Rhodium-Catalyzed Reaction of Diazoacetates, Thiols and Azodicarboxylates: An Unusual 1,2-Aza Shift from a Sulfonium Ylide

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Abstract: A one-pot reaction of diazoacetates, thiols and azodicarboxylates in the presence of a dirhodium acetate catalyst gave *N*,*S*-ketals in good yields. This reaction proceeded via an unusual 1,2-aza shift from a sulfonium ylide intermediate.

Key words: one-pot reaction, diazo compounds, sulfonium ylides, *N*,*S*-ketals, rearrangement reaction

Ylides as reactive intermediates have been known to undergo synthetically useful transformations.[1] The reaction of carbenes with sulfur compounds represents a useful approach to generate sulfonium ylides. The sulfonium ylides have been extensively reported to undergo rearrangement reactions such as 1,2-Stevens[2] and 2,3-sigmatropic rearrangements.[3] Sulfonium ylides have been also useful intermediates in synthetic chemistry.[4] For example, the sulfonium ylides were utilized in the Corey–Chaykovsky reaction for oxirane formation.[5] In contrast, the reaction of carbonyl-stabilized sulfonium ylides with electrophiles was scarcely reported despite the potential usefulness in constructing complex sulfur-containing molecules. Oku's group recently reported that dirhodium(II) acetate catalyzed intramolecular reaction of diazoketones bearing a sulfide group with a Lewis acid activated aldehyde to give a carbon–carbon-bonded cyclic product.[6] However, the intermolecular reaction of carbonyl-stabilized sulfonium ylides with electrophiles is unknown.

We have recently unveiled a new type of three-component ylide trapping process, in which in situ generated ammonium and oxonium ylides were trapped by electrophiles such as imines, aldehydes, and azodicarboxylates.[7] For example, nucleophilic addition of an ammonium ylide generated from ethyl diazoacetate (EDA) and aniline to diethyl azodicarboxylate gave an aminal in good yield (Scheme 1).[7e]

We anticipated that this strategy would be applicable similarly to sulfonium ylide to afford *N*,*S*-acetal compounds. *N*,*S*-Acetal analogues were useful intermediates in the synthesis of natural and biomedicinal molecules, such as gliotoxin and HIV-protease inhibitors.[8]

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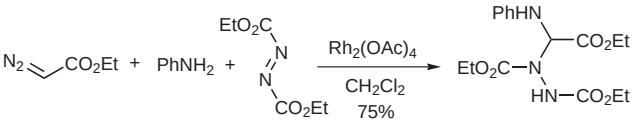
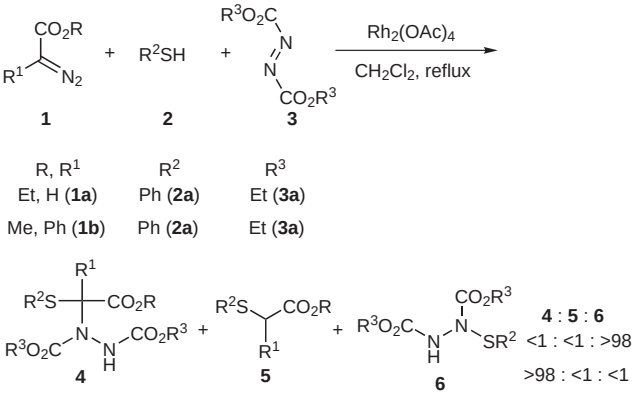


Scheme 1 The rhodium-catalyzed reaction of EDA, aniline and DEAD

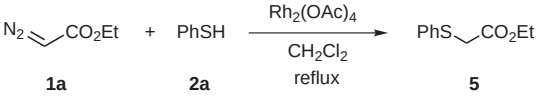
To our surprise, under similar reaction conditions, using thiophenol instead of aniline gave unexpected results. There was no three-component product formed from the reaction of EDA, diethyl azodicarboxylate, and thiophenol catalyzed by dirhodium acetate. Instead, we mainly obtained the adduct **6**, which was generated from the direct addition of thiophenol to DEAD (Scheme 2).



Scheme 2 The rhodium-catalyzed reaction of diazoacetate, thiols, and azodicarboxylates

Control experiment indicated that product **6** could be formed in 85% yield in the absence of the rhodium catalyst. In addition, the two-component reaction of EDA with benzenethiol gave the S–H insertion product in the presence of the rhodium catalyst[9] (Scheme 3).

Interestingly, different results were observed when using methyl phenyldiazoacetate instead of EDA. Hence, reaction of methyl phenyldiazoacetate, thiophenol and DEAD



Scheme 3 S–H Insertion of EDA with thiophenol

proceeded well to give the *N*,*S*-acetal **4a** in 70% yield, and the two-component side product **6** and the S–H insertion product **5** were insignificant in the reaction mixture.

