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A simple synthetic protocol for the protection of amides, lactams, ureas, and carbamates

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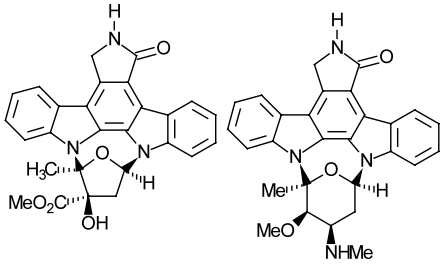
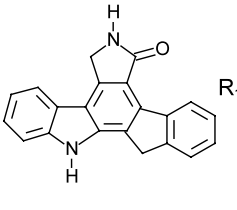
Abstract—A new procedure for protecting the amide, lactam, urea, and carbamate NH group with a triphenylmethyl (Tr) group is described. The utility of this method is illustrated with molecules that contain other functional groups. A mild deprotection using trifluoroacetic acid makes this a useful method for attaching amide groups on resin for combinatorial synthesis.

1. Introduction

The indolocarbozoles, K252a **1** and Staurosporine **2**, exhibit a wide range of biological activities.[1] In continuation of our exploration of these ring systems, we prepared **3**[2] and sought a method of protection of the lactam nitrogen where by routine substitution reactions could be carried out on the indole nitrogen, for example. Ultimately, the identification of a suitable protecting group could be applied to both solution- and solid-phase combinatorial methods.



1 **2**



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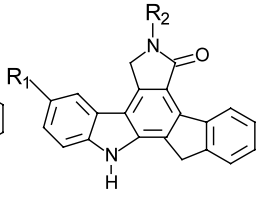
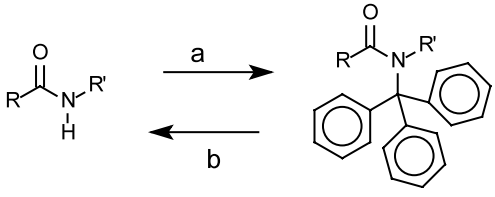


4 $R_1 = H; R_2 = CPh_3$
4a $R_1 = CPh_3; R_2 = H$

There are relatively few methods available for the protection of an amide group.[3,4] After examination of a number of approaches we found that **3** could be readily protected at the lactam nitrogen using a triphenylmethyl-protecting group[5] and further found this approach to be a versatile for protection of amides and lactams, ureas and carbamates. The triphenylmethyl (Tr) substituted indenocarbazole **4** was isolated in excellent yield (72%) by reacting indenocarbazole **3**, triphenylmethanol and *p*-toluenesulfonic acid (*p*-TsOH) in refluxing toluene (Scheme 1).[6] During the course of our investigation, a similar amide protection scheme was published using an amide, 4,4′-dimethoxybenzhydrol in acetic acid, acetic anhydride, and a catalytic amount of sulfuric acid[7].



Scheme 1. *Reagents and conditions*: (a) triphenylmethanol, *p*-TsOH, benzene, reflux; (b) TFA, CH_2Cl_2, water, rt.

Keywords: novel procedure; protecting group; amides; lactam; ureas; carbamates.

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2. General procedure

A solution of amide (0.864 mmol), triphenylmethanol (0.576 mmol, 0.67 equiv.) and *p*-TsOH (0.288 mmol) in benzene (15 mL) was refluxed using Dean–Stark apparatus under argon. Completion of the reaction was monitored by analytical TLC. The solution was cooled to room temperature, quenched with 2% aqueous sodium bicarbonate solution, and extracted with ethyl acetate (3×5 mL). The organic layer was washed with water, brine, dried and evaporated. The reaction product was purified on a silica gel column using hexane and ethyl acetate (varying proportions based on the product) as eluent.

3. Results and discussion

This synthetic strategy was subsequently extended to other organic molecules such as amides, lactams, ureas,

Table 1.

