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N-(Phenylselenomethyl)phthalimide as new reagent for mild protection of alcohols as Pim-ethers

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ABSTRACT

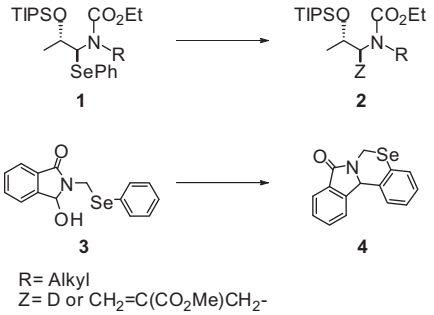
A mild activation of *N*-(phenylselenomethyl)phthalimide by iodonium ion in the presence of alcohols to give the corresponding *O*-phthalimidomethyl derivatives (Pim-ethers) is provided. Simple cleavage of the phthalimido group with ethylenediamine is also reported thus making this approach a new and efficient method of protecting alcohols.

Nowadays organoselenium reagents are widely employed in many synthetic transformations due to their wide availability, to the numerous chemical manipulations which can be effected by the selenium moiety before or during its removal, and to the mild reaction conditions required in various steps.[1] Despite many types of organoselenium compounds available, mixed *N,Se* acetals have been scarcely employed as intermediates.[2]

For example, mixed *N,Se* acetals **1** were used as good α-amidoalkyl radical precursors for the stereoselective preparation of deuterated and allylated products **2** (Scheme 1).[3] More recently, there has been a report of the treatment of functionalized *N,Se* acetal **3** with triflic acid to generate *N*-acyliminium ion which after tandem intramolecular isomerization/cyclization produced new fused *N,Se*-heterocyclic system **4** (Scheme 1).[4]

Herein, we report the heterolytic cleavage of the *C–Se* bond on the mixed *N,Se* acetal **5** by the action of iodonium ion. In the presence of an alcohol **6** in the reaction medium, the corresponding *N,O* acetal **7** can be obtained thus performing the protection of the hydroxyl group as phthalimidomethyl (Pim) ether derivative (Scheme 2). As in the case of the activation of MOM- and MEM-phenyl selenides[5] the reaction probably proceeds by the attack of iodonium ion, generated from *N*-iodosuccinimide, to the selenium atom to give the α-imidocarbenium ion together with the phenylselenyl iodide and the succinimide intermediates. Then the imidocarbenium ion reacts with the oxygen atom of the alcohol to give the corresponding *N,O* acetal while phenylselenyl iodide is converted into diphenyl diselenide and iodine

To our knowledge there are only two procedures to perform the phthalimidomethylation of alcohols which use *N*-bromomethylphthalimide[6] or *O*-phthalimidomethyl trichloroacetimidate.[7] The known[4] and stable *N,Se* acetal **5** can be easily prepared in excellent yield from *N*-chloromethylphthalimide.[8] Initially, a variety of selenophilic activators such as copper(II) chloride, silver triflate, *N*-bromosuccinimide, and *N*-iodosuccinimide in different solvents



Scheme 1. Use of *N,Se* acetals **1** and **2**.

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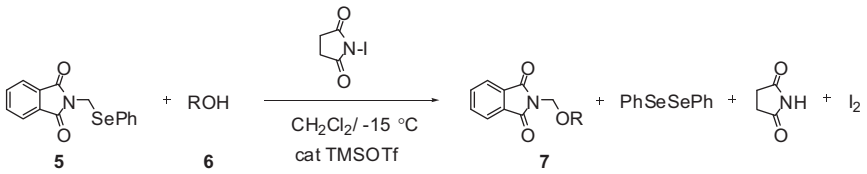


Scheme 2. Reaction of alcohols **6** with phthalimidomethyl phenyl selenide **5**.

have been used to evaluate their ability to promote the phthalymidomethylation of alcohol **6a** under a standard set of reaction conditions (0.1 M, RT, 1.2 equiv of **5** and 1.2 equiv of activator). We found that *N*-iodosuccinimide (NIS) was the most effective promoter in dichloromethane solution and in the presence of TMSOTf as catalyst. Consistent results were obtained with 1.4 equiv of NIS, 1.4 equiv of **5**, and 0.07 equiv of TMSOTf in dichloromethane at −15 °C with reaction times ranging from 1 to 2 h.[9] The reaction of **5** with primary, secondary, and tertiary alcohols, such as **6a**–**i**, in the presence of TMSOTf as catalyst, gave the corresponding phthalimidomethyl derivatives **7a**–**i** (Table 1). The NMR spectral analysis of the products agreed with the assigned structures.