A variety of thiols were employed into the reaction. As can be seen from Table 1, excellent selectivity of the three-component products to the S–H-insertion products (**4**:**5** > 99:1) was observed regardless of the electronic property of the substituents on the phenyl ring (Table 1, entries 1–3). When aliphatic thiols were used in the reaction, the ratio of **4**:**5** decreased significantly (Table 1, entries 4–6). In addition, decreased yield of **4** was obtained with the thiol bearing a β-ester functionality (Table 1, entry 7). There was no reaction occurring by using dimethylsulfide (Table 1, entry 8).

Table 1 Reaction of Methyl Phenyldiazoacetate (**1b**) with DEAD (**3a**) and Thiols **2**[a]

Entry	**2**	Yield of **4** (%)[b]	Ratio of **4**:**5**[c]
1	PhSH	70 (**4a**)	>99:1
2	*p*-NO_2PhSH	60 (**4b**)	>99:1
3	*p*-MeOPhSH	45 (**4c**)	>99:1
4	EtSH	68 (**4d**)	84:16
5	*n*-PrSH	63 (**4e**)	76:24
6	BnSH	55 (**4f**)	68:32
7	$HSCH_2CO_2Et$	35 (**4g**)	55:45
8	Me_2S	NR[d]	–

[a] All reactions were carried out in refluxing CH_2Cl_2 in the presence of $Rh_2(OAc)_4$ (1 mol%) with **1b**:**2**:**3a** = 1.0:1.1:1.2 mmol.
[b] Isolated yields after chromatography.
[c] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] No diazo decomposition occurred in refluxing CH_2Cl_2.

The scope of the reaction was further expanded to other diazoacetates and azodicarboxylates with thiophenol. The three-component reaction was found to be quite versatile to give the desired products **4** in moderate to good yields and consistently high ratio of **4**:**5** (Table 2). Lower ratio of **4**:**5** was observed when sterically hindered di-*tert*-butyl azodicarboxylate was used (Table 2, entry 4). The reaction was not limited to phenyldiazoacetates, we were pleased to find that the similar results were obtained when dimethyl diazomalonate was used (Table 2, entry 5). The structure of **4h** was conformed by single-crystal X-ray analysis (Figure 1).[10]

The major reaction pathway to form the *N*,*S* acetals **4** was found to be quite different from the ylide-trapping process proposed previously.[7] In the present study, addition of thiol to azodicarboxylate was a rapid process. We found that significant amount of **6** was formed at the time of additon of the diazo compounds. It was suspected that the formation of **4** resulted from the reaction of the diazo compounds **1** with the adduct **6**. To prove this possibility, pure **6** was prepared and isolated. Reaction of **6** with

Table 2 Reaction of Diazoacetate **1** with Azodicarboxylates **3** and Thiophenol (**2a**)[a]

Entry	R^1 (R = Me)	R^3	Yield of **4** (%)[b]	Ratio of **4**:**5**[c]
1	*p*-$MeOC_6H_4$ (**1c**)	Et (**3a**)	80 (**4h**)	>99:1
2	Ph (**1b**)	Et (**3a**)	70 (**4a**)	>99:1
3	*p*-$NO_2C_6H_4$ (**1d**)	Et (**3a**)	50 (**4i**)	>99:1
4	Ph (**1b**)	*t*-Bu (**3b**)	50 (**4j**)	83:17
5	CO_2Me (**1e**)	Et (**3a**)	67 (**4k**)	>99:1

[a] All reaction were carried out in refluxing CH_2Cl_2 in the presence of $Rh_2(OAc)_4$ (1 mol%) with **1**:**2a**:**3** = 1.0:1.1:1.2 mmol.
[b] Isolated yields after chromatography.
[c] Determined by ^{1}H NMR of crude reaction mixtures.

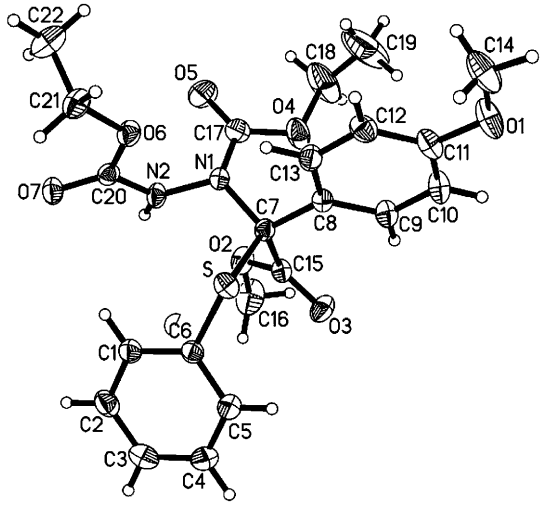
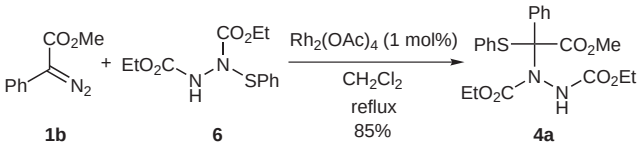


