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A Practical, One-Pot Multicomponent Synthesis of α-Amidosulfides and Their Application as Latent *N*-Acylimines in the Friedel–Crafts Reaction

Nicolas George,[a] Mathieu Bekkaye,[a] Géraldine Masson,*[a] and Jieping Zhu*[b]

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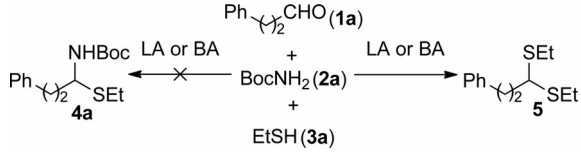
A novel one-pot, three-component synthesis of *N*-acyl or *N*-carbamoyl-α-amidosulfides **4** is described. The three-component reaction of aldehydes **1**, primary carbamates (or amides) **2** and phenylsulfinic acid (**6a**) afforded α-amidosulfones **7**, which after addition of sodium thiolate were in situ transformed into stable α-amidosulfides **4** in good to excellent yields. We demonstrated that silver salts or Brønsted acids were able to promote the formation of aliphatic and aromatic *N*-acylimines from **4** in quantitative yield under mild conditions. The phosphoric acid catalyzed Friedel–Crafts alkylation of 3-substituted indoles with α-amidosulfides **4** leading to 2,3-disubstitued indoles was also documented.

Introduction

α-Amidosulfides (N,S-acetals) are an important class of structural motifs found in numerous pharmaceutical agents[1] and heterocycles such as 4-thiazolidinones.[2] Interestingly, although N,S-acetals are sufficiently stable under mild acidic and basic conditions, which makes them valuable protecting groups,[3] they can also act as useful synthetic intermediates in organic synthesis.[4] For instance, α-amidosulfides constitute an interesting stable masked form of *N*-acyl- and *N*-carbamoylimines (or iminium ions) in the presence of a soft Lewis acid.[4a–4f,5,6] Recently, we reported a silver tetrafluoroborate mediated cyclization of tethered α-amidosulfides and silyl enol ethers and successfully applied this transformation in the synthesis of (–)-quinocarcin as well as the aglycon of (–)-lemonomycin.[5m,5n] Interestingly, in spite of their synthetic utilities, few methods are known for the preparation of α-amidosulfides, and most of them involve multistep processes that have limited application scope.[7] Therefore, the development of general, simple, and convenient methods for the construction of α-amidosulfides will be of great interest.

Results and Discussion

In continuation of our work in multicomponent reactions (MCRs),[8] we were interested in developing a one-pot synthesis of α-amidosulfides.[9] Our initial studies were carried out with 3-phenylpropionaldehyde (**1a**), *tert*-butyl carbamate (**2a**), and ethanethiol (**3a**) in the presence of Lewis or Brønsted acids. Unfortunately, formation of α-amidosulfide **4a** was never observed under a variety of conditions tested. In most cases, dithiane **5** was isolated as a main product (Scheme 1).[10]



Scheme 1.

In this context, we envisaged another approach involving the nucleophilic addition of thiol to highly reactive *N*-carbamate imines generated in basic media from α-amidosulfones **7**.[11,12] To investigate the feasibility of this approach, we selected sodium ethanethiolate (**8a**) as a base to trigger the formation of imine from **7** and also as a nucleophile to trap the in situ generated imine. To evaluate this hypothesis, we initiated our studies by treating sodium ethanethiolate (**8a**) with α-amidosulfone **7a** prepared from aldehyde **1a**, phenylsulfinic acid (**6**), and *tert*-butyl carbamate (**2a**).[12] When the reaction was carried out in ethanol at room temperature α-amidosulfide **4a** was isolated in 83% yield (Table 1, Entry 1). In spite of these encouraging results, the N,O-acetal resulting from nucleophilic addition of ethanol to the imine intermediate was also isolated as a side product. This competitive reaction was suppressed by using a sterically bulky protic solvent such as *tert*-butyl alcohol (Table 1, Entry 2) or aprotic solvents (THF or DMF; Table 1, Entries 3 and 4). Because conditions for the three-component synthesis of α-amidosulfone **7a** and those of the subsequent substitution process leading to **4a** are poten-

