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Reaction of Thiolesters with Nitrogen Ylides

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The pairing of unstabilized nitrogen ylides generated in situ with functionalized thiolesters under ambient conditions resulted in a new intramolecular carbon–carbon bond forming reaction. The scope of the reaction was illustrated with a series of substituted thiolester substrates. This reaction represents a new method for the synthesis of 2-substituted tetrahydrothienyl compounds through a unique 1,2-thiolate shift. Whereas nitrogen ylides have been used in synthesis previously, very few examples exist in which unstabilized nitrogen ylides have been utilized in synthetically meaningful transformations.

Introduction

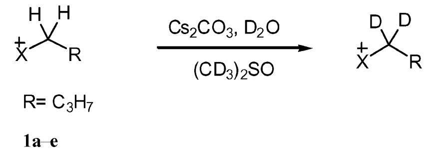
Having an indispensable role in biological chemistry, the electrophilic thiolester functionality has been one of the most important chemical building blocks.[1] In the past couple of decades, their usefulness finally overreached the boundaries of biochemistry and their role became firmly embedded in the synthetic arsenal of organic chemists. The chief advantages of thiolesters, such as their stability and accessibility, have been used in the synthesis of highly functionalized ketones[2] and aldehydes,[3] and they have also played important parts in the synthetic chemistry of proteins.[4] Various thiolester substrates can be easily prepared from commercially available starting materials through very mild methods.[5]

Results and Discussion

In our ongoing effort to investigate the reactivity of the electrophilic thiolester functionality and its use in carbon–carbon bond forming processes, we have been looking for matching nucleophilic partners that could be prepared and used under ambient reaction conditions. The candidates that could fulfill those considerations are ylides. Although processes involving heteroatom-stabilized ylides have been extensively studied and their role in organic synthesis well recognized, the chemistry of nitrogen ylides and their synthetic application certainly deserves closer attention.[6] Because phosphorus ylides and their intramolecular reaction with thiolesters have been already reported,[7] we turned our attention to the reactivity of ylides stabilized by nitrogen-containing functionalities. Although they found some synthetic use, particularly in the form costabilized by other substituents,[6] unstabilized nitrogen ylides have received only marginal attention. The relative synthetic obscurity of the such species is connected to problems with the formation of the ylides and their subsequent stability.[6]

As with their phosphorus counterparts, successful nitrogen ylide reaction patterns depend on abstraction of the α-proton in the precursors − the ylide formation. In order to gain some insight into this process, we evaluated different nitrogen-containing functional groups influencing the proton abstraction and the ylide stability. The comparison of ammonium derivatives **1a**–**d** treated by alkali carbonates in various solvents in the hydrogen/deuterium exchange experiment pointed to the pyridinium (**1a** derivative) and, to a lesser extent, to the 4-aminocarbonylpyridinium group (**1c** derivative) as the best ylide stabilizing, synthetically feasible functional groups (Table 1).

Table 1. Isotope exchange experiment.[a]



1a–**e**

	X	Room temp., 10 min H/D exchange [%]	90 °C, 1 h H/D exchange [%]
1a	pyridine	<2	>99
1b	nicotinamide	<2	decomp.
1c	isonicotinamide	<2	55
1d	Et_3N	<2	<2
1e[b]	Ph_3P	>99	>99

[a] To the $(CD_3)_2SO$ solution of bromide **1a**–**e** (approx. 15 mg bromide in 0.5 mL of the solvent) was added one drop of D_2O. Deuterium exchange was observed by NMR spectroscopy. [b] The triphenylphosphonium compound was used as a benchmark for its known reactivity.

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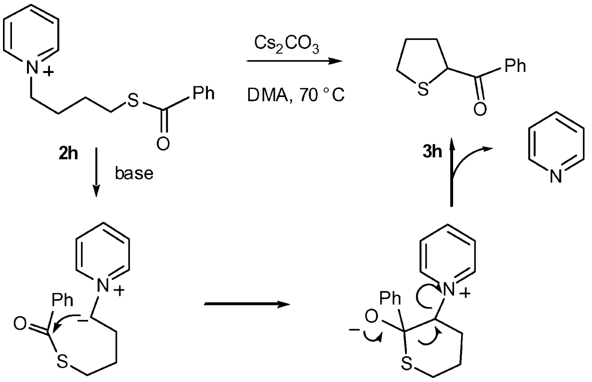
After the initial isotope exchange experiment with **1**, which helped us to estimate the reaction conditions, we proceeded to the investigation of the ylides as nucleophiles in the chemical transformation of thiolesters. In order to validate the proposed idea and examine the plausibility of this reaction, we focused on the intramolecular approach. Hence, benzoyl thiolester **2** with a tethered ammonium functionality was prepared and subjected to various basic conditions (Scheme 1).

