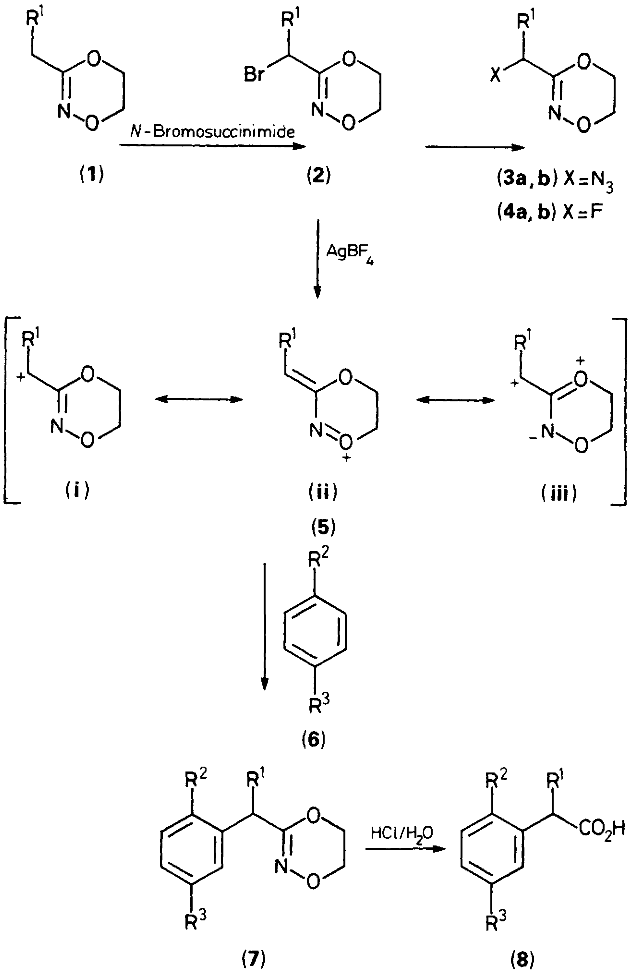
The Ag$^+$ induced aromatic substitution reactions of 3-(1-bromomethyl)-5,6-dihydro-1,4,2-dioxazine derivatives *via* an α-acyl cation equivalent are described.

Nitrones and oxime ethers have been shown to have dual properties in supporting negative or positive charge at the position next to the C=N group. Such compounds can be efficiently metallated on the α-carbon atom to form reagents (α-acyl anion equivalents) that are useful synthetic intermediates in alkylation and addition reactions.[1] Eschenmoser showed that nitrones derived from α-chloro aldehydes are good intermediates for generating equivalents of α-acyl cations.[2] We have shown that α-bromoacetone *O*-alkyloximes can be used to form analogous intermediates in the ketone series. These α-acyl cation equivalents are able to participate in aromatic substitution reactions with electron rich aromatic systems. On this basis, useful methodology for the synthesis of α-aryl aldehydes[3] and α-aryl ketones[4] was described. Here we extend this general methodology to the synthesis of carboxylic acids. We present the first examples of masked α-acyl cations based on the 5,6-dihydro-1,4,2-dioxazine system and their use as intermediates for the synthesis of α-aryl carboxylic acids (Scheme 1).

Reaction of *N*-bromosuccinimide and benzoyl peroxide with 3-methyl-5,6-dihydro-1,4,2-dioxazine derivatives (**1a,b**) in the dark affords the 3-(1-bromomethyl)-5,6-dihydro-1,4,2-dioxazine derivatives† (**2a,b**), respectively, in high yields. The halogen atom could be exchanged for azide or fluorine by treatment of (**2c,d**) with NaN_3 or KF[5] (2 equiv.) for 12 h to give (**3a,b**) (80% yield)‡ and (**4a,b**) (80% yield), respectively.§

The bromides (**2a,b**) were also converted to a reactive intermediate of type (**5**) (masked –CO–C$^+$) which participated in aromatic substitution reactions. Addition of either (**2a**) or (**2b**) (10 mmol) in dry $ClCH_2CH_2Cl$ (20 ml) to a solution of $AgBF_4$ (10 mmol) and aromatic substrates (**6**) (Scheme 1) in $ClCH_2CH_2Cl$ (20 ml) at 25 °C, followed by efficient stirring in darkness for 18 h, and then workup with a 10% KCN/H_2O solution provides good yields (82—91%) of the aromatic substitution products (**7a—f**). Acid treatment ($HCl/H_2O/MeOH$ 1:5:5) for 10 h at 65 °C and distillation gave the corresponding 2-arylcarboxylic acids, (**8a—f**) in high yields (80—90%).

Electron rich aromatic systems, as well as benzene, react under these reaction conditions. Reaction with 1,4-dimeth-



Compound		R^1	R^2	R^3
(1–4)	a	Me		
	b	Ph		
(6–8)	a	Me	OMe	OMe
	b	Ph	OMe	OMe
	c	Me	Me	Me
	d	Ph	Me	Me
	e	Me	H	H
	f	Ph	H	H

Scheme 1

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† Preparation of 3-substituted 5,6-dihydro-1,4,2-dioxazines: a solution of potassium hydroxamate (R^1 = Me, R^1 = phenyl) from K_2CO_3 (150 mmol) and the corresponding hydroxamic acids (60 mmol) in $MeOH/H_2O$ (6:1) (140 ml) were stirred with 1,2-dibromoethane (100 mmol) for 24 h at 25 °C. After work up, the products were purified by distillation [(**1a**) b.p. 78 °C/22 mm, 48% yield; (**1b**) b.p. 55 °C, 110 °C/1 mm, 60% yield.[6]] Compounds (**2a**) and (**2b**) were prepared as follows: 5,6-dihydro-1,4,2-dioxazine derivatives (**1a**) and (**2a**), respectively (100 mmol), *N*-bromo-succinimide (130 mmol), and dibenzoylperoxide (500 mg) in dry CCl_4 (200 ml) were heated under reflux in the dark. After work up, the bromo-derivatives were purified by chromatography (Al_2O_3, $CHCl_3$/hexane 1:4) [(**2a**) b.p. 75 °C/2 mm, 67% yield; (**2b**) b.p. 110 °C/0.01 mm, 78% yield.[7]].

‡ All new compounds were obtained in pure state by fractional distillation or column chromatography and were unequivocally characterized by spectroscopic, mass spectral, and microanalyses data.

§ Hydrogenolysis of the azide (H_2 and $Pd/CaCO_3$) afforded the corresponding amino derivatives.

oxybenzene or *p*-xylene with a 1 : 1 molar ratio of the aromatic compound to $AgBF_4$ afforded (**7a—d**). Reaction with benzene gave good yields (65%) only when a two-fold excess of benzene was used in the reaction. No significant changes in reaction conditions were needed to obtain similar yields with (**2a**) or (**2b**).

Compared to *O*-alkyloximes, we observed higher reactivity in the aromatic substitution reaction. 3-(1-Bromomethyl)-5,6-dihydro-1,4,2-dioxazine derivatives react with benzene, whereas under similar conditions, α-chloronitrones and α-bromo-*O*-alkyloximes do not. This may be explained on the basis of some destabilizing contribution, due to the presence of the imino-ester oxygen in (**5i—iii**).

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