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NOVEL METHOD FOR α-SUBSTITUTION OF AMINES *VIA N*-METHOXYCARBONYL-α-*t*-BUTYLDIOXYAMINES

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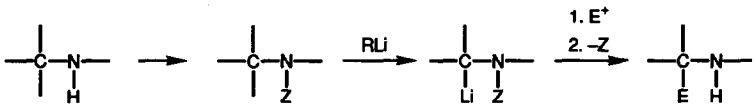
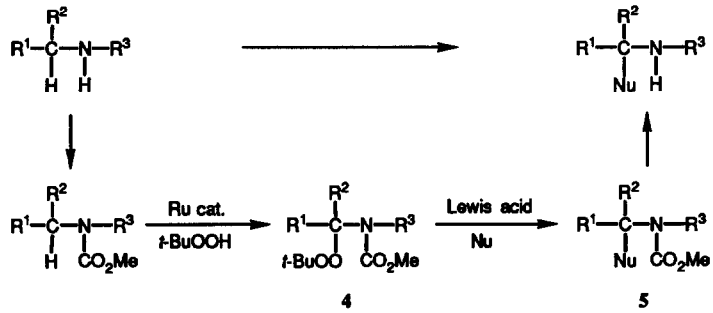
Summary: α-Substitution of amines can be performed by ruthenium-catalyzed oxidation of *N*-methoxycarbonylamines with *t*-butyl hydroperoxide followed by treatment with nucleophiles in the presence of titanium tetrachloride.

Substitution at α-position adjacent to the nitrogen of amines is of importance in view of synthesis of nitrogen-containing natural products and biologically active compounds. Introduction of a substituent has been performed by using electrophilic reagents.[1] *N*-Protected amines with an electron-withdrawing group Z (**1**) such as formamidines (Z = CH=NR),[2] aminooxazolidines (Z = C(OR)=NR),[3] amides (Z = C(O)R),[4] and nitrosoamines (Z = NO)[5] undergo lithiation with organolithium reagents to give carbanions (**2**). Treatment of **2** with electrophiles and removal of the protecting group Z gives α-substituted amines (**3**). Alternative methods are the introduction of substituents by using nucleophiles. Tungstate-catalyzed oxidation of secondary amines with hydrogen peroxide, reactions of the nitrones thus obtained with nucleophiles, and catalytic hydrogenation give α-substituted amines.[6] The other method for α-substitution with nucleophiles is the electrochemical reaction of *N*-acylated amines and substitution reactions.[7]



1 **2** **3**

Recently, we have found that cytochrome P-450 type oxidation of amines[8] and amides[9] proceeds highly efficiently upon treatment with *t*-butyl hydroperoxide in the presence of ruthenium(II) catalysts to give *t*-butyldioxygenated products (**4**). As a consequence of exploring synthetic utility of this oxidation reaction, we have found that the reaction of *t*-butyldioxyamides **4** thus obtained with nucleophiles in the presence of a Lewis acid gives *N*-acyl α-substituted amines (**5**) highly efficiently. Thus, the selective carbon-carbon bond formation at the α-position of amines can be performed by *N*-protection of amines, the ruthenium-catalyzed oxidation with *t*-butyl hydroperoxide, treatment with nucleophiles in the presence of a Lewis acid, and removal of the *N*-protecting group (eq 1).



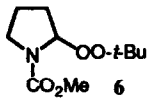
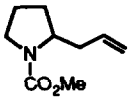
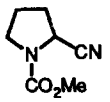
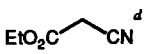
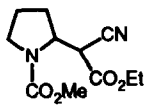
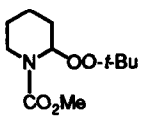
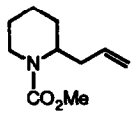
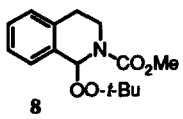
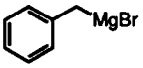
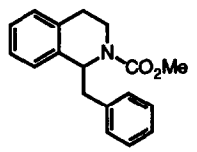
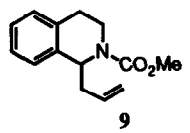
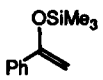
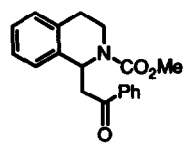
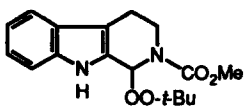
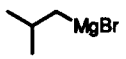
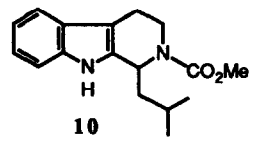
N-Alkoxycarbonyl- and *N*-acylamines can be converted into the corresponding *t*-butyldioxyamides efficiently by the ruthenium-catalyzed oxidation with *t*-BuOOH.[9] Typically, the treatment of 1-(methoxycarbonyl)-pyrrolidine with *t*-BuOOH in the presence of 3 mol% of $RuCl_2(PPh_3)_3$ in benzene gave 1-(methoxycarbonyl)-2-(*t*-butyldioxy)pyrrolidine (**6**) in 60% isolated yield. Similar treatment of 2-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole gave 1-(*t*-butyldioxy)-2-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido-[3,4-*b*]indole (**7**) in 92% isolated yield.

