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Amide bond formation from selenocarboxylates and aromatic azides

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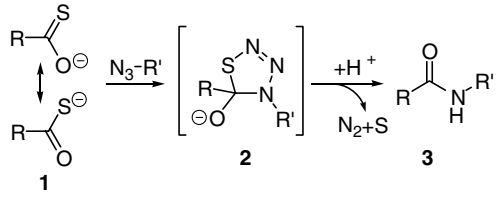
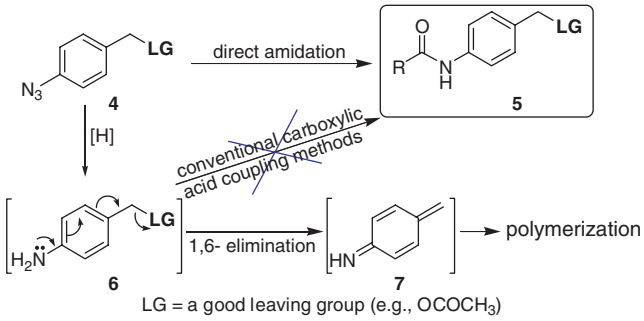
Abstract—A new method of amide bond formation was developed through the reaction of potassium selenocarboxylates with aromatic azides at room temperature. Potassium selenocarboxylates were prepared in situ by the treatment of diacyl selenides with potassium methoxide at 5 °C under N_2. After the addition of azide, the reaction was allowed to gradually warm to room temperature and was stirred for 0.5–2 h. Excellent yields were obtained when electron deficient aromatic azides were used.

Formation of an amide bond is usually achieved through the reaction of an activated carboxylic acid with an amine. However, there are situations where certain functional groups are incompatible with the presence of a free amine. One such situation is the spontaneous decomposition of 4-aminobenzyl esters through 1,6-elimination.[1] As an alternative to an amine, the use of non-nucleophilic and non-basic starting material and intermediates is needed. The azido group has received attention because it is easily transformed into various nitrogen-containing functional groups. The reaction of a thio acid with an organic azide to give the corresponding amide was first reported by Hakimelahi and Just.[2] Later, it was proposed that the reaction went through a rapid in situ reduction of the azide to the corresponding amine prior to amide bond formation.[3] Recently, evidence was presented that excluded the formation of an amine as the reactive intermediate and revised the mechanism to proceed via a thiatriazoline intermediate **2** as shown in Scheme 1.[4] The reaction was accelerated by the presence of bases such as 2,6-lutidine. Subsequently, other applications and modifications of the thio acid-azide amidation have appeared.[5–7]

In our research, quick decomposition of compound **6** in the form of 4-aminobenzyl-LG (where LG = a good leaving group) to quinonimine methide **7** and subsequent polymerization, as shown in Scheme 2, made it impossible to prepare the corresponding amide **5**.



Scheme 1. Mechanism proposed for the reaction of thio acids with azides.



Scheme 2. Direct amidation from aromatic azides avoids 1,6-elimination of 4-aminobenzyl derivatives.

The spontaneous 1,6-elimination of **6**, therefore, precluded the use of general amidation procedures that require a free amine to react with an activated carboxylic acid to form the amide **5**. Thus, we needed an alternative method to prepare these aryl amides. Ideally, we would achieve this using our aromatic azide starting

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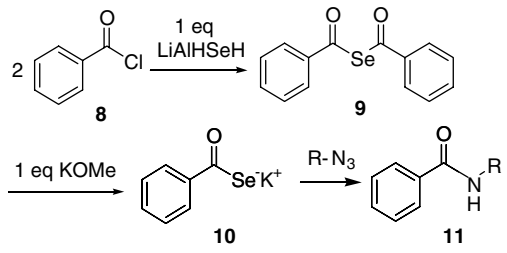
materials (i.e., **4** → **5**). The thio acid/azide reaction is very rapid if the azide is electron deficient, but the unactivated phenyl azide was shown to require refluxing in chloroform for several hours for good conversion.[4] We wondered if selenocarboxylates would couple more rapidly with azides than thiocarboxylates, since selenoderivatives are typically more reactive than their corresponding sulfur analogs.[8] The enhanced reactivity would potentially lower reaction temperature and shorten reaction time. Although selenocarboxylic acids are known to be unstable to heat and sensitive to oxygen, the corresponding alkali metal and piperidinium salts are relatively stable, especially in the case of aromatic selenocarboxylates.[9] For example, no significant change occurred in potassium 4-methylbenzeneselenocarboxylate when it was exposed to air for 5 h. Under oxygen-free conditions, most aromatic selenocarboxylate salts can be stored at −17 °C for at least one month.[10] Potassium benzeneselenocarboxylate (**10**) was thus chosen for our present studies.