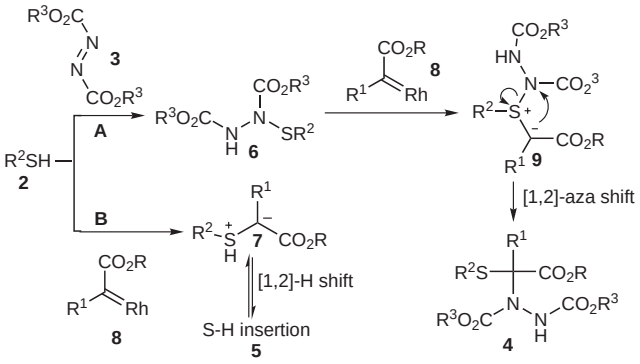
Figure 1 X-ray structure of compound **4h**

methyl phenyldiazoacetate **1b** did give **4a** in 85% isolated yield (Scheme 4).



Scheme 4 Reaction of methyl phenyldiazoacetate (**1b**) with **6**

A mechanism for this reaction is proposed in Scheme 5. There are two competitive reaction pathways involved in the reaction: (A) The adduct **6** is trapped by a carbenoid intermediate **8** to form a ylide **9**, the *N*,*S*-acetal **4** is formed by an unusual [1,2]-aza shift of **9**. A similar aza shift was reported in a ring-expanding reaction.[11] (B) The carbenoid intermediate **8** react directly with thiol **2** to give ylide **7**, which then undergoes a [1,2]-H shift to give an S–H-insertion product **5**. The ratio of **4**:**5** was much related to the relative concentration of **6**:**2** in the reaction mixture.[12]



Scheme 5 A proposed mechanism of the reaction

In conclusion, we have reported a reaction of diazoacetates, thiols, and azodicarboxylates to give sulfur-containing *N*,*S*-acetals in good yield. Although the product type is similar to that from the previous reported ammonium ylide trapping process, the current reaction proceeds via an unusual [1,2]-aza shift of the sulfonium ylides **9**.

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(10) Crystal Structure Data for **4h**. $C_{22}H_{26}N_2O_7S$, *Mw* = 462.51, colorless, Triclinic, *P1*, *a* = 10.343 (2), *b* = 10.796 (2), *c* = 11.630 (2) Å, α = 106.74 (2)°, β = 102.61 (2)°, γ = 101.02 (2)°, *V* = 1167.93 (46) Å^3, *Z* = 2, *T* = 287 (2) K, ρ_{calcd} = 1.315 Mg·m^{-3}, *F*(000) = 488, λ = 0.71073 Å, μ = 0.183 mm^{-1}, *GOF* = 0.977, *R*(*F*) = 0.0435 and *wR*(*F*)2 = 0.1061 for 4930 observed reflections, $I > 4\sigma$, 1.91° < *c* < 25.50°. CCDC 299823 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax +44 (1223)336033; or deposit@ ccdc.cam.ac.uk].

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(12) **Typical Procedure for the Reaction of Diazo Compounds with Thiols and DEAD**

To a refluxing CH_2Cl_2 (8 mL) solution of $Rh_2(OAc)_4$ (2.7 mg, 1 mol%), benzenethiol **2a** (66.0 mg, 0.60 mmol) and DEAD (143.6 mg, 0.83 mmol) under argon atmosphere was added methyl phenyl diazoacetate (**1b**, 96 mg, 0.55 mmol) in CH_2Cl_2 (4 mL) over 1 h via a syringe pump. After completion of the addition, the reaction mixture was cooled to r.t. Then, the solvent was removed. The crude product was purified by flash chromatography on silica gel by using 20% EtOAc–light PE as eluent to give a white solid **4a** in 70% yield.

Methyl 2-(*N*,*N*′-Dicarboethoxyhydrazinyl)-2-phenyl-2-(phenylthio)acetate (4a)

R_f = 0.22 (30% EtOAc–light PE); mp 126.5–128.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 7.2 Hz, 2 H), 7.20–7.39 (m, 8 H), 6.51 (s, 1 H), 4.27–4.34 (m, 2 H), 3.96–4.04 (m, 2 H), 3.66 (s, 1 H), 1.04–1.43 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.5, 156.6, 155.7, 137.9, 137.3, 130.2, 129.3, 128.6, 128.4, 127.9, 127.7, 81.7, 63.1, 62.2, 52.8, 14.5, 13.9. HRMS: *m/z* calcd for $C_{21}H_{24}N_2O_6S_1$: 455.1247; found: 455.1237 $[M + Na]^+$.