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ELECTROREDUCTIVE N-ALKYLATION OF AMIDES, CARBAMATES, AND N-HETEROCYCLES[1)]

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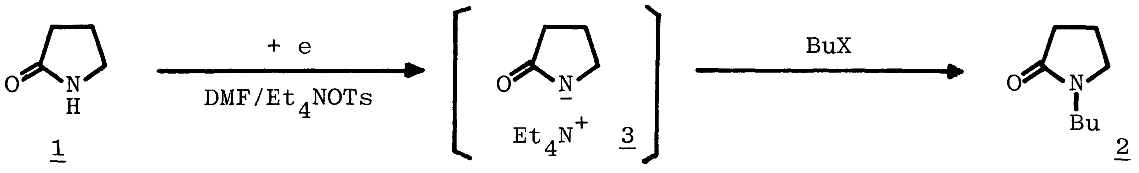
The N-alkylation of amides, lactams, carbamates, and N-heterocycles was easily attained in good yields by the electroreduction of the substrates in the presence of alkyl halides.

The N-alkylation of amides is often important in the synthesis of secondary and tertiary amines[2)] having different alkyl groups. The reaction of N-anions of amides with alkyl halides is, for instance, one of the typical methods of N-alkylation. These methods are, however, not always practical, since the use of excess amounts of a strong base[3-6)] (sodium metal, sodium hydride, KOH/phase-transfer catalysts,[7,8)] KOH/DMSO,[9)] or fluoride ion[10)]) is requisite for the formation of N-anions.

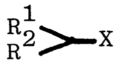
In this paper, we wish to report a new electroreductive method of N-alkylation of amides, carbamates, and N-heterocycles in which the reaction conditions are mild and the use of a strong base[11)] is not necessary.

As shown in Scheme 1, N-butylation[13)] of 2-pyrrolidone (1) to yield 2 was easily attained in good yield through the electroreduction of 1 in the presence of butyl chloride (X=Cl, Y=93%) or butyl methanesulfonate (X=OMs, Y=95%).



Scheme 1.

This reaction seems to proceed via the electroreductive formation of N-anion 3[14)] followed by its alkylation (Scheme 1), since the use of more easily reducible alkyl halides such as butyl bromide or iodide resulted in the decrease in the yields of 2 (X=Br, Y=55%), (X=I, Y=40%).

As the other examples are summarized in the Table 1, this electroreductive method is quite effective to the N-alkylation of a variety of amides (runs 1-8), carbamates (runs 9 and 10), and N-heterocycles (runs 11-14). It is also noteworthy that the alkylation of amides using secondary alkylating reagents (runs 1, 2, 6, and 10) gave satisfactory results in contrast with the difficulty often observed in the alkylation of amides with s-alkyl halides () under basic conditions.[18)] In addition, this new N-alkylation is effective not only for simple alkyl groups but also for groups possessing functional moiety such as protected hydroxy (run 3) or carbonyl group (run 4).

A typical procedure for the electroreductive N-alkylation is as follows. A solution of an amide (10 mmol) and an alkyl halide (12 mmol) in DMF (20 ml) containing tetraethylammonium *p*-toluenesulfonate (TEATS) (10 mmol) as a supporting electrolyte was electrochemically reduced in a divided cell equipped with a platinum cathode (2 x 2 cm) and anode. The anodic solution was 15 ml of DMF and TEATS (5 mmol). After 1.3 *F*/mol of electricity was passed at room temperature, the cathodic solution was poured into a saturated aqueous solution of NaCl and extracted with ether (3 x 50 ml). The residue obtained by evaporation of solvent was column chromatographed (silica gel, EtOAc:hexane=1:5) to give N-alkylated products.

Since the electrochemically generated N-anion such as 3 will react with alkyl halides[19)] immediately after it is formed,[21)] the reaction medium is always kept neutral. Thus, this method is applicable to the N-alkylation of β-lactams which are unstable under basic conditions. As shown in Scheme 2, the electroreduction of a β-lactam 4 in the presence of methyl or s-butyl methanesulfonate gave the corresponding N-alkylated products in good yields.

4

R = Me, 91%
R = s-Bu, 60%

Scheme 2.

Because of the simplicity of operation, satisfactory yield, and wide utility, the present method is highly useful in the synthesis of N-substituted amides, lactams, carbamates, and N-heterocycles.

Table 1. Alkylation of Amides, Carbamates, and N-Heterocycles

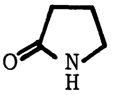
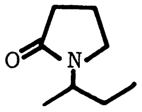
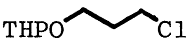
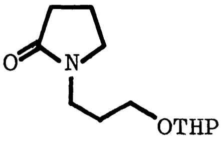
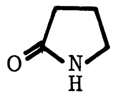
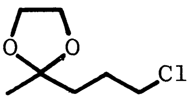
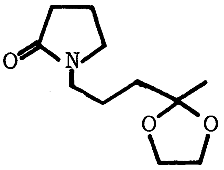
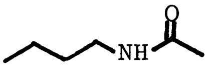
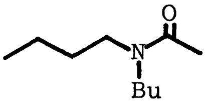
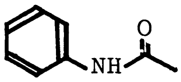
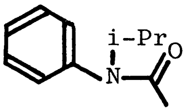
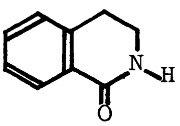
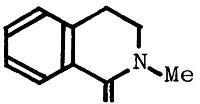
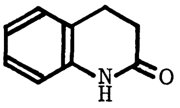
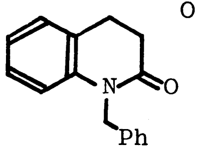
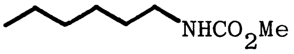
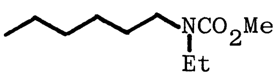
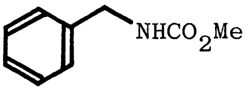
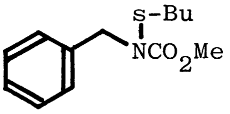
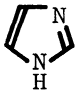
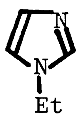
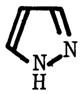
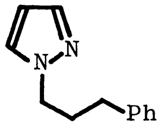
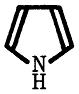
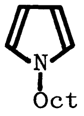
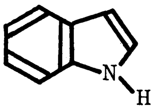
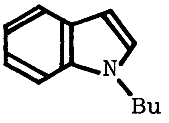
Run	Amide Carbamate N-Heterocycles	Alkylating reagnet	Product[a)]	Yield/%[b)]
1		s-BuCl		68
2	"	s-BuOMs	"	70
3	"			80

Table 1 (continued). Alkylation of Amides, Carbamates, and N-Hegerocycles

Run	Amide Carbamate N-Heterocycles	Alkylating reagent	Product[a)]	Yield/%[b)]
4				63
5		BuOMs		67
6		i-PrOMs		71[c)]
7		MeOMs		91
8		$PhCH_2Cl$		87
9		EtOMs		89
10		s-BuOMs		85[c)]
11		EtOMs		73
12		$Ph(CH_2)_3Cl$		67
13		Oct Cl		80
14		BuOMs		91

a) All the products gave satisfactory spectroscopic data for the assigned structure. b) Isolated yields. c) 2 *F*/mol of electricity were passed.

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18) The alkylation of benzamide with isopropyl bromide using phase-transfer catalysts,[7] for example, gave the corresponding product only in 32% yield.
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