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Improved solubility and stability of trialkylammonium selenocarboxylate in organic solvents for efficient amidation with azides

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Abstract—Trialkylammonium selenocarboxylate, formed in situ from the reaction of diacyl diselenide with piperidine in the presence of diisopropylethylamine, was found to react readily at room temperature with electron-deficient azides to form amides in excellent yields. The trialkylammonium selenocarboxylate salt formed has good solubility and stability in organic solvents. The enhanced stability allowed mild heating to improve the amidation yields with electron-rich azides.

Amide bonds are usually formed through the reaction of an activated carboxylic acid with a free amine. However, not all functional groups are compatible with the presence of a free amine. One such example is the decomposition of 4-aminobenzyl esters due to 1,6-elimination.[1,2] An alternative amidation method is to react thio acids with azides to form amides through a thiatriazoline intermediate without involving the amine intermediates.[3–6] We and others have reported recently that selenocarboxylates react with azides to form amide bonds in a similar fashion to thio acids.[2,7] Selenocarboxylates have greater reactivity as compared to thio acids. The enhanced reactivity of selenocarboxylates would accelerate the reaction, shorten the reaction time, and potentially lower the reaction temperature. For our initial efforts,[2] we used potassium selenocarboxylates to react with azides because alkali metal salts of selenocarboxylates were known to be relatively stable.[8] However, to better solubilize potassium selenocarboxylates and potassium methoxide used to prepare selenocarboxylates,[9] we used DMSO as a co-solvent for the reaction. The mild oxidizing property of DMSO accelerated the decomposition of selenocarboxylates, which adversely affected the yield of product formation. Using an HPLC assay, we found that the half-life of selenocarboxylate was only 25 min under the mixed solvent conditions of DMSO and ethyl acetate at room temperature.[2] With electron-deficient azides and excess (2 equiv) potassium selenocarboxylate, the reaction was fast and the short half-life of selenocarboxylate did not present a problem. When electron-rich azides were used, the reactions under the same conditions required longer time to complete. The poor stability of selenocarboxylate under these reaction conditions led to much lower conversion yields. Our efforts then focused on the use of organic amine salts of selenocarboxylates, and on finding conditions to improve the solubility and stability of selenocarboxylates and to increase the reaction yields with electron-rich azides. Here, we report the preparation of diisopropylethylammonium benzeneselenocarboxylate (**4**) as a model substrate and its subsequent direct amidation with azides in a much improved set of reaction conditions.

In our previous method,[2] diacyl selenides were used to prepare selenocarboxylates. Here, we used a diacyl diselenide instead, as diacyl diselenides are more stable than diacyl selenides. As shown in Scheme 1, dibenzoyl diselenide (**2**) was prepared from benzoyl chloride (**1**) upon treatment with LiAlHSeH in THF and subsequent oxidation with iodine and potassium iodide.[10,11] The dibenzoyl diselenide was easily purified by silica gel flash column chromatography and can be stored for several months at −20 °C without significant decomposition. To prepare selenocarboxylate, dibenzoyl diselenide was

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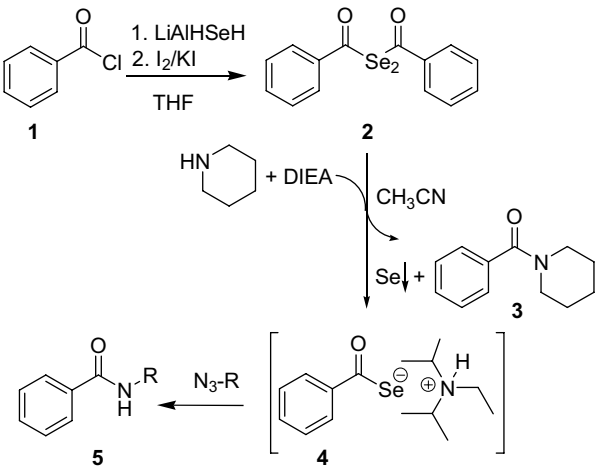
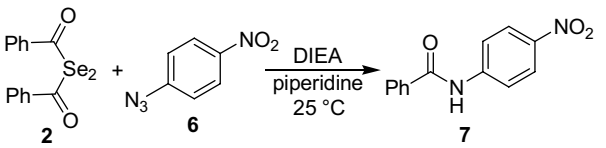


Scheme 1. In situ generation of benzeneselenocarboxylate and subsequent amidation with azides.

dissolved in acetonitrile and then treated under an argon atmosphere with 1 equiv of diisopropylethylamine (DIEA) and 1 equiv of piperidine to form the selenium metal, the stable *N*-benzoylpiperidine (**3**) and diisopropylethylammonium benzeneselenocarboxylate (**4**). The DIEA benzeneselenocarboxylate (**4**) was used directly without purification to react with various azides to form amide products **5** in a one-pot process. Since azides do not react with diacyl diselenide, they can be dissolved together prior to the addition of DIEA and piperidine to simplify the operation and to improve the product yields. Because of the increased stability of DIEA benzeneselenocarboxylate, as discussed later, we were also able to decrease the amount of selenocarboxylate from the earlier 2 equiv excess to only 1.2 equiv for electron-deficient azides.

