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The photosolvolysis of N-arylmethyladenines. Photoremovable N-arylmethyl protective groups for N-containing compounds.

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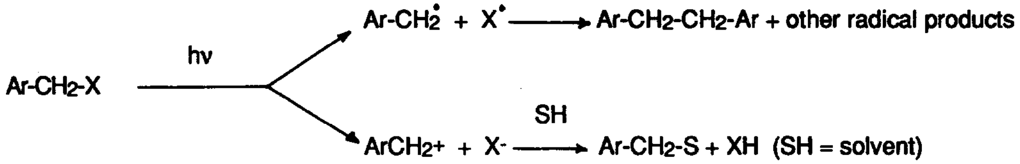
Summary: N-arylmethyladenines are photolyzed in water, giving adenine and the corresponding arylmethanols. The reaction is not only observed when the arylmethyl group is a meta-substituted benzyl , but also with more complex substituents like imidazo[1,2-a]pyridin-6-ylmethyl. Meta-substituted arylmethyl groups are proposed as photoremovable N- protective groups in adenine chemistry.

Since the initial study by ZIMMERMAN and SANDEL (1), the photolysis of arylmethyl derivatives Ar-CH_2-X has been extensively studied (2). Ionic (leading to photosolvolysis) and radical species, are generally involved in the reaction, the mechanisms depending on the nature of the Ar and X groups, and of the solvent (Scheme 1) :

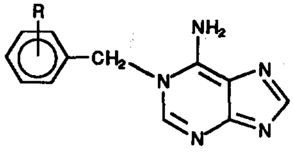


Scheme 1

Arylmethylamines and N-arylmethyl substituted nitrogen containing compounds were not known to be photosolvolyzable (3), except arylmethylammoniums (4). Thus, photoremovable arylmethyl groups have been used for the protection of amines only through their carbamates (5) or sulfonamides (6) derivatives.

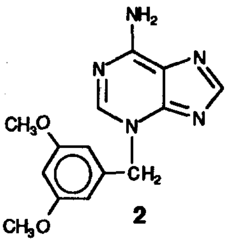
N-protective groups are needed in adenine chemistry for specific N-alkylation. For this purpose, the available protective groups include benzyl, whose removal is obtained by sulfuric acid treatment or hydrogenolysis (7), or 4-nitrobenzyl which is eliminated as quinonimine methide after reduction of the nitro group to amine (8). We show here that many N-arylmethyl substituents may be photoremoved from the adenine nucleus and from other N-containing functional groups.

The five N-(3,5-dimethoxybenzyl)adenines **1a**, **2-5** and the 1-arylmethyladenines **1b-f** have been prepared by known methods (9). 1-(3-Aminobenzyl)adenine **1g** was obtained by dithiothreitol reduction of the corresponding azido derivative (10). The uv and ^1H nmr spectra of compounds **1-5** were in accordance with the spectra of the N-benzyladenines (11). We chose meta-substituted benzyl substituents because of the beneficial "meta" effect generally observed for the photosolvolysis of substituted benzyl derivatives (1).



1

	R
a	3,5-dimethoxy
b	H
c	3-methoxy
d	3-fluoro
e	3-chloro
f	3-bromo
g	3- amino



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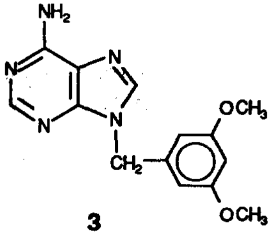

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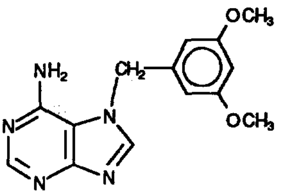

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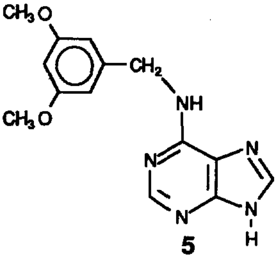
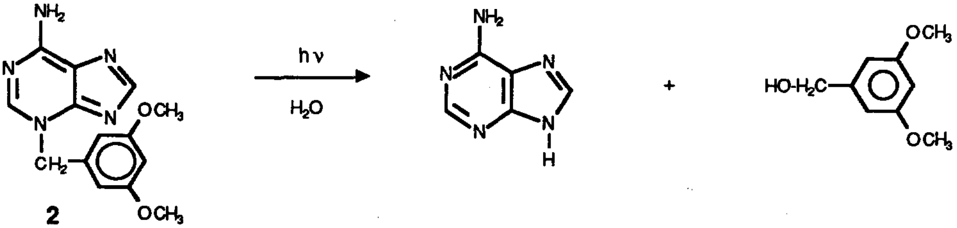


