New Photolabile Amino Protecting Groups: Photogeneration of Amines from [(3′,5′-Dimethoxybenzoinyl)oxy]carbonyl Carbamates

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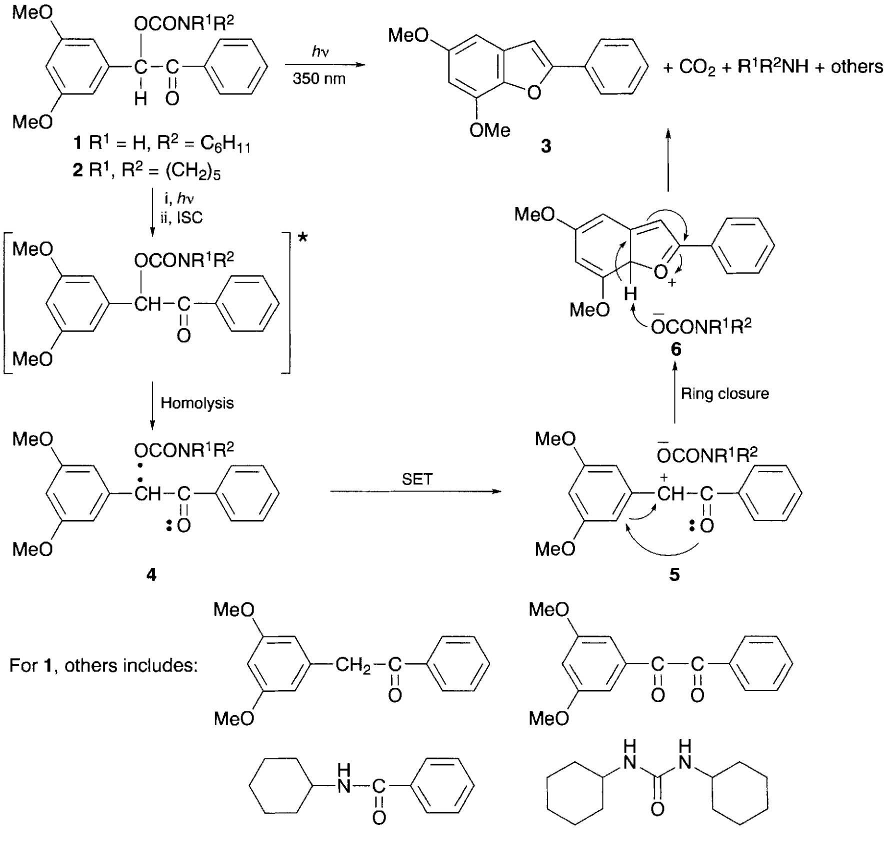
A novel class of photolabile amino protecting groups, based on [(3′,5′-dimethoxybenzoinyl)oxy]carbonyl groups, is presented and their scope and versatility demonstrated by the photogeneration of free primary and secondary amines.

Recently, we developed a strategy for base photogeneration by masking amines and diamines as photoactive carbamates.[1] Under the action of light, these neutral carbamates decompose to liberate the free base. However, we found the commonly used photolabile amino protecting groups, *e.g.* the 3,5-dimethoxy-α,α-dimethylbenzyloxycarbonyl and *o*-nitrobenzyloxycarbonyl moieties, undergo somewhat complex photoreactions which may also be complicated by deleterious side reactions upon prolonged photolysis. In order to expand the current applicability of photogenerated amines, we have investigated new photochemistry that would allow the efficient unmasking of amino groups. With this goal in mind, we focused on the rich photochemistry offered by the α,α-dimethyl-3,5-dimethoxy desyl chromophore. While the parent desyl chromophore is well known to undergo photocleavage *via* classical photochemical pathways such as α-cleavage (Norrish Type I), *meta*-methoxy substitution causes photocyclization to become the major photocleavage pathway. For instance, Sheehan *et al.*[2] reported that photolysis of 3′,5′-dimethoxybenzoin acetate affords 5,7-dimethoxy-2-phenylbenzo[*b*]furan as the major product. In this case, photocyclization is accompanied by formation of acetic acid. This unique photoreactivity has led to the use of methoxy-substituted benzoins as photolabile carboxyl protecting groups.[2,3] More recently, the photocyclization of substituted benzoins has been applied to the caged release of phosphate derivatives.[4,5]

Based on the unique mode of photochemistry offered by 3′,5′-dimethoxybenzoin esters, we investigated the 3′,5′-dimethoxybenzoin chromophore as a novel photolabile amino protecting group. We now report preliminary results on the photogeneration of amines from 3′,5′-dimethoxybenzoin carbamates.

