Weinreb Amide Based Building Blocks for the Synthesis of α- and β-Organylseleno Aryl Ketones

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Dedicated to Dr. H. R. Sonawane

Abstract: A new strategy for the synthesis of α- and β-organylseleno aryl ketones has been achieved. The strategy is based on the use of hitherto unreported 2,2′-diselenediylbis(*N*-methoxy-*N*-methylacetamide) and 3,3′-diselenediylbis(*N*-methoxy-*N*-methylpropanamide). The envisaged synthetic equivalents combine the usefulness of Weinreb amide (WA) functionality and those innate with selenium for the first time. The synthesis of the targets, α- and β-organylseleno aryl ketones could be achieved by the reductive cleavage of Se–Se bond, followed by the alkylation on selenium, and the addition of arylmagnesium halide onto the WA functionality therein.

Key words: Weinreb amide, reductive alkylation, glycosylseleno ketones, Grignard addition

With the growing importance and the significance of organoselenium compounds, recent review summarizing the advances in organoselenium chemistry by Wirth was most timely and justified.[1] Despite the growing importance of organoselenium compounds and chemistry, attempts to incorporate selenium atom in carbohydrates and their derivatives have been limited and scarce.[2] In our quest towards glycosylseleno ketones **1** as a new structural motif and hitherto unreported in the literature, we became interested in exploring a convenient strategy for the synthesis of α-organylseleno arylketones **2** and β-organylseleno arylketones **3** which would allow us to incorporate simple to highly functionalized organyl residue *R* on selenium (Figure 1).

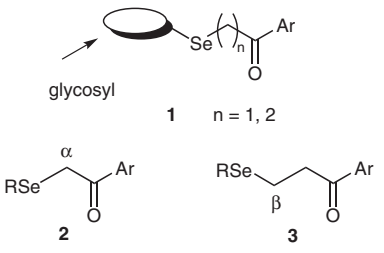
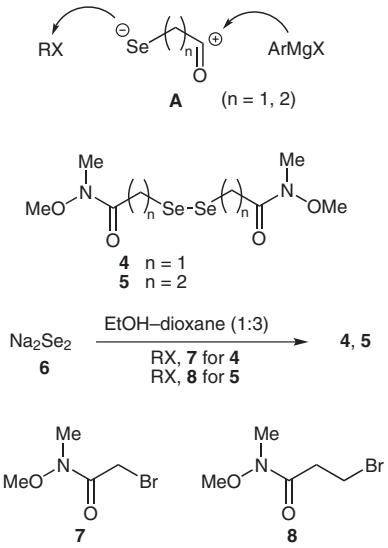


Figure 1

The incorporation of organyl seleno unit at the α- and β-position of the carbonyl compounds have been restricted to a simple organyl residue on selenium such as phenyl, butyl, ethyl, and benzyl.[3–6] The synthetic scheme based on a 1,4-addition strategy remains confined to seleno phenol and simple α,β-unsaturated carbonyl ketones.[7] The absence of a convenient scheme for the synthesis of **2** and **3** with highly functionalized organyl residues *R* on selenium intrigued us.

With this in the background, we conceived a strategy for the synthesis of target **1**, banking on synthon **A**. It would facilitate incorporation of functionalized alkyl residues on selenium through nucleophilic substitution with alkyl halides and delivery of an aryl group through ArMgX. The envisaged synthetic equivalents **4** and **5** for synthon **A** combines the usefulness of the Weinreb amide (WA) functionality[8,9] and the convenience of reductive cleavage of Se–Se bond[10] for the first time (Scheme 1). Building blocks **4** and **5** were envisaged through simple dialkylation of sodium diselenide (**6**)[11] with 2-bromo-*N*-methoxy-*N*-methylacetamide (**7**)[12] or 3-bromo-*N*-methoxy-*N*-methyl propanamide (**8**),[13] respectively, as an alkylating agent. Indeed, sodium diselenide (**6**) generated in situ through the reduction of selenium metal with sodium borohydride in dioxane–ethanol mixture (3:1), reacted readily with **7** and **8** at 0–10 °C, affording **4** and **5** in 45% and 65% yield, respectively, as yellow-colored syrup after silica gel column chromatography[14] (Scheme 1).



Scheme 1

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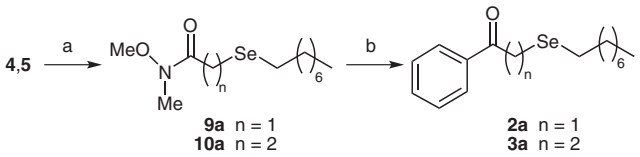
To implement the proposed strategy, synthetic equivalents **4** and **5** were subjected to reductive alkylation with *n*-octyl bromide as a representative alkyl halide (Scheme 2). To a suspension of $NaBH_4$ in ethanol, the building blocks **4** and **5** dissolved in ethanol were added separately at 0–10 °C and stirred until the yellow color of these building blocks disappear (maximum time period 10 min). To this reaction mixture, a solution of *n*-octyl bromide (1.2 equiv) in EtOH was added at 0 °C, followed by stirring of the reaction mixture at room temperature. TLC revealed complete consumption of starting material during 1–1.5 hours furnishing the intermediates α- and β-octylseleno WA **9a** and **10a** in good isolated yields of 69% and 80%, respectively.