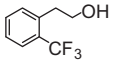
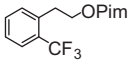
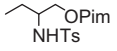
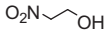
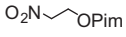
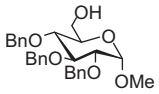
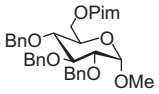
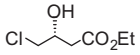
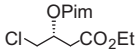
The results reported in Table 1 clearly demonstrated that the protection reactions proceeded smoothly to afford the corresponding Pim-ethers **7a–i** in good to excellent yields (68–92%). The various functionalities present in the substrates (e.g., carbon–carbon triple bond, tosylamino, ether, ester, acetal, nitro, and carbonyl groups) were compatible with the mild reaction conditions employed. The yields of compounds **7d** and **7e** were comparable with those obtained by using *O*-phthalimidomethyl trichloroacetimidate.[7] The hydroxy group of α-hydroxyketone **6f** as well as of the β-hydroxy nitro compound **6c** were successfully protected as Pim-derivatives **7f** and **7c** in excellent yields (86% and 83%, respectively). It should be noted that tertiary alcohols **6h** and **6i**, that might be subjected to dehydration reaction,[6] gave the corresponding Pim-ethers **7h** and **7i** in good yields (83% and 74%, respectively) establishing the first examples of the protection of tertiary alcohols as Pim-ether derivatives. The use of the phthalimidomethyl moiety for the hydroxy group protection has been scarcely employed[10] although the Pim-derivatives of thiol and carboxylic acid are well documented.[11] However the phthalimidomethyl group is compatible with and orthogonal to all important hydroxy protecting groups.[7] It offers selective removal with nucleophiles particularly in the carbohydrate chemistry thus complementing the repertoire of the available hydroxy protecting groups which are sensitive to acids, bases, or hydrogenolysis. In this context we found that the phthalimidomethyl group could be smoothly removed in a one-pot reaction without the use of carcinogenic hydrazine hydrate.[11] The simple treatment of compounds **7a**, **7b**, **7d**, **7h,** and **7i** with an excess of ethylenediamine (5 equiv) in methyl alcohol at room temperature gave the starting alcohols **6a**, **6b**, **6d**, **6h,** and **6i**, respectively in excellent yields (Table 2). The reaction performed

Table 2
Phthaloyl group cleavage of some representative Pim-ethers **7** with 5 equiv of ethylenediamine in methanol at RT

Entry	Pim-ether **7**	Time (h)	Alcohol[a] **6**	Yield[b] (%)
1	**7a**	10	**6a**	82
2	**7b**	8	**6b**	77
3	**7d**	8	**6d**	84
4	**7h**	9	**6h**	90[c]
5	**7i**	8	**6i**	88[c]

[a] All products were characterized by ^{1}H and ^{13}C NMR.
[b] Yields of isolated products; ⩾97% pure material by ^{1}H NMR.
[c] Yield estimated on the crude mixture by ^{1}H NMR relative to internal standard.

Table 1
Phthalimidomethylation[a] of alcohols **6** with phthalimidomethyl phenyl selenide **5** promoted by NIS and catalytic TMSOTf

Entry	Alcohol **6**[b]		Product **7** Pim = phthalimidomethyl		Yield[c] (%)
1		**6a**		**7a**	80
2		**6b**		**7b**	68
3		**6c**		**7c**	86
4		**6d**		**7d**	81[d]
5		**6e**		**7e**	92[d]
6		**6f**		**7f**	83
7		**6g**		**7g**	82
8		**6h**		**7h**	83
9		**6i**		**3m**	74

[a] Reaction times ranging from 1 to 2 h.
[b] All products were characterized by ^{1}H and ^{13}C NMR and mass spectroscopy.
[c] Yields of isolated products; ⩾97% pure material by ^{1}H NMR.
[d] A similar yield was obtained with *O*-phthalimidomethyl trichloroacetimidate.[7]

in isopropyl alcohol[12] or in ethanol at reflux[13] did not give better yields.

The easy and efficient removal of phthalimidomethyl group to give the starting alcohols makes this approach a new and efficient method of protecting alcohols.

In conclusion a general and mild procedure for the activation of phthalimidomethyl phenyl selenide **5** with iodonium ion and subsequent reaction with alcohols to give the corresponding Pim-ether derivatives **7** has been described. Phthalimidomethyl phenyl selenide **5** can be stored at +4 °C for a long period of time without any detectable decomposition. Furthermore, the selenium atom can be recovered at the end of the procedure as diphenyl diselenide and then reused for the synthesis of compound **5**. Reported limitations on the use of the phthalimidomethyl protecting group have also been overcome by introducing a new cleavage procedure.