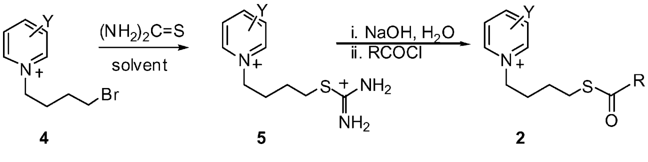


Scheme 1. Tetrahydrothiophene formation.

Under the reaction conditions, we observed the clean formation of 2-tetrahydrothienyl phenyl ketone (**3**) in high yield. The likely mechanism featuring a 1,2-thiolate shift with the ammonium moiety acting as the leaving group is depicted in Scheme 1.

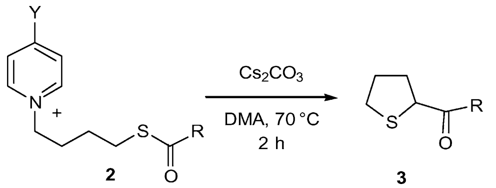
Although various combinations of bases (TBAF, K_2CO_3, NaOH) and solvents (THF, DMF, toluene) were explored with some success, the treatment of the substrate with Cs_2CO_3 in DMA (*N*,*N*-dimethylacetamide) was found superior to the others. As expected, after the isotope exchange experiment (Table 1), the reaction of the triethylammonium and 3-aminocarbonylpyridinium derivatives did not lead to ring closure.

We expected that the synthetic outcome of the reaction would open a new alley to 2-substituted tetrahydrothiophenes. The importance of the process is underscored by the fact that the same structural motifs can be found in a variety of biologically relevant molecules.[8] In order to illustrate the full synthetic potential of the reaction and its tolerance towards different functionalities, a series of stable substrates was prepared from common, easily accessible intermediates (Scheme 2). The whole series was treated with Cs_2CO_3 and the resulting substituted 2-tetrahydrothienyl ketones were furnished in good-to-excellent yields (Table 2).



Scheme 2. Preparation of the substrate.

Table 2. Acyltetrahydrothiophene **3** formation from quaternary salts **2**.



	R	Product	Y	Yield [%]
2a	CH_3	**3a**	$CONH_2$	53 (90[a])
2b	$C_{11}H_{23}$	**3b**	$CONH_2$	42
2c	4-methylphenyl	**3c**	$CONH_2$	85
2d	4-chlorophenyl	**3d**	$CONH_2$	76
2e	3-pyridyl	**3e**	$CONH_2$	52
2f	2-thienyl	**3f**	$CONH_2$	87
2g	2-furyl	**3g**	$CONH_2$	80
2h	phenyl	**3h**	H	88
2i	$C_{11}H_{23}$	**3b**	H	48 (80[a])
2j	2-thienyl	**3f**	H	78
2k	2-furyl	**3g**	H	69

[a] Yield determined by UPLC-MS.

Although focus of our research was on intramolecular ylide–thiolester cyclization, we wanted to address the possibility of the intermolecular version of the reaction as well. Under the reaction conditions, however, no reaction of the thiolesters with unfunctionalized nitrogen ylides was observed.

Conclusions

Overall we have presented here the utilization of unstabilized nitrogen ylides as nucleophiles in synthetic chemistry. Different ammonium groups and their ability to form the ylides were examined. Validity of our conclusions and the reaction scope were illustrated for the novel intramolecular reaction: by pairing the ylides with thiolester electrophiles we achieved easy access to 2-substituted tetrahydrothiophenes.

Experimental Section

In the 10-mL screw-cap sealed ampoule with a magnetic stirrer, starting salt **2a**–**k** (0.5 mmol) and Cs_2CO_3 (0.326 g, 1 mmol) were suspended in dry DMA (2 mL). The reaction mixture was heated at 70–100 °C whilst stirring (bath temperature) for 4–6 h under an Ar atmosphere and then slowly cooled to room temperature. According to the UPLC-MS control, the conversion of starting quaternary salts **2** was higher than 90%. The dark suspension was diluted with water (5 mL), acidified to pH 3–4 by 5% aqueous hydrochloric acid, and extracted with diethyl ether containing a few drops of hexane. After drying of the ethereal portion with $MgSO_4$ and evaporation, the residue was purified by filtration through a layer of silica gel and washed with hexane containing 0–0.5% ether. After solvent evaporation, pure tetrahydrothiophene derivatives **3a**–**h** were obtained (Table 2).

Supporting Information (see footnote on the first page of this article): Complete description of all the experimental procedures, as well as the characterization of all the new compounds.

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