Alkali metal salts of selenocarboxylates can be prepared by the treatment of trimethylsilyl selenocarboxylic esters with alkali metal fluorides,[11] the reaction of acyl chlorides with alkali metal selenides,[12,13] the reaction of diacyl selenides with alkali metal hydroxide,[14] or the treatment of carboxylic acids with Woollins' reagent in refluxing toluene.[5] We selected the method using diacyl selenides with potassium methoxide[15] as shown in Scheme 3 since diacyl selenides are relatively stable and readily prepared. Moreover, aromatic diacyl selenides can be purified by silica gel flash column chromatography.[16] We obtained dibenzoyl selenide (**9**) through the reaction of 2 equiv of benzoyl chloride (**8**) with 1 equiv of LiAlHSeH. The latter was freshly prepared by reacting lithium aluminum hydride with selenium powder.[17,18]

For our coupling reaction, potassium benzeneselenocarboxylate (**10**) was generated in situ by mixing dibenzoyl selenide (**9**) with 1 equiv of potassium methoxide in DMSO/EtOAc (1:1) at 5 °C under N_2 (Scheme 3). DMSO was used to increase the solubility of potassium methoxide. After azide addition, the reaction was allowed to gradually warm to room temperature and was stirred for 0.5–2 h until TLC and/or LC–MS showed the disappearance of the starting azide or no further change of the reaction mixture.

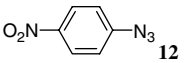
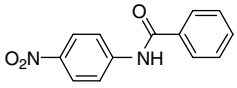
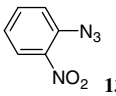
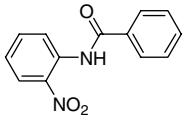
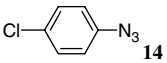
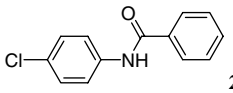
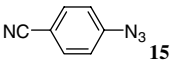
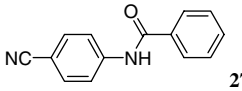
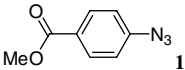
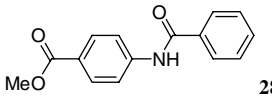
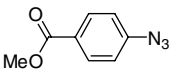
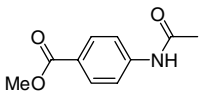
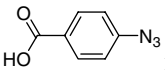
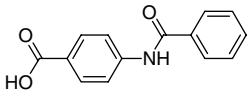
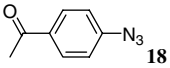
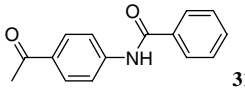
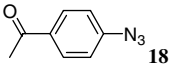
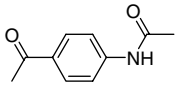
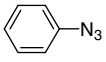
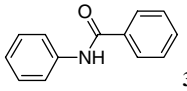
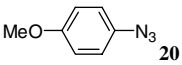
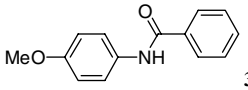
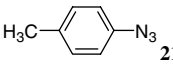
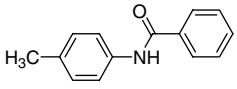
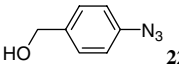
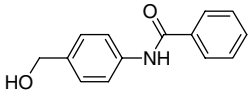
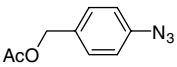
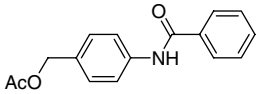
A series of homologous aromatic azides (**12**–**23**) bearing various electron-donating and electron-withdrawing functionalities were selected to explore the scope of the amidation reaction and to give a better assessment of the electronic and steric effects on the reaction outcome. As with thiocarboxylate analogs, it was found that electron-deficient azides were much more reactive than electron-rich azides.[19] Aromatic azides **12**–**18** bearing electron-withdrawing groups such as NO_2, Cl, CN, $COCH_3$, COOH, and COOMe (Table 1, entries 1–9) gave excellent yields while phenyl azide **19** (Table 1, entry 10) and aromatic azides **20**–**22** with electron-donating groups such as OCH_3, CH_3, and CH_2OH (Table 1, entries 11–13) gave lower yields of desired amides with most of the azide starting materials recovered. Electron-withdrawing groups at the *para* or *ortho* position probably stabilize the transition state delocalization of the negative charge on the nitrogen, for example, **39** as shown in Scheme 4, and thus facilitate the formation of the amide bond. Interestingly, the reaction is slower when the nitro group is at the *ortho* position as in **13** than when it is at the *para* position as in **12**. However, moving the nitro substituent from the *para* to the *ortho* position in the starting azide did not affect the overall yield of amidation under our current conditions (Table 1, compare entries 2 and 1). Acetylation of 4-azidobenzyl alcohol **22**, as in compound **23**, increased the amidation yield from 44% to 70% (Table 1, compare entries 14 and 13), and may reflect an inductive electronic stabilization in the amidation reaction. The successful formation of 4-benzoylaminobenzyl acetate (**37**) from 4-azidobenzyl acetate (**23**) (Table 1, entry 14) indicates that the reaction does not involve in situ reduction of azide **23** to the corresponding amine prior to amide bond formation, since such reduction would have lead to the formation of quinonimine methide and subsequent polymerization instead of the desired amide, as discussed earlier and shown in Scheme 2. The reaction of the aliphatic selenocarboxylate (Table 1, entries 6 and 9) gave comparable yields to aromatic selenocarboxylates. These results are consistent with earlier reports wherein the reaction yields depend primarily upon the electronic properties of azides. Based on these results, a mechanism similar to that proposed for thiocarboxylates[3] is proposed for this amidation reaction (Scheme 4).