Lewis acid mediated reactions of *t*-butyldioxyamides with various nucleophiles proceed at -78°C to give the corresponding substituted amides. $TiCl_4$ and $BF_3{\cdot}OEt_2$ have been proven to be effective Lewis acids for the substitution reactions , although $AlCl_3$ gave unsatisfactory results.

A typical example for the introduction of substituents at the α-position of amines is the preparation of 1-allyl-2-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (**9**) . To a mixture of 2-methoxycarbonyl-1,2,3,4-tetrahydro-isoquinoline (0.358 g, 1.87 mmol) and $RuCl_2(PPh_3)_3$ (0.057 g, 0.06 mmol) in dry benzene (2.0 mL) was added a 2.8 M solution of *t*-BuOOH in dry benzene (1.9 mL, 5.9 mmol) dropwise at room temperature over a period of 2 h. After complete addition, sodium bisulfite (1 g) was added to the mixture to remove excess *t*-BuOOH. The solvent was removed under reduced pressure, and chromatography on silica gel (ether : hexane = 2:1) gave 1-(*t*-butyldioxy)-2-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (**8**) (0.458 g, 91%) as a colorless oil. To a solution of $TiCl_4$ (0.13 mL, 1.2 mmol) in dry dichloromethane (2 mL) was added a solution of **8** (0.280 g, 1.00 mmol) in dry dichloromethane (0.5 mL) dropwise over a period of 5 min at -78°C. After stirring for 5 min, a solution of allyltrimethylsilane (0.19 mL, 1.2 mmol) in dry dichloromethane (0.5 mL) was added dropwise over a period of 5 min. The reaction mixture was stirred for 4 h at -78°C. Usual work up followed by chromatography on silica gel gave **9** (0.205 g, 89%).

Table I summarizes the representative results of the titanium tetrachloride-promoted reaction of *t*-butyldioxyamides with various nucleophiles. The reactions of *t*-butyldioxyamides with allylsilanes and silyl enolates give *N*-acyl α-allylamines and N-acyl γ-carbonylated amines, respectively. The reactions with cyanotrimethylsilane give *N*-acyl-α-cyanoamines, which can be readily converted into α-amino acids upon hydrolysis (Entry 2).[10] The reactions of active methylene compounds such as malonate and cyanoacetate proceed efficiently in the presence of triethylamine to give β-amino acid derivatives (Entry 3). Benzyl isoquinoline alkaloids can be readily derived from the reaction of 1-(*t*-butyldioxy)-1,2,3,4-tetrahydroisoquinolines with benzylmagnesium bromides (Entry 5). Furthermore, the reaction of *t*-butyldioxypyridoindole **7** with isobutylmagnesium bromide gave 1-(2-methylpropyl)-2-methoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (**10**) (Entry 8), which is a *N*-protected form of a β-carboline alkaloid isolated from *Elaeagnus*

Table I. Lewis-Acid Promoted Reaction of *N*-Methoxycarbonyl-α-*t*-butyldioxyamines with Nucleophiles[a]

entry	peroxide	nucleophile	product[b]	yield,%[c]
1	 **6**			71
2	**6**	Me_3SiCN		77
3	**6**	 [d]		53
4				79
5	 **8**			71
6	**8**		 **9**	89
7	**8**			74
8	 **7**		 **10**	61[e]

[a] All reactions were carried out according to the standard procedure deseribed in the text. [b]The product showed satisfactory IR, NMR and mass spectra. [c]Isolated yield based on the starting peroxide. [d]Triethylamine (1.5 equiv.) was added. [e]$TiCl_4$ (2 equiv.) and isobutylmagnesium bromide (2 equiv.) were used.

commutata.[11]

The present α-substitution reaction can be rationalized by assuming the formation of iminium ions.[12] Thus, the reaction of *t*-butyldioxyamides with titanium tetrachloride gives iminium ion intermediates, which are trapped with nucleophiles to give substituted amides.

Further work is now in progress on the extension of this reaction to the other system and application to the synthesis of nitrogen-containing natural products.

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