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p-HYDROXYPHENACYL ATP[1]: A NEW PHOTOTRIGGER

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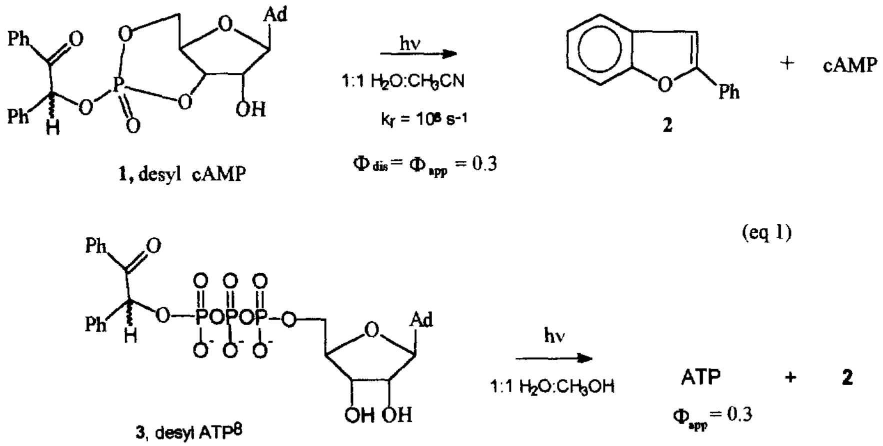
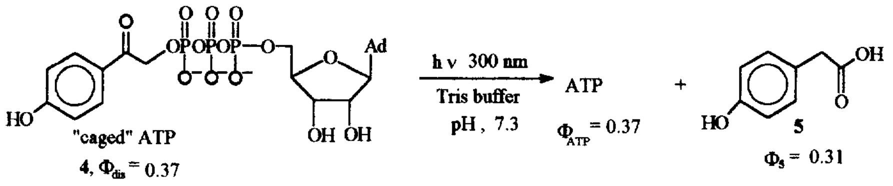
Abstract: A new photoactivated "caged" ATP, *p*-hydroxyphenacyl ATP (**4**), is introduced to replace the *o*-nitrophenethyl and desyl analogues as a more efficient, rapid release phototrigger for ATP.

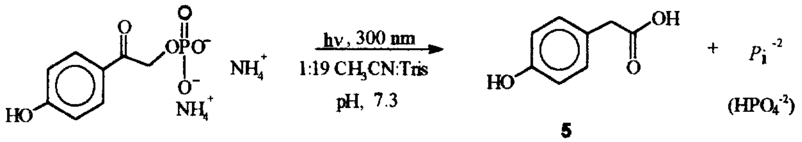
The rapid, efficient release of biochemical substrates has been the focus of attention of many biochemists,[2] physiologists,[3] and chemists[4] for almost two decades since the reports of Engels and Schlaeger[5] and Kaplan et al.[6] on the photorelease of nucleotides from their "caged" precursors. We have recently reported a new approach to this field employing the desyl group as the "cage" or photoprotecting group for the light-activated release of cAMP[7] and ATP[8] (eq. 1). This photoprotecting group has since found application for the release of phosphate (P_i)[7] and several amino acids.[1,9] While this "cage" group efficiently and rapidly releases the attached nucleotide or amino acid upon photolysis, the efficacy of the desyl group as a cage is severely limited because of the poor aqueous solubility of its derivatives, and the difficulty of separating the individual diastereomers created by the chiral center present in the desyl group.



We report here a second generation of the α-keto "cage" which alleviates these major limitations that accompany the desyl group while at the same time preserving the high efficiency and rapid photorelease of the coupled substrate and also maintaining the ready synthetic accessibility realized with the desyl series. Modeled on the combined results of Sheehan et al.[10] and our own studies[7a,b] on *p*-methoxyphenacyl derivatives, the new phototrigger group, *p*-hydroxyphenacyl, photoreleases ATP from its caged ester with an efficiency of 0.37 (eq. 2). In addition to the high efficiency and rate for the release of ATP, the beneficial features of this derivative are the absence of the added chiral center, the excellent aqueous solubility and the hypochromic shift of the UV absorption upon rearrangement of the cage to *p*-hydroxyphenylacetic acid (**5**). This shift allows a greater degree of conversion of the phototrigger to ATP. Qualitatively similar results have been obtained for the photorelease of inorganic phosphate from *p*-hydroxyphenacyl phosphate **6**.



(eq 2)



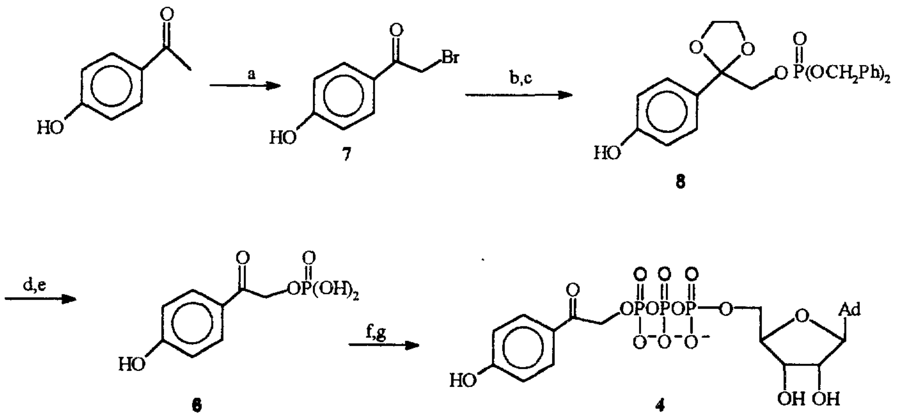
6, "caged" phosphate

The "caging" group is synthetically accessible by the straightforward, efficient route illustrated for **4** and **6** in Scheme 1 and is accomplished in overall unoptimized yields of ~20% and ~50% from commercially available *p*-hydroxyacetophenone. The application of this strategy has been extended to the synthesis of the *p*-hydroxyphenacyl phototriggers for the amino acids L-glutamate and GABA.[9a]