[a] Centre de Recherche de Gif,
Institut de Chimie des Substances Naturelles, CNRS,
91198 Gif-sur-Yvette Cedex, France
Fax: +33-1-69077247
E-mail: masson@icsn.cnrs-gif.fr
[b] Institute of Chemical Sciences and Engineering,
Ecole Polytechnique Fédérale de Lausanne (EPFL),
EPFL-SB-ISIC-LSPN,
1015 Lausanne, Switzerland
Fax: +41-21-6939740
E-mail: jieping.zhu@epfl.ch
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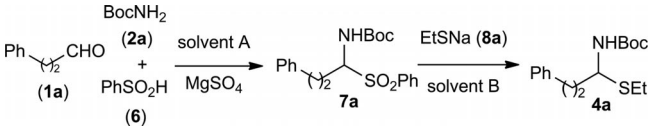
tially compatible, we next sought to merge these two steps into a one-pot process. Thus, a CH_2Cl_2 solution of aldehyde **1a**, **6**, and **2a** in the presence of $MgSO_4$ was stirred at room temperature for 12 h.[13] Upon complete consumption of the aldehyde, **8a** was added. The resulting mixture was stirred for an additional 3 h, and the corresponding α-amidosulfide **4a** was obtained in 72% overall yield (Table 1, Entry 5). Subsequently, it was found that the reaction performed in a mixture of solvents (CH_2Cl_2/THF, 1:1) produced compound **4a** in 96% yield from **1a**, which is much higher than the two-step procedure (Table 1, Entry 6 vs. 3).

Table 1. Optimization of reaction conditions.

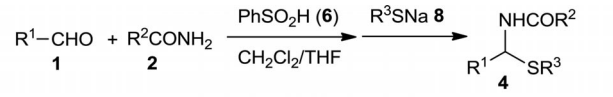


Entry[a]	Solvent A[b]	Solvent B[c]	Time [min]	Yield [%]
1	CH_2Cl_2	EtOH	5	83[d] (69)[e]
2	CH_2Cl_2	*t*BuOH	5	92[d] (76)[e]
3	CH_2Cl_2	THF	180	91[d] (75)[e]
4	CH_2Cl_2	DMF	60	92[d] (76)[e]
5	CH_2Cl_2	CH_2Cl_2	180	72[f,g]
6	CH_2Cl_2/THF	CH_2Cl_2/THF	180	96[f,g]

[a] General conditions: **1a/2a/6** = 1.0:1.2:1.2 (c = 0.1). [b] Solvent used for the synthesis of **7a**. [c] Solvent used for the synthesis of **4a**. [d] Yield refers to chromatographically pure product calculated from **7a**. [e] Yield refers to chromatographically pure product calculated from **1a**. [f] Sequential one-pot 3CR/substitution process. [g] Yield refers to chromatographically pure product calculated from **1a**.

The scope of this novel synthesis of α-amidosulfides was next examined by varying the aldehydes, carbamates (amides), and thiolates. As shown in Table 2, the sequential multicomponent process can be applied to both aliphatic and aromatic thiolates, affording corresponding α-amidosulfides **4** in high yields (Table 2, Entries 1–3 and 7–10). Benzamide derivatives **2** also participated in the reaction to give **4** in reasonable to excellent yield (Table 2, Entries 11–15). When benzyl carbamate was subjected to the same conditions, the yield was significantly reduced. However, when the amidosulfone prepared in CH_2Cl_2 was treated with sodium thiolate in THF, desired amidosulfide **4** was isolated in excellent yield (Table 2, Entry 16). For the aldehyde part, aliphatic including linear or α-branched aldehydes participated well in this transformation. Except in the case of bulky pivaldehyde (Table 2, Entry 9), reactions of heptanal, benzyloxyacetaldehyde, isobutyraldehyde, cyclopropanecarboxaldehyde, and cyclohexanecarboxaldehyde gave the expected products in good yields. On the other hand, benzaldehyde failed to participate in this one-pot procedure, due to problems inherent to the synthesis of aromatic α-amidosulfones from phenylsulfinic acid **6**. Nevertheless, using presynthesized α-amidosulfones **7** (aromatic aldehyde, benzylcarbamate, sodium phenylsulfinate, formic acid/water)[14] expected amidosulfides **4** were isolated in excellent yields (Table 2, Entries 16–19).

