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A new type of amide formation from thiocarboxylic acid and alkyl azide

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Abstract—We studied the coupling of thiocarboxylic acid and alkyl azide using various triaryl phosphines. Amide formation greater than 95% was achieved when the free-formation of Staudinger intermediate with electron deficient triaryl phosphines was employed. © 2002 Elsevier Science Ltd. All rights reserved.

Amide formation from carboxylic acids and amines has been studied comprehensively and numerous procedures have been developed and implemented. Most of the amide formation involves the generation of free amino groups and activation of carboxylic acid as the method of choice, but an efficient chemoselective amide formation is still in demand to synthesize various chemicals.

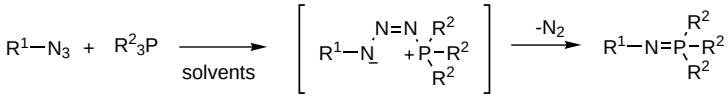
Formation of Staudinger intermediate[1] (phosphazenes from azides and tertiary phosphines) is a convenient way of generating nucleophilic amine from azide (Scheme 1). Studies by Vilarrassa et al. have shown that this intermediate can be coupled to acids, acid halides or acid anhydrides to yield an amide in an inter- or intramolecular manner.[2] Recent studies by Saxon et al. and Nilson et al. presented further improvement of the reaction providing an efficient tool for successful ligation of peptides or proteins.[3]

In an attempt to prepare thioamides, we have found that amide can be obtained from monothiocarboxylic acids and phosphazenes. In this paper we describe the first successful amide formation from monothiocarboxylic acid and azide with various triaryl phosphines.

First we tried the previously reported condition[2a] to obtain an amide product from thiobenzoic acid and benzyl azide. After heating a mixture of all the reagents in various solvents, we could not produce an amide with more than 40% yield. We also found various equivalents of benzyl azide, triphenyl phosphine and organic bases resulted in lower yields. So we prepared a phosphazene intermediate by first heating a mixture of benzyl azide and triphenyl phosphine. We observed the gas (N_2) evolved from the reaction mixture and monitored the phosphazene formation by NMR.[4] After 10–48 hours of heating we observed no more phosphazene formation from various triaryl phosphine and benzyl azides in CH_3CN. The electron rich tri-4-methoxyphenyl phosphine required a longer time than tri-4-fluorophenyl phosphine. When thiocarboxylic acid was added to the phosphazene solution, fast transformation to an amide was observed.[5]

With variations of phosphines and solvents, we attempted a coupling reaction of benzyl azide and thiobenzoic acid (Scheme 2).[6]

Among the phosphines we tried, triphenyl phosphine was the best, yielding up to 91% coupling product in CH_3CN (entry 1). Other solvents, such as methylene



Scheme 1. Staudinger intermediate from azide and phosphine.

Keywords: Staudinger intermediate; amide; thiocarboxylic acid; azide; phosphine.

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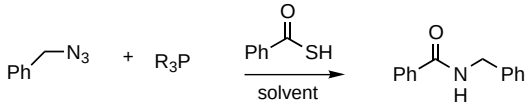
chloride, dioxane and DMF, gave lower yields (entries 2–5). Benzene and hexane gave very low yields (entries 6–7). Vilarrasa et al. reported better yields of amide formation from propionic acid, benzyl azide, and Ph_3P in refluxing benzene (95%) and refluxing hexane (78%) when compared with the same reaction in refluxing CH_3CN (61%).[2a] When BOP or PyBOP was used, no product was obtained, implying that reduced benzyl amine is not an intermediate for the amide formation (Table 1).

Based on the result of Table 1 in which triphenylphosphine is the best reagent, we evaluated benzyl azide coupling with two thioacids using substituted phenyl and furyl phosphines in acetonitrile (Scheme 3). Interestingly, with both thiobenzoic acid and thioacetic acid, tri-4-fluorophenyl phosphine gave better yields than triphenyl phosphine, while tri-4-methoxyphenyl phosphine gave lower yields. When tri-2-furyl phosphine was employed, the same or slightly better yields were obtained (entries 5, 10). These substituent effects indicate that this reaction is sensitive to the electron density at phosphine (Table 2).

In order to expand this type of reaction, we changed benzyl azide to azido methylacetate (Scheme 4). We consider this azide a glycine analogue that can be applied to peptide chemistry.

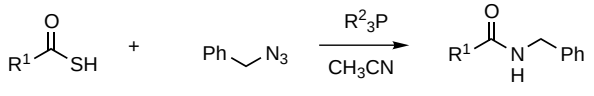


Scheme 2. Amide formation from benzyl azide and thiobenzoic acid.

Table 1. Reaction of benzyl azide and thiobenzoic acid

Entry	R_3P	Solvent	Yield (%)
1	Ph_3P	CH_3CN	91
2	Ph_3P	CH_2Cl_2	35
3	Ph_3P	1,4-Dioxane	62
4	Ph_3P	DMF	85
5	Ph_3P	$CHCl_3$	45
6	Ph_3P	Benzene	23
7	Ph_3P	Hexane	14
8	Bu_3P	CH_3CN	26
9	BOP[a]	CH_3CN	0
10	PyBOP[b]	CH_3CN	0

[a] Benzotriazolyl-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate.
[b] Benzotriazolyl-oxy-trispyrroldino-phosphonium hexafluorophosphate

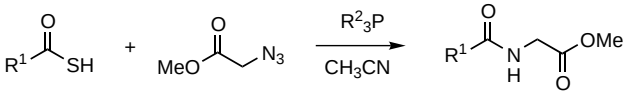


Scheme 3. Amide formation from thiocarboxylic acid and benzyl azide with triaryl phosphine.