We selected 4-nitrophenyl azide (**6**), one of the most electron-deficient aromatic azides that reacted quickly with selenocarboxylate, to explore different solvent systems for the amidation reaction. As shown in Table 1, aqueous organic solvents containing 50% water (entries 1–3) gave good yields of the amide product suggesting that the amidation reaction does not require anhydrous

Table 1. Effect of solvents on reaction time and yield[a]



Entry	Solvent system	Time (h)	Yield[b] (%)
1	CH_3OH/H_2O (1:1, v/v)	3	75
2	$(CH_3)_2CHOH/H_2O$ (1:1,v/v)	3	73
3	CH_3CN/H_2O (1:1, v/v)	1	83
4	CH_3CN (neat)	0.5	95
5	$CHCl_3/CH_3OH$ (1:1, v/v)	2	78

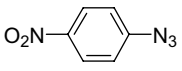
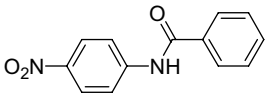
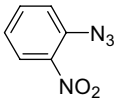
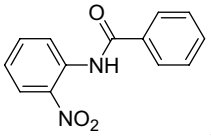
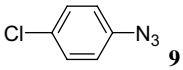
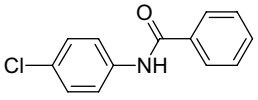
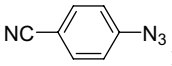
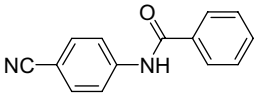
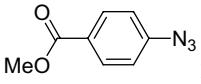
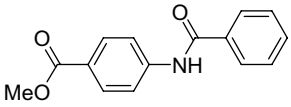
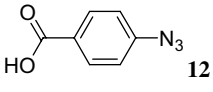
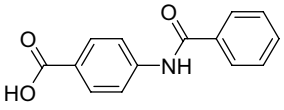
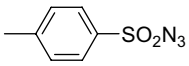
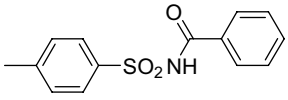
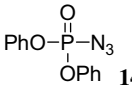
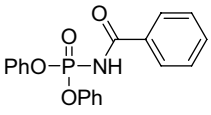
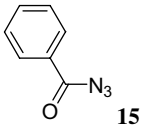
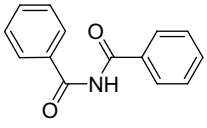
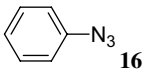
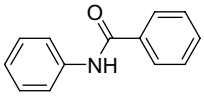
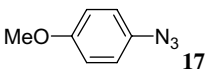
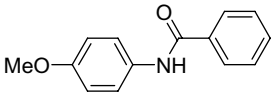
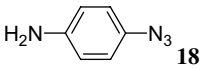
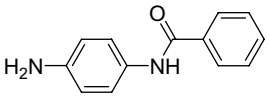
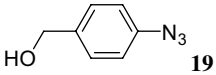
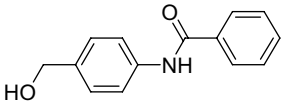
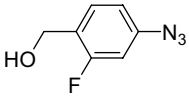
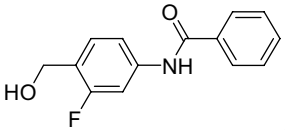
[a] General conditions: 4-nitrophenyl azide **6** (0.2 mmol), dibenzoyl diselenide **2** (0.24 mmol), DIEA (0.24 mmol), and piperidine (0.24 mmol) in the given solvent system at room temperature.
[b] Isolated yield (%).

conditions. However, the presence of too much water would adversely affect the solubility of the organic azides in the reaction medium, resulting in heterogeneity of the reaction mixture. Even for the electron-deficient 4-nitrophenyl azide (**6**), it took 3 h for the reaction to complete in 50% aqueous methanol and isopropanol (entries 1 and 2, Table 1). When acetonitrile was used, the solubility of the azide improved and the reaction was complete within 1 h in 50% acetonitrile (entry 3, Table 1). The same reaction, if run in neat acetonitrile, took less than 30 min to complete (entry 4, Table 1). Mixed solvents of chloroform and methanol slowed down the amidation reaction and lowered the yield (entry 5, Table 1). Hence, neat acetonitrile was selected as the solvent of choice for the amidation reaction.

