Novel Photolabile Protecting Group for Carbonyl Compounds

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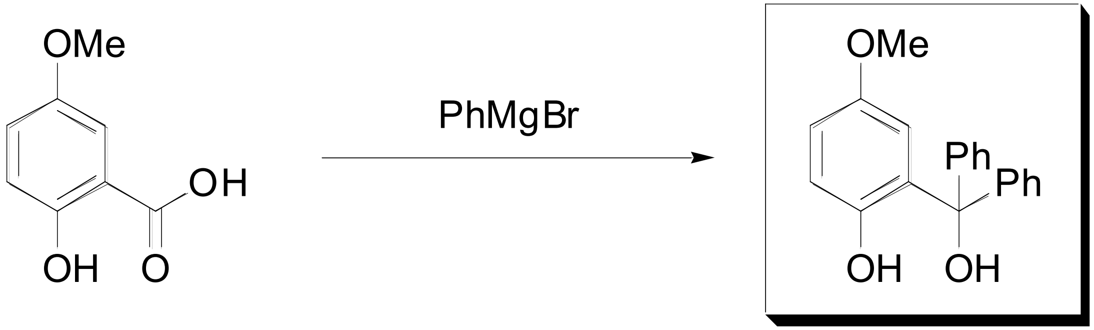
Overview

- Background & History
- Synthesis
- Protection Cycle
- Substrate Selectivity
- Evidence for Proposed Mechanism
- Stability
- Conclusion

- The value of protecting groups in synthesis is difficult to overstate
- One of the major difficulties lies in their susceptibilities to reaction conditions and in differentiating similar moieties that are protected
- One solution to this is to design a protecting group that makes use of uncommon reaction conditions

History of Photolabile Protecting Groups

- Research into this type of protecting group goes back many decades
- Groups that can be simply and efficiently protected include: alcohols, amines, amides, carboxylic acids and phosphates
- Despite the large volume of photolabile groups available, it has been challenging to design one for the aldehydes and ketones
- Several attempts have been made, with varying degrees of success
- Most of these protecting groups are susceptible to reactive organometallic reagents and reducing reagents, and are also non-trivial to synthesize



- Synthesized in one step from 5-methoxysalicylic acid
- Easily scaleable

Protection Cycle

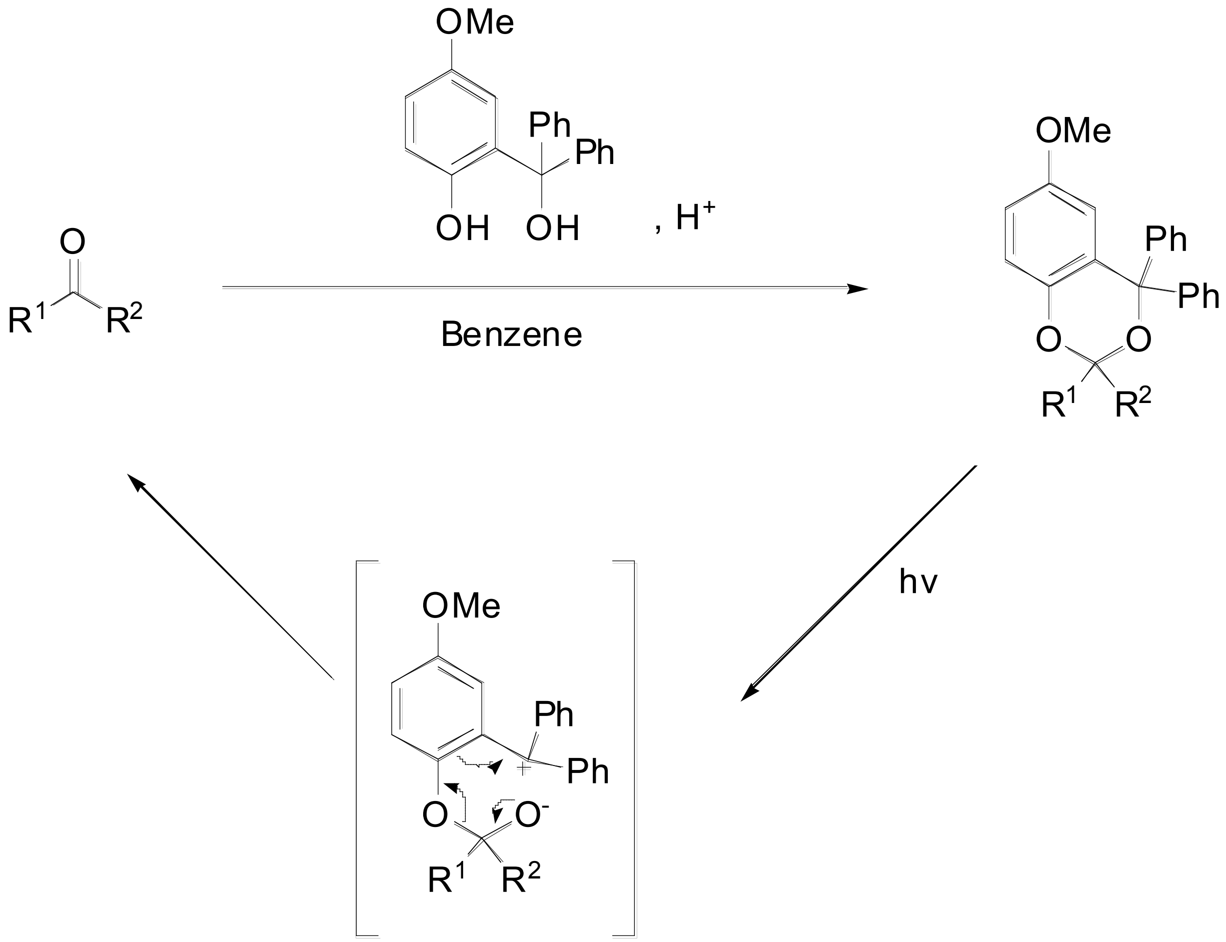
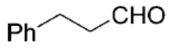