5

The photolysis (254 nm) of the compounds **1-5** in saturated water solutions (~10^{-3} M) produced adenine in almost quantitative yield (hplc control)(12). Arylmethanols were generally the other products, as exemplified by the photolysis of **2** (Scheme 2), where 3,5-dimethoxybenzyl alcohol was characterized by hplc, glc and ms from dichloromethane extracts of the aqueous reaction medium; none of the usual radical products of photolysis observed from 3,5-dimethoxybenzyl derivatives (1) were detected, thus indicating that photosolvolysis was probably the unique mechanism involved. The photolyses of the compounds **1-5** in water-methanol mixtures gave similar results, producing not only adenine and the arylmethanols, but also the corresponding aryl methyl ethers. These water-methanol mixtures (generally 50-50) may dissolve larger samples of the compounds **1-5**, and their use is recommended for preparative purposes.



Scheme 2

The quantum yields of photolysis of compounds **1a**, **2-5** were determined from 10^{-3} M aqueous solutions.They were found to range from 10^{-3} to 2.10^{-5}, and their value generally increased with pH. The influence of the aryl group on the rate of photolysis was determined by measuring the half-time of photolysis of the 1-benzyladenines **1** in $2\text{x}10^{-4}$ M aqueous solutions (Table 1) :

Table 1
Half-time of photolysis of 1-arylmethyladenines 1[a]

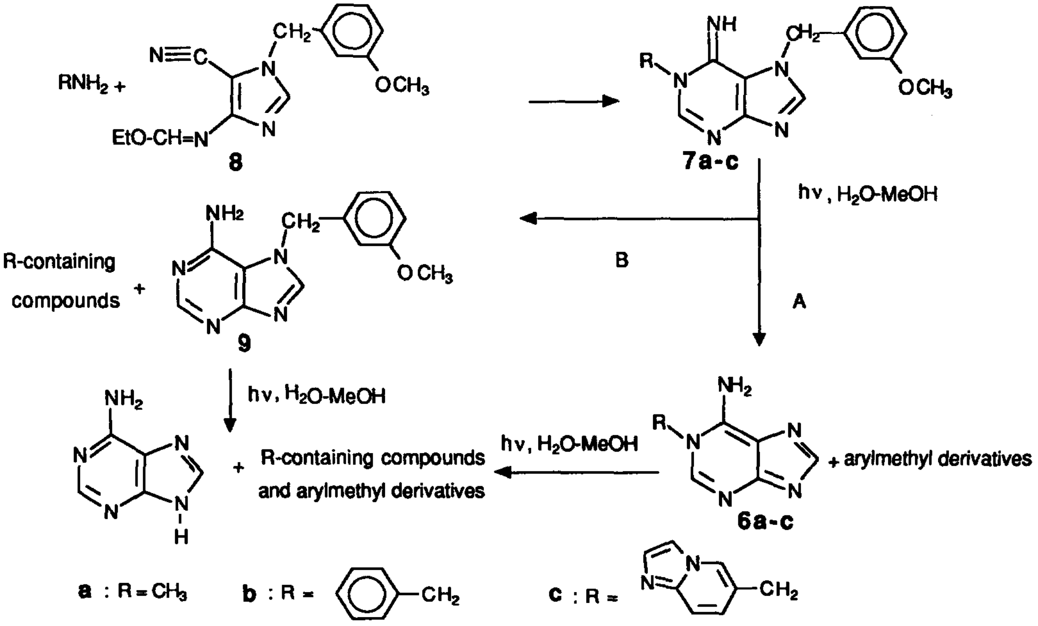
N°	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**
$t_{1/2}$ min	15	27	4	9	4	2,5	6

[a] $2\text{x}10^{-4}$ M aqueous solution at pH 9 in a 0.5 l reactor; 450 w medium pressure mercury lamp.