Table 2. Reaction of benzyl azide in acetonitrile

Entry	Thioacid	R_3P	Yield (%)
1	Thiobenzoic acid	Ph_3P	91
2		$(4\text{-F-Ph})_3P$	91
3		$(3\text{-F-Ph})_3P$	97
4		$(4\text{-}CH_3O\text{-Ph})_3P$	62
5		$(2\text{-Furyl})_3P$	91
6	Thioacetic aid	Ph_3P	72[a]
7		$(4\text{-F-Ph})_3P$	54[a]
8		$(3\text{-F-Ph})_3P$	81[a]
9		$(4\text{-}CH_3O\text{-Ph})_3P$	50[a]
10		$(2\text{-Furyl})_3P$	89[a]

[a] Yields were determined by NMR integration of the methylene peaks against benzyl acetate as an internal standard.



Scheme 4. Amide formation from azido methylacetate and triaryl phosphine.

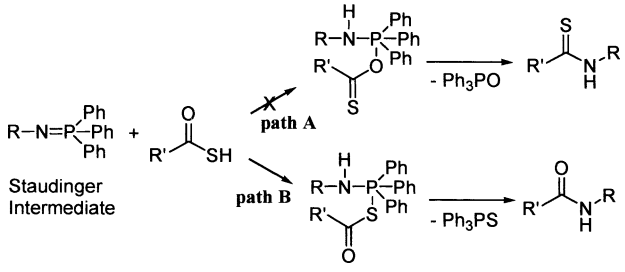
The results of the coupling reactions of azido methylacetate and two thioacids are listed in Table 3. Similar to benzyl azide reactions, electron deficient phosphine gave the highest yield, up to 96%. Phenyl and methoxyphenyl phosphines gave lower yields with both thioacids. Again 2-furyl phosphine gave a similar or better yield compared to triphenyl phosphine.

Considering the reaction mechanism, two intermediates could possibly be formed (Scheme 5). If the reaction

Table 3. Reaction of azido methylacetate and thiocarboxylic acid in CH_3CN

Entry	Thioacid	R_3P	Yield (%)
1	Thiobenzoic acid	Ph_3P	49
2		$(4\text{-F-Ph})_3P$	96
3		$(4\text{-}CH_3O\text{-Ph})_3P$	62
4		$(2\text{-Furyl})_3P$	94
5	Thioacetic aid	Ph_3P	68[a]
6		$(4\text{-F-Ph})_3P$	96[a]
7		$(4\text{-}CH_3O\text{-Ph})_3P$	49[a]
8		$(2\text{-Furyl})_3P$	69[a]

[a] Yields were determined by NMR integration of the methylene peaks against benzyl acetate as an internal standard.



Scheme 5. Possible intermediate for amide formation.

follows path A, thioamide will be obtained, but we failed to detect thioamide formation. On the other hand, a stable amide product was obtained, confirming that the reaction went through path B. The equilibrium between thiono- and thiolo-carboxylic acid and differences in bond length and nucleophilicity may play a crucial role in yielding amide products.

In conclusion, we were able to obtain amide products from monothiocarboxylic acid and alkyl azide for the first time in satisfactory yields. From the optimization of the reaction, we found that electron deficient aryl phosphine is the best reagent in CH_3CN. This reaction would be generally applicable to chemoselective amide formation from thiocarboxylic acid and azide. Further applications in the syntheses of glycopeptides and peptidomimetics are in progress and the results will be published in due course.

Acknowledgements

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4. Chemical shift of benzylic proton in $CDCl_3$ was moved, upon mixing with triphenylphosphine, from 4.32(s) to 4.41(s), then slowly to 3.87(s), corresponding to benzyl azide, phosphazide and phosphazene, respectively.
5. Upon addition of thiobenzoic acid to the phosphazene solution, NMR shift of 4.66 (d, $J=5.7$ Hz) appeared quickly.
6. General procedure: Triphenyl phosphine (342 mg, 1.3 mmol) was added to a solution of benzyl azide (145 mg, 1.09 mmol) in acetonitrile (10 mL) and the mixture was stirred for 1 h at 0°C and 40 h at 65°C. To this mixture was added thiobenzoic acid (100 mg, 0.72 mmol) and the solution was stirred for 24 h at room temperature. After the reaction mixture was concentrated, water (10 mL) was added and the solution was extracted with EtOAc (10 mL×3). The combined organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. After purification via SiO_2 chromatography, 139 mg of *N*-benzyl benzamide was obtained (91% yield). ^1H NMR ($CDCl_3$, 200 MHz) δ 7.9–7.75 (2H, m), 7.6–7.4 (8H, m), 6.7–6.4 (1H, bs), 4.66 (2H, d, $J=5.7$ Hz); mass Calcd for $C_{14}H_{15}NO$: 211, Found: 211.