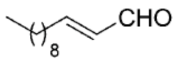
Table 1. Protection and Photorelease of the Carbonyls

entry	carbonyl compounds	protection yield (%)	deprotection yield (%)	irradiation time (min)
1	**1a**	99[a]	90[e]	60
2	**1b**	91[a]	89 ($Z/E = 1.4$)[e]	40
3	**1c**	95[a]	85[f]	50
4	**1d**	>99[a]	74[e]	60
5	**1e**	99[a]	89[e]	60
6	**1f**	97[b]	80[g]	80
7	**1g**	93[c]	84[e]	80
8	**1h**	91[c]	86[g]	60

[a] **2** (0.3 mmol), *p*TsOH (0.02 mmol), and carbonyl compound (0.2 mmol) in 1.0 mL of benzene, 23 °C, 24 h. [b] **2** (0.3 mmol), *p*TsOH (0.02 mmol), carbonyl compound (0.2 mmol), and $CuSO_4$ (0.8 mmol) in 1.0 mL of benzene, 23 °C, 24 h. [c] **2** (0.3 mmol), *p*TsOH (0.02 mmol), carbonyl compound (0.2 mmol), and P_2O_5 (0.8 mmol) in 1.0 mL of benzene, 23 °C, 24 h. [d] Irradiated with a 450 W medium-pressure mercury lamp equipped with a Pyrex filter sleeve. [e] Isolated as the oxime derivatives. [f] Isolated as the semicarbazone derivative. [g] Isolated as the ketone without derivatization.



1a



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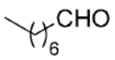

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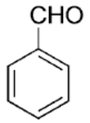

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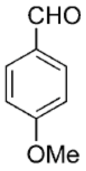

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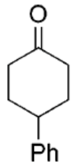

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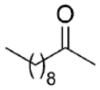
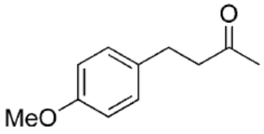


1g



1h

- To test the proposed deprotection mechanism of the zwitterionic intermediate the groups in the trityl position were varied
- When one phenyl group was transposed to a proton, let to a deprotection yield of 33%
- When both phenyls were changed to methyl groups, the deprotection yield dropped to less than 6%
- Further testing revealed that the meta-methoxy group is vital to the deprotection, with no deprotection detected in the absence of the methoxy group