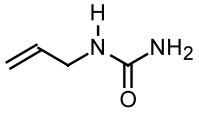
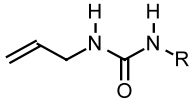
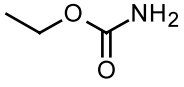
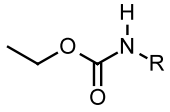
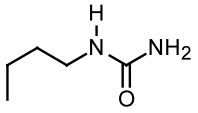
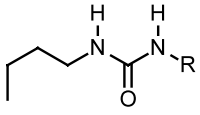
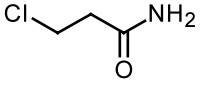
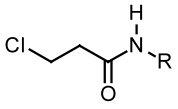
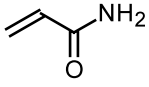
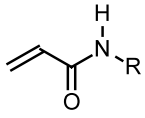
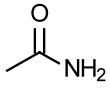
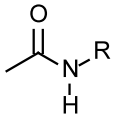
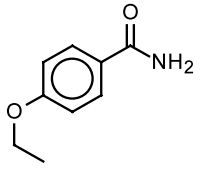
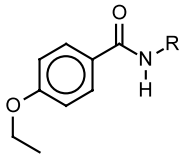
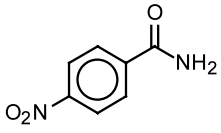
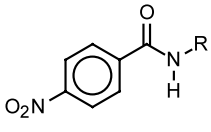
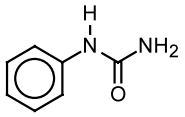
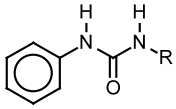
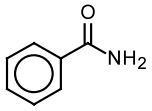
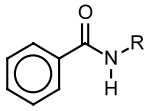
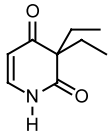
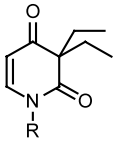
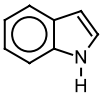
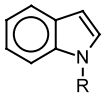
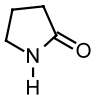
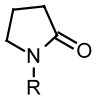
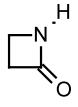
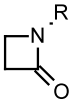
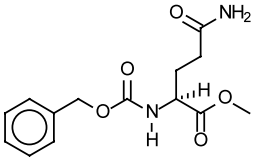
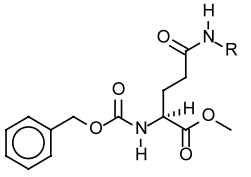
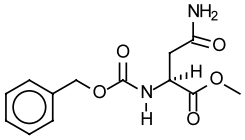
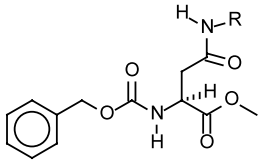
Entry	Starting Material	Reaction Time,[h] h	Product	Isolated Yield,[i] %
3	**3**	**15** [a,b,g]	**4**	**72**
5		**4**		**98**
6		**3**		**99**
7		**6**		**83**
8		**3**		**95**
9		**3**[e]		**93**
10		**5**		**98**
11		**5**		**91**
12		**3.5**		**98**

Table 1. (*Continued*)

13		**2.5**		**91**
14		**30**[a,f]		**88**
15		**6**		**4**
16		**1**		**97**
17		**9**[a,b,d]		**72**
18		**10**[d]		**35**
19		**3**		**91**
20		**20**[a]		**71**

[a] 1-Methyl-2-pyrrolidinone was used as co-solvent.
[b] Toluene was used as the solvent.
[c] Mixture of benzene and toluene was used as solvent.
[d] Excess of starting material was used.
[e] 1.9 equiv. of starting material was used.
[f] 3 equiv. of starting material was used.
[g] 1.4 equiv. of triphenylmethanol and 1 equiv. of indenocarbazole **3** was used.
[h] Unless otherwise indicated benzene was used as solvent.
[i] Reported yields are based on triphenylmethanol.

carbamate, and the results are shown in Table 1.[8] This procedure is compatible with the presence of functional groups such as olefin, nitro, chloro, and ester. Also, the presence of electron withdrawing or donating groups on aromatic benzamide derivatives did not affect the yields as illustrated by entries 11 and 12. A lower yield was observed in the case of triphenylmethyl pyrithyldione (entry 15). It is noted that the five- and four-membered ring lactams (entries 17 and 18) are unstable during these reaction conditions and may account for the lower observed yields. In these two instances, there was no improvement in yield even after the addition of excess starting materials. Additionally, a selective protection of primary amide in the presence of a hindered carbamate can be achieved by this method (entries 19 and 20).

This communication describes a simple procedure for the regiospecific protection of an amide nitrogen. In general, a triphenylmethyl protected product was

deprotected using TFA to liberate the expected product in excellent yield.[9] Nonetheless, deprotection of **4** with TFA gave **3** and **4a** (40–50%). Use of several cationic scavengers such as anisole, thioanisole, dimethylsulfide, phenol, thiophenol, ethanedithiol, benzylmercaptan, triethylsilane, tributylphosphine, and water has been reported.[10] None of these scavengers in different combinations and proportions decrease the formation of **4a**. However, the protection of **3** with 4,4′-dimethoxybenzhydrol furnished the expected product, which upon deprotection with 5% TFA returned **3** and small amount (<3%) of the corresponding byproduct.[6]

Acknowledgements

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6. (a) Triphenylmethyl indenocarbazole **4** was characterized by ^{1}H and ^{13}C NMR, IR, mass spectroscopic methods and elemental analysis; (b) Deprotection of triphenylmethyl indenocarbazole **4** with trifluoroacetic acid (with or without cationic scavengers) resulted in the isolation of indenocarbazole **3** and one other side-product, **4a**.
7. Henneuse, C.; Boxus, T.; Tesolin, L.; Pantano, G.; Marchand-Brynaert, J. *Synthesis* **1996**, 495–501.
8. All new compounds were fully characterized by HPLC, NMR, and mass spectroscopic methods.
9. The triphenylmethyl group was deprotected from Z-Gln(Tr)-OMe using 90% TFA in dichloromethane and water to isolate Z-Gln-OMe in 84% yield (entry 19).
10. (a) Albericio, F.; Kneib-Cordonier, N.; Biancalana, S.; Gera, L.; Masada, R. I.; Hudson, D.; Barany, G. *J. Org. Chem.* **1990**, *55*, 3730–3743; (b) Beck-Sickinger, A. G.; Schnorrenberg, G.; Metzger, J.; Jung, G. *Int. J. Peptide Protein Res.* **1991**, *38*, 25–31.