Scheme 3. Direct amidation of azides via selenocarboxylates.

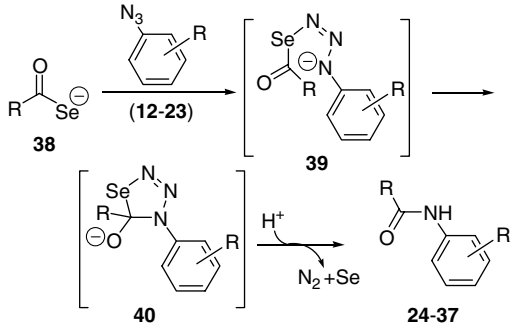
The selenocarboxylate-azide amidation is highly chemoselective. All reactions were very clean giving >90% yields based on recovered starting materials; and no other side reactions were observed. All unreacted azide starting materials could be recovered. The lower conversion yields for the less reactive azides could be due to the limited stability of selenocarboxylates under the current reaction conditions. To test this hypothesis, we used the reaction of benzeneselenocarboxylate **10** with 4-nitrophenyl azide (**12**), the fastest amidation reaction in Table 1, to monitor the stability of selenocarboxylate under the reaction conditions. When benzeneselenocarboxylate **10** was incubated with 4-nitrophenyl azide (**12**) in DMSO/EtOAc (1:1) under our standard conditions, complete and quantitative amidation was achieved in less than 5 min as monitored by HPLC. To monitor the stability of selenocarboxylate under these conditions, dibenzoyl selenide (**9**) was mixed with 1 equiv

Table 1. Amidation reaction of selenocarboxylates with azides[a]

Entry	Azide starting material	Amide product	Time (h)	Yield (%)[b]
1	 **12**	 **24**	0.5	98
2	 **13**	 **25**	1.0	95
3	 **14**	 **26**	0.5	96
4	 **15**	 **27**	0.5	98
5	 **16**	 **28**	1.0	98
6	 **16**	 **29**	1.0	91
7	 **17**	 **30**	2.0	87
8	 **18**	 **31**	1.0	88
9	 **18**	 **32**	1.0	76 (19)[c]
10	 **19**	 **33**	2.0	25 (65)[c]
11	 **20**	 **34**	2.0	7 (88)[c]
12	 **21**	 **35**	2.0	7 (85)[c]
13	 **22**	 **36**	2.0	44 (51)[c]
14	 **23**	 **37**	2.0	70 (24)[c]

[a] General conditions: diacylselenide (2 mmol), KOMe (2 mmol), EtOAc/DMSO (1:1), 5 °C, 10 min; then azide (1 mmol), 5 °C– rt.
[b] Isolated yield (%) of the amide product.
[c] The yield of the recovered azide starting material is shown in parenthesis.

of potassium methoxide in DMSO/EtOAc (1:1) at 5 °C to form the selenocarboxylate. The benzeneselenocarboxylate **10** formed was allowed to stand at room temperature and aliquots were combined with 2 equiv of



Scheme 4. Mechanism proposed for the reaction of selenocarboxylates with aromatic azides.