Stability to reaction conditions

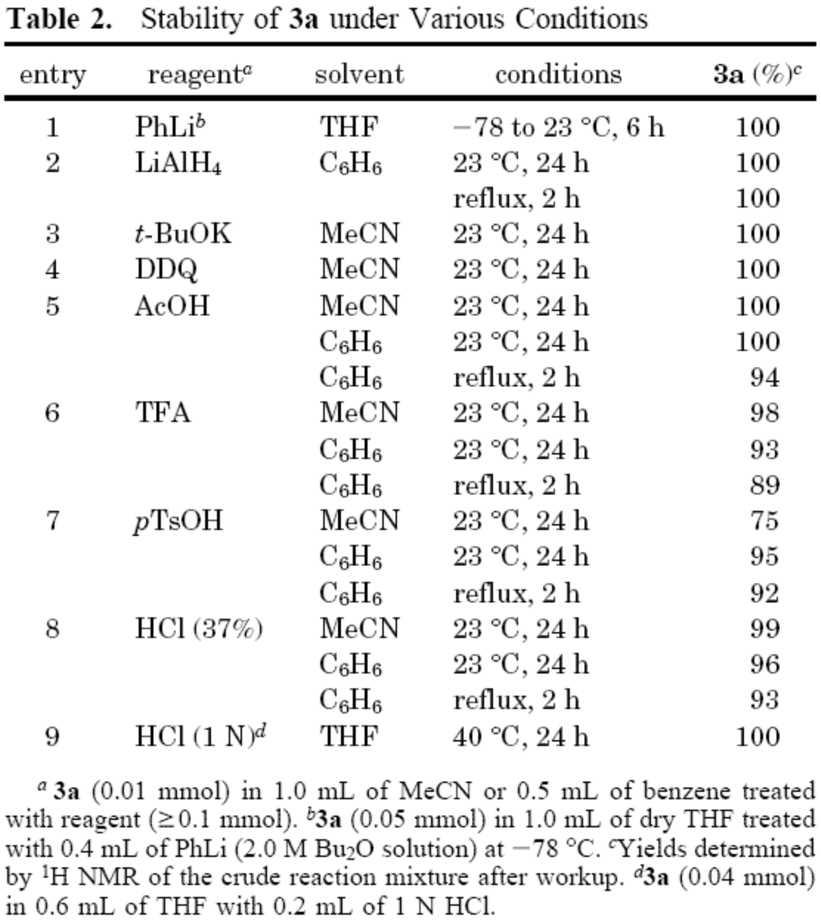


Table 2. Stability of **3a** under Various Conditions

entry	reagent[a]	solvent	conditions	**3a** (%)[c]
1	PhLi[b]	THF	−78 to 23 °C, 6 h	100
2	$LiAlH_4$	C_6H_6	23 °C, 24 h	100
			reflux, 2 h	100
3	*t*-BuOK	MeCN	23 °C, 24 h	100
4	DDQ	MeCN	23 °C, 24 h	100
5	AcOH	MeCN	23 °C, 24 h	100
		C_6H_6	23 °C, 24 h	100
		C_6H_6	reflux, 2 h	94
6	TFA	MeCN	23 °C, 24 h	98
		C_6H_6	23 °C, 24 h	93
		C_6H_6	reflux, 2 h	89
7	*p*TsOH	MeCN	23 °C, 24 h	75
		C_6H_6	23 °C, 24 h	95
		C_6H_6	reflux, 2 h	92
8	HCl (37%)	MeCN	23 °C, 24 h	99
		C_6H_6	23 °C, 24 h	96
		C_6H_6	reflux, 2 h	93
9	HCl (1 N)[d]	THF	40 °C, 24 h	100

[a] **3a** (0.01 mmol) in 1.0 mL of MeCN or 0.5 mL of benzene treated with reagent (≥0.1 mmol). [b] **3a** (0.05 mmol) in 1.0 mL of dry THF treated with 0.4 mL of PhLi (2.0 M Bu_2O solution) at −78 °C. [c] Yields determined by ^1H NMR of the crude reaction mixture after workup. [d] **3a** (0.04 mmol) in 0.6 mL of THF with 0.2 mL of 1 N HCl.

Conclusion

- A novel protecting group using the unique photochemical strategy
- An extremely stable protecting group that contains minimal functionality to interfere with the substrate
- High efficiency of protection and deprotection