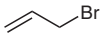
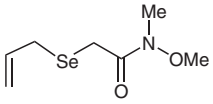
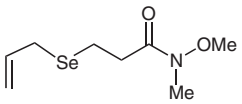
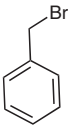
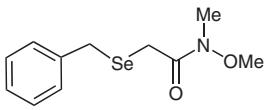
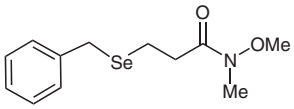
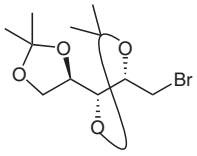
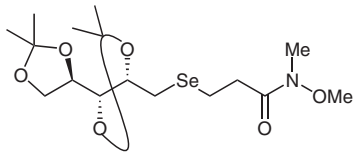
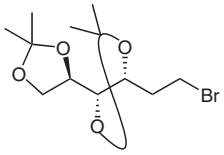
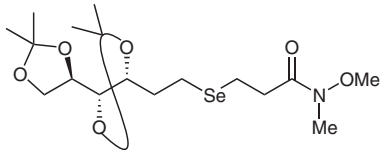
To our satisfaction other simple and functionalized alkyl halides[15] reacted cleanly with the synthetic equivalents **4** and **5** under the same reaction conditions to furnish the corresponding α-organylseleno amides **9b**,**c** and β-organylseleno amides **10b**–**e** having WA functionality as a useful handle for further functionalization (Table 1). All products displayed satisfactory spectral and analytical details.



Scheme 2 *Reagents and conditions*: (a) (i) $NaBH_4$ (0.9 equiv), **4** or **5** (1.0 equiv), EtOH (10.0 V), 0–10 °C, 10 min; (ii) octyl bromide (1.2 equiv) in EtOH (5.0 V), 0 °C to r.t., 1.0–1.5 h, 69% for **9a** and 80% for **10a**; (b) for compound **2a**: ArMgBr (1.2 equiv; reverse addition), THF (20 V), 10–15 °C, 0.5 h, 45%; for compound **3a**: ArMgBr (2.0 equiv), THF (20 V), 5–10 °C, 1.5 h, 68%.

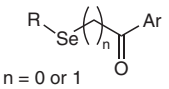
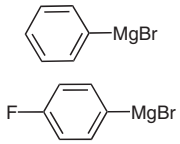
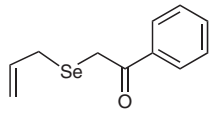
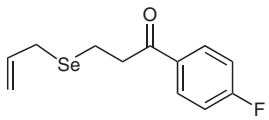
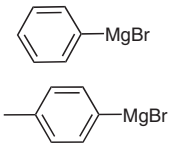
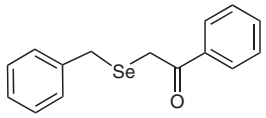
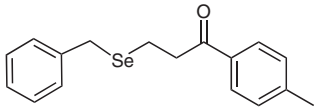
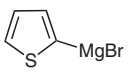
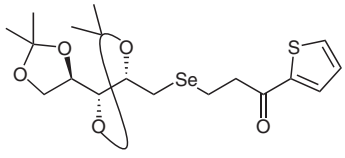
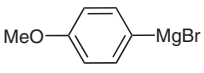
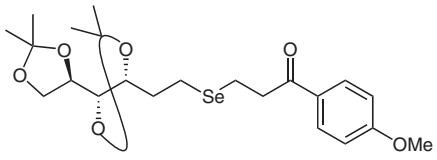
Having successfully obtained the α- and β-organylseleno WA **9** and **10**, our next aim was to subject them towards aryl Grignard addition onto the WA functionality. Aware of the fact that the Grignard reagents do have the ability to

Table 1 Reductive Alkylation of Building Blocks **4** and **5** with Alkyl Bromides

Entry	RX	n = 1 or 2	Yield (%)
1	 **11**	 **9b**	66
		 **10b**	78
2	 **12**	 **9c**	70
		 **10c**	82
3	 **13**	 **10d**	78
4	 **14**	 **10e**	80