The stability of DIEA benzeneselenocarboxylate in acetonitrile was measured using an HPLC assay via the reaction of selenocarboxylate with *p*-toluenesulfonyl azide (**13**), the fastest amidation reaction in Table 2. When DIEA benzeneselenocarboxylate (**4**) was incubated with 2 equiv of *p*-toluenesulfonyl azide (**13**) in acetonitrile at room temperature or 55 °C, a complete and quantitative amidation was achieved in less than 5 min, as monitored by HPLC.[12] To monitor the stability of DIEA benzeneselenocarboxylate (**4**), dibenzoyl diselenide (**2**) was mixed with 1.2 equiv of DIEA and 1.2 equiv of piperidine at room temperature under an argon atmosphere. The DIEA benzeneselenocarboxylate formed was then allowed to stand at room temperature or at 55 °C and aliquots were combined with 2 equiv of *p*-toluenesulfonyl azide (**13**). The amide product, *N*-(*p*-toluenesulfonyl) benzamide (**28**), was analyzed to determine the amount of DIEA benzeneselenocarboxylate that remained in solution. Figure 1 shows the stability of DIEA benzeneselenocarboxylate at 25 °C and 55 °C. The half-life of DIEA benzeneselenocarboxylate was found to be 11.3 h at 25 °C. This is an improvement of 27 times in stability if compared to the half-life of 25 min under our previous conditions of using DMSO as a co-solvent.[2] Even when the temperature was raised to 55 °C, the half-life of the selenocarboxylate was 1.4 h under our present conditions.

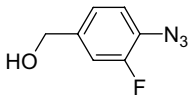
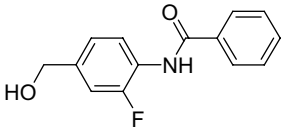
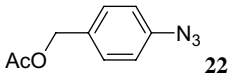
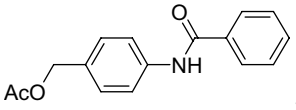
After we confirmed the increased stability of DIEA benzeneselenocarboxylate under our new reaction conditions, a variety of azides (**6**, **8**–**22**) were used to explore the effect of this improved stability on the amidation reaction.[13] For electron-deficient azides, we found as shown in Table 2 that using 1.2 equiv of selenocarboxylate was sufficient to give excellent conversion rates to the corresponding amides with isolated yields between 87% and 96%. For electron-rich azides that are less reactive, 2 equiv of selenocarboxylate and mild heating were used to obtain good yields based on azides. The position of substitution on the phenyl azide also affects the rate of amidation. When the nitro group was in the para position (entry 1, Table 2), the reaction was complete within 30 min. When the nitro group was moved to the ortho position, the reaction was slower and required 1 h to complete (entry 2, Table 2), suggesting the presence of steric effects in addition to the electronic effects on the amidation reaction. Since DIEA selenocarboxyl-

Table 2. Amidation reaction of selenocarboxylates with azides[a]

Entry	Azide starting material	Amide product	Selenocarboxylate[b] (equiv)	Temperature (°C)	Time (h)	Yield[c] (%)
1	 **6**	 **7**	1.2	25	0.5	95
2	 **8**	 **23**	1.2	25	1.0	93
3	 **9**	 **24**	1.2	25	2.0	95
4	 **10**	 **25**	1.2	25	1.0	96
5	 **11**	 **26**	1.2	25	2.0	87
6	 **12**	 **27**	1.2	25	1.0	89
7	 **13**	 **28**	1.2	25	0.08	96
8	 **14**	 **29**	1.2	25	3.0	88
9	 **15**	 **30**	2.0	55	12[d]	51
10	 **16**	 **31**	2.0	55	6.0	81
11	 **17**	 **32**	2.0	55	6.0	65
12	 **18**	 **33**	2.0	55	6.0	54
13	 **19**	 **34**	2.0	55	12[d]	56
14	 **20**	 **35**	2.0	55	6.0	78

(*continued on next page*)

Table 2 (*continued*)

Entry	Azide starting material	Amide product	Selenocarboxylate[b] (equiv)	Temperature (°C)	Time (h)	Yield[c] (%)
15	 **21**	 **36**	2.0	55	12[d]	37
16	 **22**	 **37**	2.0	55	6.0	68

[a] General conditions: azide (0.2 mmol), diacyl diselenide (0.24 or 0.4 mmol), DIEA (0.24 or 0.4 mmol), piperidine (0.24 or 0.4 mmol), acetonitrile (8 mL).
[b] Equiv of selenocarboxylate formed in situ.
[c] Isolated yield (%) of the amide product.
[d] Reactions were left overnight (~12 h) for convenience.[15]