p-Hydroxyphenacyl ATP (**4**) was shown to be stable for over 24 h in H_2O, in D_2O and in three other buffered media in contrast to the results reported by Iwamura[7d] for **1**. Quantum efficiencies for **4** and **6** in Tris buffer were also measured and are shown in Table 1. Finally, the photorelease of ATP from **4** was quenched with sodium 2-naphthalenesulfonate and displayed good linear Stern-Volmer behavior. Analysis of the concentration dependence of the SV quenching indicated that this process indeed proceeds through the triplet state of the phenacyl chromophore which promotes cleavage of the phenacyl-phosphate bond with a unimolecular rate constant of 6.0×10^8 s^{-1} in the release of ATP.

Other substituted phenacyl phosphates (**9a** - **f**) which we synthesized and examined proved to be less useful for release of phosphate (*Pi*). For example, the unsubstituted and *m*-methoxy analogues did not produce ionic products, but fragmented to radical intermediates that coupled or simply reduced to the unsubstituted phototrigger. The *p*-NHR derivatives **9d** - **f** did release phosphates but much less efficiently and were not accompanied by rearrangement of the phenacyl moiety. The major products from **9d,e** were the hydroxyacetophenones **10d,e**.

SCHEME 1



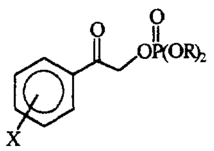
a) $CuBr_2$, EtOAc, rt; 71%; b) $(BnO)_2PO_2^- \, ^+N(Me)_4$, benzene; 85%; c) $HOCH_2CH_2OH$, p-TsOH; 82%; d) Pd/C, H_2; e)1% HCl(aq); DEAE, Sephadex, NH_4OAc; 96% f) Im-ADP, HMPA; 42%, g) Cellulose, $NH_4^+HCO_3^-$

TABLE 1. Stability and quantum efficiencies for 4-hydroxyphenacyl adenosine-5′-triphosphate (**4**) and 4-hydroxyphenacyl phosphate (**6**).

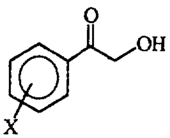
Phototriggers	Conditions	pH	Stability in Buffer,	Quantum Efficiencies[a]		
			H_2O, or D_2O (control)[b]	Φ_{-4}	Φ_{ATP}	Φ_5
4	Tris Buffer	7.3	>24 h	0.37	0.37	0.31
4	Ringers I, II, III	6.5	>24 h	-d-	-d-	-d-
6	Tris Buffer[c]	7.3	-d-	0.38	----	0.12

[a] Irradiated at 300 nm at rt.; [b] no irradiation at rt.; [c] 5% CH_3CN added; [d] not determined.

The mechanism for cleavage of the *p*-hydroxyphenacyl phosphates and nucleotides involves participation by the aryl group during the release of the phosphate moiety. A plausible sequence is illustrated in Scheme 2. Precedence for homolytic cleavage followed by electron transfer for the singlet-state photochemistry of benzyl carboxylic esters has been presented by Pincock[11] and has great appeal. Lipson, Deniz and Peters[12] have provided additional support for electron transfer from initially formed caged radical pair producing the ion pair in the photosolvolysis of benzhydryl chlorides. Such a mechanism may be applicable to our triplet reactions.

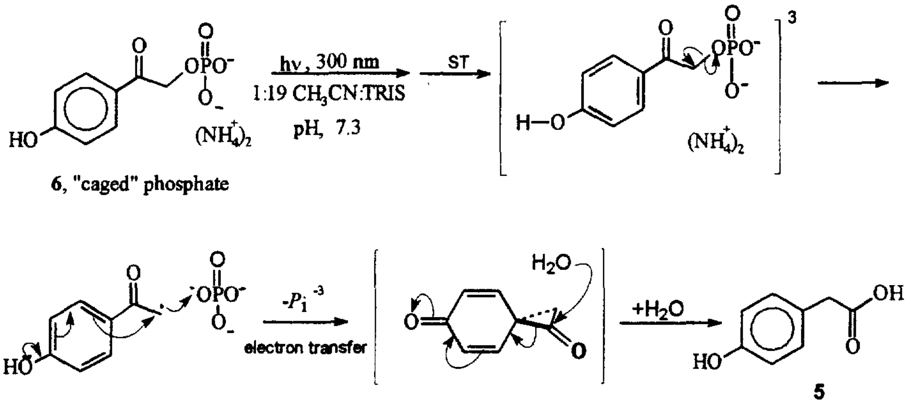


9a X = H, R = Et
b X = *m*-MeO, R = Et
c X = *p*-MeO, R = Et
d X = *p*-NH_2, R = $(NH_4^+)_2$
e X = *p*-$NHCO_2CH_3$; R = $(NH_4^+)_2$
f X = *p*-$NHCOCH_3$; R = $(NH_4^+)_2$



10a-f

SCHEME 2



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