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gem-CYCLODIALKYLATION
A Facile Synthetic Route to N-Substituted Heterocycles[1]

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ABSTRACT

N-alkylated and N-arylated pyrroles, pyrrolidines, and piperidines are synthesized in high yield by the reaction between cyclic ethers and primary amines over a heterogeneous titania catalyst.

We have found that the anatase form of titania gives high activity and selectivity as a heterogeneous catalyst for the *gem*-cyclodialkylation (GCD) reaction between cyclic ethers and primary amines. We believe this reaction has the potential to provide a wide variety of cyclic amine intermediates and products in a straightforward, facile manner.

Synthesis of N-substituted heterocycles frequently involves the reaction of an alkyl or aryl halide with the appropriate N-heterocycle in the presence of base[2]. N-substituted heterocycles are also synthesized via ring closure of α,ω-diols or dihalides over acidic metal oxide catalysts such as Al_2O_3 at 300-350°C[3].

The GCD reaction between a cyclic ether and a primary amine over Al_2O_3 at 400°C was reported by Yur'ev *et al*[4]. Furan and tetrahydrofuran were converted to pyrroles and pyrrolidines in 20-60% yields. An activated alumina catalyst[5] was later reported to give somewhat higher activity.

In our laboratory, the GCD reactions were carried out over a titania catalyst in an externally heated, packed-bed, flow-through reactor equipped with liquid and gaseous feed lines. Pre-mixed reactants were fed at 0.2 - 0.4 hr^{-1} LHSV. The reactor temperature was 250 - 300°C. IR, NMR, GC, and GC-MS techniques were used to analyze the products. No catalyst pretreatment was

required. The best results were obtained when an excess of the cyclic ether was used. No ether decomposition products were detected except under the most severe conditions. Conversion results are reported as the percent amine converted to products and selectivity as the percent of reacted amine converted to the desired GCD product.

A straightforward GCD reaction is that between a linear primary alkyl amine and THF. Good selectivities to N-alkyl pyrrolidines are obtained even as chain length increases from methyl (95%) to octadecyl (81%). Unsaturation in the cyclic ether reduces reaction rate but still gives reasonable selectivity to pyrroles (Table 2). Dihydrofuran undergoes disproportion to give pyrroles and pyrrolidines as products.

Aromatic amines are also very reactive in the GCD reaction. Anilines react with both saturated and unsaturated cyclic ethers to form the respective N-arylpyrrolidines and pyrroles with excellent selectivity. Bulky substituents *ortho* to the nitrogen do not severely interfere with the formation of the desired N-aryl pyrrolidine. 2,6-Diisopropylaniline gives the expected pyrrolidine in 77% yield. Steric hindrances on the cyclic ether can also be tolerated. For instance, aniline reacts with 2,5-dimethyltetrahydrofuran to form N-phenyl-2,5-dimethylpyrrolidine in 88% yield. (Table 1).

Electron withdrawing groups in the *ortho*-position of the aniline do not prevent the GCD reaction. Hydroxy-, chloro-, and cyano- groups result in yields of 92, 59, and 43%, respectively. By-products from the latter two reactants result from loss of the substituent from the ring. These reactions are rather slow, requiring higher temperatures, which results in higher by-product formation (Table 1).

The size of the cyclic ether is not limited to five-membered rings. Aniline reacts with tetrahydropyran and 1-oxa-cycloheptane to form the respective N-arylated heterocycles in good yield (Table 1).

The GCD reaction also occurs with substituted amines such as acetamide to give N-acetylpyrrolidine.

N-substituted lactams are easily formed from lactones and a primary amine. Five, six, and seven membered lactones will react to form the respective lactams. Even N-phenyl-2-imidazolidone was formed in 47% yield from aniline and the cyclic carbamate, 2-oxazolidone (Table 1).

Diamines also react with cyclic ethers over titania catalysts to give GCD products. *ortho-* and *meta*-Phenylenediamine give mostly mono-alkylation, but the *para-* isomer gives 72:22 mono-/di-alkylation in a much cleaner reaction. Diethyltoluene diamine and triethylbenzene diamine both yield products that are predominantly mono-substituted.The same holds true for 4,4'-diaminodiphenylmethane. Ethylenediamine gives the monoalkylated product in 87% yield (Table 3).

Table 1 - GCD Reactions of Aryl Amines

Ether	Amine	Conv., %	Selectivity, %
Tetrahydrofuran	Aniline	97	96
"	2,6-Diethylaniline	69	96
"	2,6-Dimethylaniline	57	90
"	2-Isopropylaniline	93	91
"	2,6-Diisopropylaniline	49	77
"	2-Aminophenol	74	96
"	2-chloroaniline	20	42
"	Anthranilonitrile	6	43
Furan	Aniline	56	97
Tetrahydropyran	Aniline	74	98
2,5-DimethylTHF	Aniline	70	88
Oxepane	Aniline	42	80
γ-Butyrolactone	Aniline	93	97
Caprolactone	Aniline	44	45
2-Oxazolidone	Aniline	-	100

Table 2 - GCD Reactions of Aliphatic Amines

Ether	Amine	Conv.,%	Selectivity, %
Tetrahydrofuran	Methylamine	63	91
"	Octylamine	35	77
"	Octadecylamine	37	81
"	Acetamide	76	45
Furan	Dodecylamine	71	42
γ-Butyrolactone	Ethanolamine	25	100

Table 3 - GCD Reactions of Diamines

Ether	Diamine	Conv., %	Selectivity, %
Tetrahydrofuran	Methylenebisaniline	47	71 (9)*
"	Ethylenediamine	65	68 (10)
"	2-Phenylenediamine	51	61 (3)
"	3-Phenylenediamine	33	73 (4)
"	4-Phenylenediamine	68	70 (19)
"	Diethyltoluenediamine	54	76 (10)
"	Triethyl-m-phenylene-diamine	49	77 (7)

* Figures in parentheses are for disubstituted product.

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