Acknowledgments

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8. *Synthesis of the N,Se acetal* ***5***: The *N,Se* acetal **5** was prepared by a slight and safer modification of the original procedure[4] where, the required phenylselenol intermediate was replaced by sodium phenylselenolate. In a 50 mL three-neck flask equipped with a reflux condenser were placed diphenyl diselenide (0.63 g, 2 mmol) and 16 mL of dry DMF. The solution was heated at 60 °C and stirred rapidly under nitrogen while $NaBH_4$ (0.15 g, 4 mmol) was added portionwise. Hydrogen was evolved and the reaction mixture turned colorless and homogeneous upon complete reduction of the selenide. The reaction was heated at 110 °C for 1 h and then cooled to room temperature. Solid *N*-chloromethylphthalimide (0.78 g, 4 mmol) was added to the orange solution. After stirring at room temperature for 12 h, 2 N aqueous hydrochloric acid (10 mL) was added carefully to the white suspension. The entire product mixture was poured into 50 mL of water and 40 mL of diethyl ether, mixed, and separated. The aqueous phase was extracted with 20 mL of diethyl ether and the combined organic phases were washed with H_2O (4 × 10 mL), 10 mL of brine, dried over sodium sulfate and concentrated. The solid residue was washed with light petroleum (2 × 10 mL) and dried over P_2O_5 to afford **5** in 82% yield and with spectral data in good agreement with those reported in the literature.[4]
9. *General procedure for the protection of alcohols* ***6*** *as Pim-derivatives*: A mixture of alcohol **6** (1 mmol), *N,Se* acetal **5** (1.4 mmol) and activated 3-Å molecular sieves (0.40 g) in dry dichloromethane (16 mL) was stirred for 0.5 h under argon atmosphere at room temperature. Solid *N*-iodosuccinimide (1.4 mmol) was added and then the mixture cooled to −15 °C. After the addition of TMSOTf (12 μL, 0.07 mmol) the reaction mixture was stirred and monitored by TLC. Reaction times ranged from 1 to 2 h. The brown colored reaction mixture was then filtered through a celite path and the filtrate washed with 20 mL of 10% aqueous sodium thiosulfate pentahydrate solution. The aqueous phase was extracted with 10 mL of dichloromethane and the combined organic phases were washed with 10 mL of brine, dried over sodium sulfate, and then evaporated under vacuum. Purification by silica gel column chromatography afforded the phthalimidomethyl-ether derivative **7**. Physical and spectral data of some selected compounds are reported. *2-[(2-Nitroethoxy)methyl]-1H-isoindole-1,3(2H)-dione (****7c****)*: Yield 86%; mp 108–110 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.04–7.88 (m, 2H), 7.86–7.71 (m, 2H), 5.22 (s, 2H), 4.55 (t, 2H, *J* = 5.10 Hz), 4.20 (t, 2H, *J* = 5.10 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.8 (2C), 134.6 (2C), 131.7 (2C), 123.19 (2C), 74.5, 67.3, 65.3. ν_{max}/cm^{-1} 2955, 1777, 1726, 1559, 1354, 1330, 1112, 977, 733. *2-[(2-Oxo-1,2-diphenylethoxy)methyl]-1H-isoindole-1,3(2H)-dione (****7f****)*: Yield 83%; mp 262–264 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.04–7.66 (m, 6H), 7.60–7.15 (m, 8H), 6.08 (s, 1H), 5.34 (AB system, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 196.1, 167.6 (2C), 135.6, 134.9, 134.3 (2C), 133.1, 131.7 (2C), 129.0 (2C), 128.7 (2C), 128.6, 128.4 (2C), 127.8 (2C), 123.7 (2C), 83.9, 66.5. ν_{max}/cm^{-1} 3073, 2968, 1773, 1717, 1679, 1357, 1231, 1104, 943, 735. GC–MS (EI): *m*/*z* (%) = 355 (6) [M−16]$^+$, 281 (27), 207 (100), 160 (19), 147 (17), 128 (60), 105 (17), 77 (13). *Ethyl 4-chloro-3-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methoxy]butanoate* (***7g***): Yield 82%; Oil; $[\alpha]_D^{24}$ 10.9 (*c* 0.92, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.96–7.85 (m, 2H), 7.84–7.70 (m, 2H), 5.25 (s, 2H), 4.38–4.20 (m, 1H), 4.01 (q, 2H, *J* = 7.15 Hz), 3.62 (d, 2H, *J* = 5.30 Hz), 2.67–2.55 (m, 2H), 1.18 (t, 3H, *J* = 7.15 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.2, 167.7 (2C), 134.3 (2C), 131.7 (2C), 123.6 (2C), 74.7, 66.2, 60.6, 45.2, 37.8, 13.9. ν_{max}/cm^{-1} 2982, 1778, 1723, 1351, 1203, 1077, 983, 855, 729. GC–MS (EI): *m*/*z* (%) = 276 (4) [M−49]$^+$, 176 (25), 160 (100), 133 (15), 104 (19), 77 (18). *2-{[(1,1-Dimethylprop-2-yn-1-yl)oxy]methyl}-1H-isoindole-1,3(2H)-dione (****7i****)*: Yield 74%; mp 88–90 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.92–7.81 (m, 2H), 7.80–7.68 (m, 2H), 5.29 (s, 2H), 2.48 (s, 1H), 1.54 (s, 6H). δ = 167.4 (2C), 134.2 (2C), 131.9 (2C), 123.5 (2C), 84.5, 72.7, 69.9, 62.6, 28.7 (2C). ν_{max}/cm^{-1} 3263, 2987, 2105, 1778, 1726, 1387, 1154, 1061, 737. GC–MS (EI): *m*/*z* (%) = 228 (10) [M−15]$^+$, 213 (10), 160 (100), 148 (15), 130 (22), 104 (21), 77 (18).
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