

SYNTHESIS OF N,N'-DISUBSTITUTED UREAS FROM CARBAMATES

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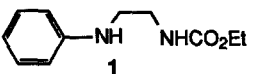
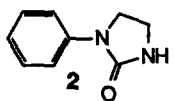
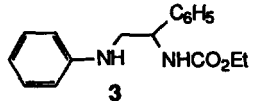
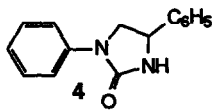
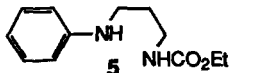
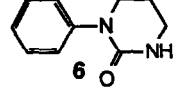
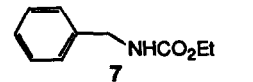

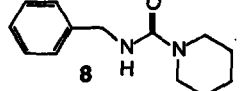
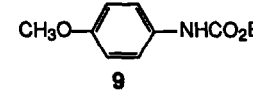

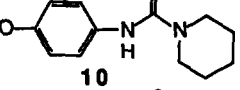
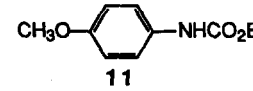
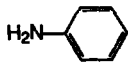
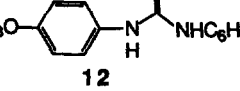
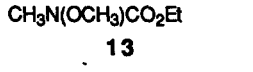

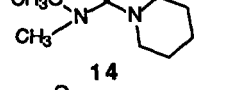
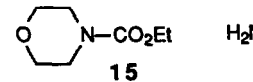
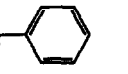
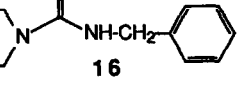
Summary: A simple synthesis of N,N'-disubstituted ureas from carbamates is described involving displacement of an alkoxy group by the magnesium salt of an amine generated *in situ* by treatment with ethylmagnesium bromide.

The urea group is a fundamental functionality of organic chemistry, and is commonly encountered in diverse natural products. Traditional methods for the general synthesis of ureas include: (1) reaction of amines with isocyanates¹ or (2) reaction of amines with carbonyl equivalents such as phosgene, carbonyldiimidazole or disuccinimido carbonate.² We were interested in effecting the conversion of carbamates to ureas as a simple, general method to access unsymmetrical N,N'-disubstituted urea compounds. It is generally accepted that simple aminolysis of alkoxy-carbamates does not proceed readily under mild conditions.³ However, this reaction can be accomplished when the OR group is a better leaving group such as a phenoxy group.⁴ We report herein that if an amine is first treated with a Grignard reagent such as ethylmagnesium bromide to form the magnesium salt, it subsequently reacts efficiently to displace an alkoxy group of a carbamate providing the corresponding urea in high yield.

Several representative examples of this method are shown in Table 1. Entries 1-3 demonstrate intramolecular reactions of N-substituted anilines to form cyclic five- and six-membered ureas in nearly quantitative yields. Entries 4 and 5 provide intermolecular examples of urea formation with a typical secondary amine, piperidine, reacting with a benzylaminocarbamate and an arylaminocarbamate respectively. Entry 6 is an example of the formation of a N,N-diarylurea and this reaction was sluggish under the standard reaction conditions used. Entry 7 provides an interesting example of the preparation of a N-alkoxyurea where preferred displacement of the ethoxy group of N-methoxy-N-methylamino ethoxycarbonyl occurred. Entry 8 illustrates that a tertiary carbamate smoothly undergoes the substitution reaction. Both entries 7 and 8 preclude the formation of an isocyanate intermediate. Mechanistically, the magnesium amide likely acts as a Lewis acid to activate the carbamate toward substitution.⁵ In the cases above urea formation does not occur without treatment of the amine with ethylmagnesium bromide. Refluxing methylene chloride offered a mild reaction temperature for heat sensitive substrates. However other solvents such as tetrahydrofuran could also be used.

The typical experimental procedure used for the examples in Table 1 is described as follows. To a solution of **1** (0.75 g, 3.6 mmol) in dichloromethane (30 mL) at 50°C was added dropwise a solution of ethylmagnesium bromide (2 mL of a 2M solution in tetrahydrofuran, 4.0 mmol). The mixture was refluxed for 24 h, allowed to cool to room temperature, and then aqueous saturated NH₄Cl (5 mL) was added. The aqueous phase was adjusted to pH = 4 by addition of 2N HCl. The organic phase was collected and the aqueous phase was further extracted with dichloromethane (2X 50 mL). The combined organic extracts were washed with saturated aqueous NaCl (50 mL), dried over MgSO₄, filtered and evaporated to provide the cyclic urea **2** (0.57 g, 98%). For the cases with incomplete reaction silica gel chromatography was used to purify the product.

TABLE 1. Ureas from carbamates.

Entry	$R^1-NHCO_2Et + NH_2-R^2$		EtMgBr dichloromethane	$R^1-NHCONH-R^2$	Reaction time (h)	Yield (%)
	Carbamate	Amine				
1					24	98
2					24	95
3					24	95
4					48	84
5					48	60
6					48	35
7					48	80
8					48	72

References

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4. Adamiak, R. W.; Stawinski, J. *Tetrahedron Letters* **1977**, 1935.
5. Support for this hypothesis is evident from the observation that trimethylaluminum can replace ethylmagnesium bromide in this reaction. Ethylmagnesium bromide is the preferred reagent due to ease of handling and cost.

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