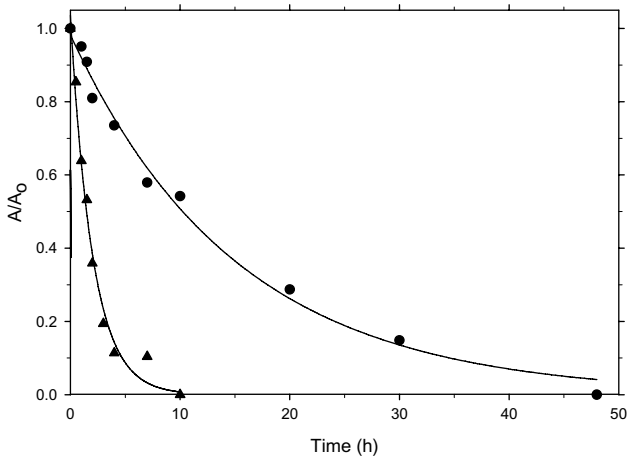


Figure 1. Stability of DIEA benzeneselenocarboxylate at 25 °C (●) and 55 °C (▲) as monitored by conversion to *N*-(*p*-toluenesulfonyl) benzamide (**28**) in an HPLC assay.

ate is more stable in acetonitrile than the corresponding potassium salt in the previous DMSO-containing solvent system, we were able to raise the reaction temperature to 55 °C to further speed up the amidation reactions for less reactive azides. The phenyl azide and *p*-methoxyphenyl azide gave amidation yields of only 25% and 7%, respectively, in the DMSO-containing solvent system.[2] Under our new conditions, the same azides gave much improved yields of 81% and 65%, respectively (entries 10 and 11, Table 2).

The effect of fluoro substitution on aromatic azide is also interesting. Electron-withdrawing groups are expected to stabilize the transition state through delocalization of the negative charge on the nitrogen, and thus facilitate amidation.[2] Fluorine substitution at the meta position, as in compound **20**, improved the amidation yield from 56% to 78% (entries 13 vs 14, Table 2). However, when fluoro substitution was moved to the ortho position, the yield of the corresponding amide was reduced to only 37% (entry 15, Table 2). This was surprising, but could be explained by the different electronic effects of fluoro substitution at the meta and ortho/para positions. Fluorine has electron-withdrawing inductive effects ($\sigma_I = 0.50$) at the meta position, and has both electron-withdrawing inductive and electron-donating resonance effects at the ortho/para positions ($\sigma^0_R = -0.31$).[14] Apparently due to the electron-donating resonance effect of the fluoro substituent in the ortho position, delocalization of the negative charge on the nitrogen in the transition state was probably hindered, thereby lowering the reaction yield.[2]

Directly introducing electron-withdrawing groups adjacent to azido, such as sulfonyl and phosphoryl, gave excellent yields of *N*-acyl sulfonamide **28** and *N*-acyl phosphoramide **29** with only 1.2 equiv of selenocarboxylate (entries 7 and 8, Table 2). Reaction of sulfonyl azide with selenocarboxylate was the fastest reaction with a near quantitative yield (entry 7, Table 2). Acyl azide, such as benzoyl azide (**15**), gave poorer yield. With 2 equiv of selenocarboxylate, the isolated yield was only 51% at 55 °C. This was due to the instability of the acyl azide itself that led to a side reaction, Curtius rearrangement, during the amidation process. Consistent with the mechanism proposed,[2] the reaction is compatible with the presence of free amines and alcohols (entries 12–15, Table 2). The formation of 4-benzoylaminobenzyl acetate (**37**) from 4-azido benzyl acetate (**22**, entry 16, Table 2) indicated the formation of amide without the prior reduction of azide to its corresponding amine, as we reported previously.[2]

To summarize, we developed a new set of conditions to increase the solubility and stability of selenocarboxylates. The half-life of the selenocarboxylate was increased by 27-fold at room temperature. Excellent yields were obtained with electron-deficient azides, and much improved yields were obtained with electron-rich azides upon mild heating. Thus, these new conditions represent a significant improvement over the earlier conditions used to couple selenocarboxylates with azides.

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12. For the stability assay, the best azide substrate was used in excess to ensure fast and quantitative consumption of all selenocarboxylate at a given time point.
13. General procedure for the preparation of amides: Diacyl diselenide (0.24 mmol) and azide (0.2 mmol) were dissolved in deaerated acetonitrile (5 ml) and stirred at room temperature under an argon atmosphere. To this was added DIEA (0.24 mmol), followed by piperidine (0.24 mmol). The mixture was stirred at room temperature or heated at 55 °C depending on the azide. The reaction was monitored using TLC and LCMS. Upon completion, the mixture was concentrated and dissolved in ethyl acetate and filtered through a celite pad to remove selenium powder. The ethyl acetate phase was washed with aqueous saturated $NaHCO_3$, water and concentrated to dryness. The crude product was then purified by silica gel flash column chromatography.
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15. Since the half-life of selenocarboxylate at 55 °C is about 1.4 h, extending the reaction beyond 6 h has little effect on the reaction yield.