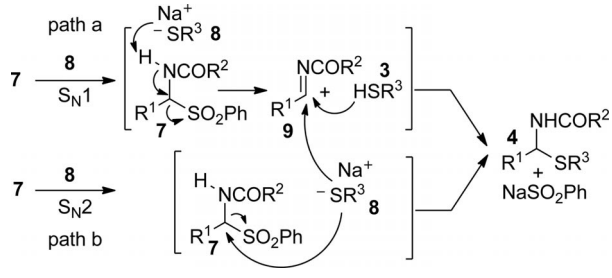
Table 2. One-pot sequential multicomponent synthesis of α-amidosulfides.



Entry	R^1	R^2	R^3	Yield [%][b]
1[a]	$Ph(CH_2)_2$	*t*BuO	Ph	77 (**4b**)
2[a]	$Ph(CH_2)_2$	*t*BuO	Bu	77 (**4c**)
3[a]	$Ph(CH_2)_2$	*t*BuO	iPr	75 (**4d**)
4[a]		*t*BuO	Et	78 (**4e**)
5[a]		*t*BuO	Et	73 (**4f**)
6[a]	$BnOCH_2$	*t*BuO	Et	68 (**4g**)
7[a]	*i*Pr	*t*BuO	Ph	69 (**4h**)
9[a]	*t*Bu	*t*BuO	Ph	43 (**4i**)
10[a]	C_6H_{13}	*t*BuO	Ph	73 (**4j**)
11[a]	$Ph(CH_2)_2$	Ph	Et	62 (**4k**)
12[a]	$Ph(CH_2)_2$	*p*-$OMeC_6H_4$	Et	75 (**4l**)
13[a]	$BnOCH_2$	Ph	Et	69(**4m**)
14[a]	*i*Pr	Ph	Et	64 (**4n**)
15[a]	C_6H_{13}	Ph	Et	70 (**4o**)
16[c]	$Ph(CH_2)_2$	BnO	Et	90 (**4p**)
17[d]	Ph	*t*BuO	Et	88 (**4q**)
18[d]	*p*-$OMeC_6H_4$	*t*BuO	Et	81 (**4r**)
19[d]	*p*-$CF_3C_6H_4$	*t*BuO	Et	96 (**4s**)

[a] General conditions: **1/2/6** = 1.0:1.2:1.2 in CH_2Cl_2/THF (1:1, c = 0.1) followed by addition of R^3SNa **8**. [b] Yield refers to chromatographically pure product. [c] Experimental conditions: **1/2/6** = 1.0:1.2:1.2 in CH_2Cl_2 (1:1, c = 0.1) followed by evaporation of CH_2Cl_2 and addition of R^3SNa in THF. [d] Prepared from α-amidosulfone **7**.

Two plausible mechanistic pathways could be postulated for the conversion of α-amidosulfones **7** into α-amidosulfides **4** (Scheme 2): Path a: An S_N1 manifold involving formation of discrete *N*-carbamoyl imine intermediate **9** followed by addition of thiolate **3**.[15] Path b: An S_N2 mechanism involving the direct displacement of benzenesulfinate by sodium ethanethiolate (**8a**). Although the exact mechanism has not been fully elucidated, we are currently in favor of path b. Firstly, we never observed the tautomerization of

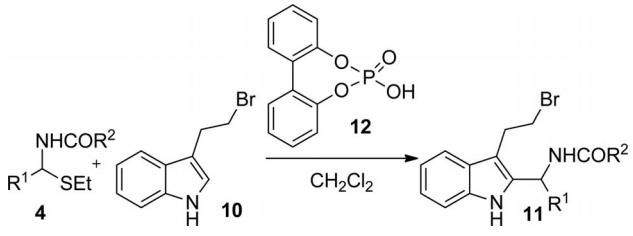


Scheme 2. S_N1 or S_N2 mechanism for the formation of α-amidosulfides **4** from **7**.

N-acyl or *N*-carbomoyl imines during these experiments,[16] which suggests a mechanism without formation of intermediate imines. Secondly, a control experiment showed that ethanethiol **3**[15] or sodium ethanethiolate (**8a**) did not react with aliphatic or aromatic *N*-Boc imines under our standard conditions.[14b,17]