attack the elemental selenium[16] and diselenides,[17] the addition of ArMgX onto WA functionality was challenging and interesting. Initial attempts involved the addition of 2.0 equivalents of preformed phenylmagnesium bromide solution in THF to a solution containing **9a** and **10a** in THF separately at –5 to 0 °C. Monitoring the progress of the reaction by TLC showed the complete consumption of the starting material after one hour in case of **9a** and concomitant formation of two nonpolar compounds, with close R_f values. In case of **10a** the reaction was clean with predominant formation of a single new nonpolar compound, but had a little unreacted starting material **10a** in the same reaction period. Workup of reaction with saturated NH_4Cl solution and purification of the products using silica gel column chromatography yielded the desired products **2a** (25%) and **3a** (60%). The presence of absorption bands in IR spectrum at 1712 and 1710 cm^{-1} for carbonyl groups and peaks at δ = 195.1 and 198.8 ppm in ^{13}C NMR spectrum confirmed the structure of the ketones **2a** and **3a**, respectively. In an attempt to increase the yield of **2a**, the variations, such as changes in the reaction medium from THF to Et_2O, increase in the equivalence of the phenylmagnesium bromide and lowering of the reaction temperature were unfruitful. However, ketone **2a** was obtained in better yields of 45% by adding 1.2 equivalents of preformed phenylmagnesium bromide solution in THF to a solution of **9a** in THF at 10–15 °C and reaction period of 30 minutes only (Scheme 2). To generalize this observation, phenylmagnesium bromide (1.2 equiv) was now added to other α-organylseleno WA **9b** and **9c** under similar reaction conditions. The reactions furnished the corresponding α-organylseleno ketones **2b** and **2c** in 48% and 50% yields respectively (Table 2). Although we could not isolate any other product in pure form as a part of our efforts towards material balance and explanation for the low yields of α-organylseleno ketones **2a–c**, possible fragmentation of α-organylseleno WA **9** through the addition of Grignard reagent onto the selenium center and expul-

Table 2 Grignard Addition on Weinreb Amides **9** and **10**

Entry	WA	ArMgBr	 n = 0 or 1	Yield (%)
1	**9b** **10b**		**2b**   **3b**	48 62
2	**9c** **10c**		**2c**   **3c**	50 65
3	**10d**		 **3d**	60
4	**10e**		 **3e**	62

sion of a stabilized enolate [$^{-}CH_2CON(OMe)Me$] cannot be excluded. Clean reaction of phenylmagnesium bromide (2.0 equiv) with β-organylseleno WA **10a**, wherein such a possibility does not exists and subsequent obtainment of ketone **3a** in better yield (68%), supports this observation and rationale (Scheme 2). The successful addition of other ArMgBr (2.0 equiv) in THF at 5–10 °C onto other β-organylseleno WA **10b**,**c** and obtainment of the corresponding β-organylseleno ketones **3b** (62%) and **3c** (65%) in good yields provides the generality of the developed reaction protocol (Table 2).

Finally, towards the targeted glycosylseleno ketones **1** as a new structural motif, ArMgBr was now added onto the WA functionality in **10d** and **10e** having a glycosyl unit as the organic residue on selenium. Successful Grignard addition onto these representative examples, furnishing the corresponding β-glycosylseleno ketones **3d** (60%) and **3e** (62%) in good yields aptly demonstrated the usefulness of these building blocks and the associated strategy for incorporating highly functionalized residues on selenium (Table 2). All products displayed satisfactory spectral and analytical details.

To conclude, new synthetic equivalents **4** and **5** based on WA functionality have been realized and successfully utilized to synthesize α- and β-organylseleno aryl ketones. In the context of reactivity, the building block **5** gave better results. The objective of synthesizing glycosylseleno ketones **1** was successfully achieved using our building block **5** and was demonstrated by preparing β-glycosylseleno aryl ketones having the glycosyl residue on selenium. The visualized concept is not limited to α- or β-positions. The concept and strategy should allow incorporation of organylseleno unit at any other positions such as γ-, δ-, and beyond. Hence the work presented herein holds promise and amenable for further exploitation according to the need and objectives of the synthetic endeavors.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(14) **2,2′-Diselenediylbis(*N*-methoxy-*N*-methylacetamide) (4)**
Yield 45%. R_f = 0.20 (hexanes–EtOAc = 6:4), yellow colored liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.14 (s, 3 H, NCH_3), 3.52 (s, 2 H, $SeCH_2$), 3.68 (s, 3 H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.6, 32.5, 61.5, 171.2. IR ($CHCl_3$): 2929, 2850, 1637, 1445, 1155 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_8H_{16}N_2O_4NaSe_2$ [M + Na]$^+$: 386.9338; found: 386.9344.
3,3′-Diselenediylbis(*N*-methoxy-*N*-methylpropanamide) (5)
Yield 65%. R_f =0.25 (hexanes–EtOAc = 6:4), yellow colored liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.94–2.98 (m, 2 H, $COCH_2$), 3.12–3.15 (m, 2 H, $SeCH_2$), 3.19 (s, 3 H, NCH_3), 3.70 (s, 3 H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 29.1, 32.4, 61.5, 171.5. IR ($CHCl_3$): 2921, 2847, 1626, 1458, 1166 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{10}H_{21}N_2O_4Se_2$ [M + H]$^+$: 392.9832; found: 392.9833.

(15) The sugar halides **13** and **14** were prepared through multistep reaction sequence from commercially available monosacchride D-(+)-glucono-1,5-lactone.

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