3′,5′-Dimethoxybenzoin cyclohexyl carbamate **1** was prepared by reaction of cyclohexyl isocyanate with the corresponding benzoin in refluxing benzene. Piperidinyl carbamate **2** was prepared by reaction of piperidine with the *p*-nitrophenyl mixed carbonate of 3′,5′-dimethoxybenzoin. Preparative photolysis of **1** (5 mmol dm^{-3} solution in acetonitrile using a Pyrex vessel) proceeded smoothly upon irradiation in a Rayonet photochemical reactor with 350 nm lamps for 2 h.‡ The major products were cyclohexylamine and 5,7-dimethoxy-2-phenylbenzo[*b*]furan **3**. The fluorescent benzo[*b*]furan **3** was isolated in excellent yield (80–85%) after flash chromatography and recrystallization. In our hands, the photoefficiency of the amine deblocking appears significantly greater than for other commonly used photolabile amino protecting groups.

The photochemical removal of the [(3′,5′-dimethoxybenzoinyl)oxy]carbonyl protecting group was readily monitored by



Scheme 1

^{1}H NMR spectroscopy by irradiating a 20 mmol dm^{-3} solution of carbamate **1** in [^{2}H$_3$]acetonitrile. The integral of the carbamate cyclohexyl methine at δ 3.40 decreased, while the expected multiplet of the cyclohexyl methine of free cyclohexylamine appeared at δ 2.52 and grew upon increased exposure at 350 nm in a Rayonet reactor. After 60 min, conversion to free cyclohexylamine reached 93%. In addition to cyclohexylamine, **3** was identified as the major by-product by ^{1}H NMR spectroscopy. A singlet, characteristic of the 3-benzo[*b*]furan proton in **3**, appears at δ 7.12 and increases in intensity with photolysis time. By comparison, photolysis of the parent benzoin cyclohexyl carbamate gives a complex photolysate in which benzo[*b*]furan cannot be identified.[§] This illustrates the important role the 3′,5′-dimethoxy substituents play in redirecting the mechanism of photocleavage.

Gas chromatography confirms the clean photogeneration of free cyclohexylamine and piperidine from 3′,5′-dimethoxybenzoin carbamates, **1** and **2**, respectively. In each case, GC-MS indicated the appropriate molecular ion for the corresponding unmasked amine. For the photolysis of cyclohexyl carbamate **1** GC-MS indicated the major by-product was the expected 5,7-dimethoxy-2-phenylbenzo[*b*]furan **3**. Other minor products, present in only trace amounts, were identified as deoxy-3′,5′-dimethoxybenzoin, 3,5-dimethoxybenzil, *N*-benzoylcyclohexylamine and dicyclohexylurea.

The spectral changes observed upon monitoring the photolysis of **1** and **2** by IR and UV–VIS spectroscopy were also consistent with the smooth photocyclization that accompanies amine liberation. Exposure to 350 nm radiation caused the gradual disappearance of both the keto carbonyl stretch (1700 cm^{-1}) and the carbamate carbonyl stretch (1723 cm^{-1}). This was accompanied by the gradual depletion of the carbamate N–H stretch at 3360 cm^{-1}, with concomitant appearance of bands owing to the photoliberated amine in the region 3500–3700 cm^{-1}. In the UV spectrum, the maximum originally at 243 nm is replaced by an intense absorption at 300 nm, resulting from photocyclization to **3**.

Based on the available mechanistic data, Givens *et al.*[4] have proposed an ion-pair mechanism to explain the photocyclization of desyl phosphate esters. This mechanism may be extended to rationalize the photogeneration of amines from **1** and **2** (Scheme 1). Initially, photodeblocking proceeds by n–π^* excitation of the carbonyl group. Subsequent homolysis produces a radical pair **4** which undergoes rapid electron transfer to yield an ion pair **5**. After ring closure, the liberated anion acts as a base and removes the bridgehead proton from **6**, forming the benzo[*b*]furan photoproduct **3**. The unstable carboxylated amine then loses carbon dioxide, liberating the free amine. This mechanism is in agreement with the photochemical *meta* effect[6] since the cleavage pathway is consistent with stabilization of benzylic carbocation **5** by the *meta*-methoxy substituents. However, photocleavage of the related phenacyl protecting group[7] is known to proceed by C–O homolysis. We therefore propose initial homolytic cleavage is followed by rapid single electron transfer to rationalize formation of the *meta*-methoxy substituted benzylic carbocation **5**. Similar mechanistic pathways have recently been shown to be important in the photochemistry of *meta*-methoxy benzylic esters.[8]

We have demonstrated the potential utility of the [(3′,5′-dimethoxybenzoinyl)oxy]carbonyl moiety as a novel photolabile protecting group for primary and secondary amines. Photochemical removal of the 3′,5′-dimethoxybenzoin chromophore is particularly clean, with minimal side products. This is in contrast to the photochemistry of many other photosensitive protecting groups. Partial support of this work at Cornell University by the Office of Naval Research is acknowledged with thanks.

Received, 23rd December 1994; Com. 4/07839J

Footnotes

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[‡] Smooth photolysis has also been observed in THF solution. In addition, preliminary evidence suggests photocyclization also occurs upon photolysis in a quartz vessel with RPR3000 Å and RPR2500 Å lamps.

[§] Despite the inefficient photocyclization, a 75% conversion to free cyclohexylamine was observed. In this case, the photoliberation of amine probably proceeds *via* classical desyl photochemistry.

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