Having examined the scope of this new N,S-acetal-forming reaction, our attention turned to the synthetic applications of α-amidosulfides **4** as stable precursors of imines.[5] A variety of silver salts ($AgBF_4$, AgOTf, AgOAc, Ag_2SO_4) known to have high affinity for sulfides[18] and Brønsted acids (*p*-toluenesulfonic acid, camphorsulfonic acid, acetic acid) were screened. Among them, AgOAc and *p*-toluenesulfonic acid gave the best results, converting aliphatic and aromatic α-amidosulfides **4a** and **4q**, respectively, into imines **9** at room temperature within 10 min. Encouraged by these results, we next investigated the aminoalkylation of 3-(2-bromoethyl) indole **10**[12p,12t,12u,19] with **4** for the synthesis of 2,3-disubstituted indoles **11**,[20,21] which are useful intermediates in the synthesis of tetrahydro-β-carbolines.[22] Phosphoric acids that are well established to be excellent catalysts for the Friedel–Crafts reaction were selected to promote both the imine formation and C-2 alkylation of **10**.[21a,23–25] After a survey of reaction parameters, solvents, and temperatures, the optimized conditions consist of performing the alkylation of **10** in CH_2Cl_2 in the presence of phosphoric acid **12** (20 mol-%). As shown in Table 3, α-amidosulfides **4a**–**l** and **4o**, whether linear or α-branched, effectively participate in this reaction, leading to 2-indolylmethanamines **11** in good yields. The development of an enantioselective version of this reaction is currently underway.

Table 3. Reaction of indole **10** with α-amidosulfide **4**.



Entry[a]	R^1	R^2	Yield [%][b]
1	$Ph(CH_2)_2$	Ph	87 (**11a**)
2	$Ph(CH_2)_2$	*p*-$OMeC_6H_4$	83 (**11b**)
3	$BnOCH_2$	Ph	60 (**11c**)
4	*i*Pr	Ph	85 (**11d**)
5	C_6H_{13}	Ph	75 (**11e**)

[a] General conditions: **4**/**10**/**12** = 1.0:1.5:0.2 in CH_2Cl_2. [b] Yield refers to chromatographically pure product.

Conclusions

In summary, we have described a novel one-pot, sequential three-component synthesis of α-amidosulfides from readily accessible starting materials. To the best of our knowledge, this represents the first one-pot procedure that is applicable to a wide range of aldehydes, amides or carbamates, and thiols. In view of the widespread use of α-amidosulfides as latent *N*-acylimine species, we believed that the ready accessibility of α-amidosulfides could popularize their use in organic synthesis as *N*-acylimine precursors. We stress that the conditions for generating the imine from α-amidosulfides (in the presence of soft Lewis or Brønsted acids)[12a–12l] is complementary to those from α-amidosulfones (basic conditions or in the presence of strong Lewis acid). Therefore, starting from α-amidosulfides, different reaction conditions could in principle be envisaged for performing the subsequent α-functionalization of amines.

Experimental Section

General Procedure for the One-Pot Synthesis of α-Amidosulfides 4: A flask equipped with a stirring bar and charged with anhydrous magnesium sulfate (0.83 equiv.) was placed under vacuum and flame dried. Phenylsulfinic acid (**6**, 1.2 equiv.) and amine **2** (1.2 equiv.) were added at room temperature, and the flask was purged with argon. The solids were dissolved in a mixture of THF/DCM (1:1, *c* = 0.1 M). A solution of appropriate aldehyde **1** (1.0 equiv.) was added dropwise, and the resulting reaction mixture was stirred overnight at room temperature. Sodium thiolate **8** (2.0 equiv.) was then added in one portion, and the solution was stirred for an additional 3 h, during which time the sodium sulfinate precipitated as a white solid. This residue was removed by filtration and washed with Et_2O, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on neutral aluminum oxide (heptane/EtOAc = 9:1) to give α-amidosulfides **4** as white solids.

4b: Yield: 96%. M.p. 74–75 °C. IR: $\tilde{\nu}$ = 3278, 2925, 2857, 1673, 1521, 1366, 1295, 1249, 1161, 1046, 1023 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 9 H), 1.84–2.07 (m, 2 H), 2.71 (t, *J* = 8.0 Hz, 2 H), 4.25 (d, *J* = 9.5 Hz, 1 H), 5.04–5.09 (m, 1 H), 7.05–7.45 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3 (3 CH_3), 32.7 (CH_2), 37.9 (CH_2), 58.7 (CH), 79.9 (Cq), 126.1 (2 CH), 127.8 (CH), 128.5 (2 CH), 128.5 (2 CH), 128.9 (2 CH), 132.5 (Cq), 133.7 (CH), 140.8 (Cq), 154.5 (Cq) ppm. HRMS (ESI-TOF): calcd. for $C_{20}H_{25}NO_2SNa$ $[M + Na]^+$ 366.1504; found 366.1504.

Acknowledgments

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