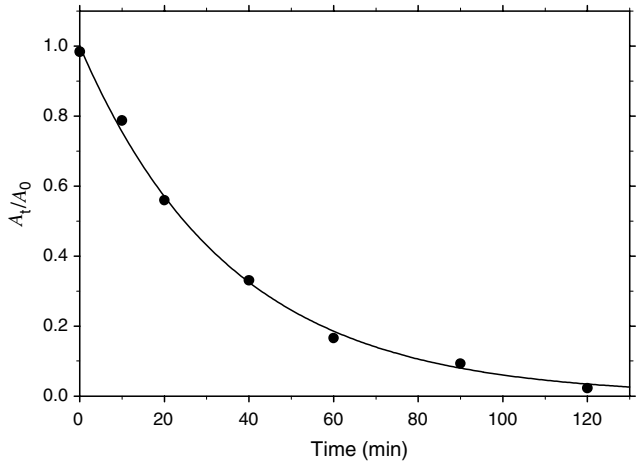


Figure 1. Stability of phenylselenocarboxylate **10** in DMSO/EtOAc (1:1) at room temperature as monitored by conversion to *N*-(4-nitrophenyl) benzamide (**24**) in an HPLC assay.

4-nitrophenyl azide (**12**). The amide product **24** was analyzed to determine the amount of benzeneselenocarboxylate that remained in solution. Figure 1 shows the plot of normalized amide product **24** formed, i.e., relative selenocarboxylate **10**, against the time when excess azide was added. Indeed, selenocarboxylate **10** was not stable and has an apparent half-life of about 25 min under these reaction conditions.[20] This is consistent with the results shown in Table 1, wherein less reactive azides gave lower yields. Increasing the reaction time and temperature did not improve the yields of amide formation for the less reactive azides. Efforts are underway to find reaction conditions underwhich selenocarboxylates are stable and thus can be used to facilitate the amidation reaction with electron-rich azides.

In summary, we developed a method for the formation of amide bonds under mild conditions through the reaction of selenocarboxylates with azides. Excellent yields were obtained when electron-deficient aromatic azides were used. The reaction is highly chemoselective and very clean with no detectable side products. It is compatible with a variety of functional groups including hydroxy, ketone, carboxylic acid, ester, and nitrile. This method offers the advantage of mild reaction conditions without going through the nucleophilic and basic free amine intermediates. It should be useful when amide bonds need to be formed between molecules with functional groups incompatible with free amines and basic conditions.

Acknowledgments

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19. *General procedure:* To a solution of diacyl selenide (2.0 mmol) in EtOAc (20 mL) was added a suspension of KOMe (2.0 mmol) in DMSO (20 mL) at 5 °C under nitrogen atmosphere. The resulting mixture was stirred at 5 °C for 10 min. Then, the starting azide (1.0 mmol) was added into the above mixture. The reaction was allowed to gradually warm to room temperature. The reaction mixture was poured into ice water when TLC showed the disappearance of the starting azide or no further change of the reaction mixture. The black selenium powder was removed by filtration. The filtrate was extracted with EtOAc. After removal of solvents, the crude product was purified by flash column chromatography.

20. *Stability measurement:* The stability of benzeneselenocarboxylate **10** in DMSO/EtOAc (1:1) at room temperature was measured by monitoring the product formation between benzeneselenocarboxylate **10** and 4-nitrophenyl azide **12** under the above general reaction conditions. The reaction between benzeneselenocarboxylate **10** and 4-nitrophenyl azide **12** to form the product amide **24** was complete in less than 5 min (data not shown). Such fast product formation allows for the accurate measurement of the amount of benzeneselenocarboxylate **10** remained in solution during our stability study. Briefly, aliquots of freshly prepared benzeneselenocarboxylate **10** in DMSO/EtOAc (1:1) were incubated at room temperature and the amount of benzeneselenocarboxylate **10** was measured at different time intervals by the reaction with 2 equiv of 4-nitrophenyl azide (**12**) for at least 1 h. The reaction mixtures were separated on a Chromolith SpeedROD RP-18e column (50×4.6 mm) at 1 mL/min with a 10-min gradient of 10–90% acetonitrile containing 0.1% formic acid on a Shimadzu 2010 LCMS system. The *N*-(4-nitrophenyl) benzamide product **24** was quantitated based on UV absorption at 220 nm, and its structure was confirmed by the mass spectrometry detector. The peak area of *N*-(4-nitrophenyl) benzamide product **24** represents the amount of benzeneselenocarboxylate **10** that remained at a given time point and was plotted against the time of incubation. The data was fitted to a single, two parameter exponential decay equation in SigmaPlot to obtain the first-order rate constant.