1-(Meta-substituted benzyl)adenines **1** exhibited, as expected, shorter half-time of photolysis than the unsubstituted compound **1b**. However, **1c** (monomethoxy-substituted) was photolyzed more quickly than **1a** (dimethoxy-substituted). In fact, in the series of compounds **1**, the competing adenine chromophore does not allow all the light absorbed by the compound to be totally used for the excitation of the aryl nucleus. Thus, we cannot expect to find a direct relationship between the rate of photolysis and the effects of the substituents of the benzyl ring, as in simple $Ar\text{-}CH_2\text{-}X$ derivatives where X is not uv absorbing.

The possibility of use of arylmethyl substituents as photoremovable N-protective groups was tested in an indirect synthesis of 1-substituted adenines. These compounds are generally prepared by direct alkylation at N-1 of adenosine, followed by the acidolysis of the ribosyl moiety (9). This last method could not be used for the synthesis of 1-(imidazo[1,2-a]pyridin-6-ylmethyl)adenine **6c**, because of the electrophilic character of the imidazo[1,2-a]pyridine nucleus. We needed this compound **6c** as a fluorescent analogue of 1-methyladenine **6a**, a hormone of starfish oocyte (10) .

The 1,7-disubstituted adenines **7a-c** bearing a 7-(3-methoxybenzyl) substituent were prepared from the corresponding primary amine (13) and the trisubstituted imidazole **8** (14) (Scheme 3). The photolysis of compounds **7a-c** (1 mmol) in methanol-water (50-50) solutions, by using a 450 w medium pressure mercury lamp, were monitored by hplc. The 1-methyl derivative **7a** gave the expected 1-methyladenine **6a** (15) as the only adenine derivative product (path A - Scheme 3)(65% isolated yield). The 1-benzyl derivative **7b** produced mainly 1-benzyladenine **6b** (path A), but also 7-(3-methoxybenzyl)adenine **9** (path B), and adenine which probably resulted from the successive photoremoval of the two substitutents (path A or B), and was the final product. A similar observation was done in the photolysis of **7c** whose chromatograms of the reaction mixture exhibited a rapidly increasing peak of adenine beside other peaks and particularly the peak of the 7 -substituted derivative **9**. We did not attempt to isolate and characterize the target compound **6c**, which was expected to be generated through path A: its use as a fluorescent reagent was questioned because uv irradiation of this compound should produce not only fluorescence emission, but also removal of the 1-substituent.



Scheme 3

In conclusion, arylmethyl groups like meta-substituted benzyl may be used as photoremovable N-protective groups for the adenine nucleus, as exemplified by the indirect access to 1-methyladenine **6a**. Complex arylmethyl-like substituents as imidazo[1,2-a]pyridin-6-ylmethyl are also good candidates for photoelimination. In adenines substituted by two arylmethyl groups, specific photoelimination has probably not to be expected.

We have also done some successful experiments of photoelimination of N-arylmethyl substituents with other N-heterocycles like 3-amino-1,2,4-triazole, and N-containing functional groups like aromatic amines, ureas, carbamates or amides. In these cases, when the N-containing group is included in a pesticide molecule, the N-arylmethyl substitution gives rise to potential photoactivable pesticides, provided this arylmethyl substituent is photolyzable under solar light (16).

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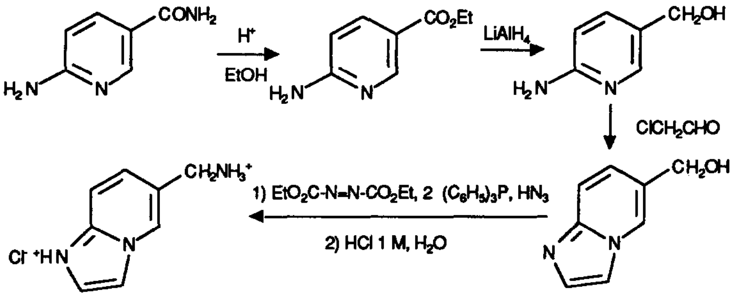
12 - In the photolysis of the 1-substituted compound **1**, even in neutral solution, we detected as an intermediate, the N^6-substituted isomers (ex. **1a**→**5**). The formation of these products may result from a Dimroth-like rearrangement of **1**. We are trying to elucidate this reaction.
13 - The imidazo[1,2-a]pyridin-6-ylmethylamine was prepared according to the following scheme:



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