Intramolecular Cyclopropanation of Bromodiazoacetates

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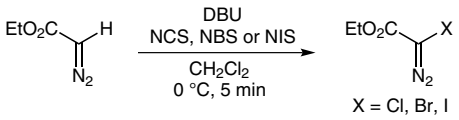
Received: 13.09.2013; Accepted after revision: 08.10.2013

Abstract: A series of allylic diazoacetates were prepared from the corresponding allylic alcohols and bromoacetyl bromide. When the allylic diazoacetates were treated with 1,8-diazabicyclo[5.4.0]undec-7-ene and *N*-bromosuccinimide, a rapid full conversion to the corresponding allylic bromodiazoacetates occurred. Exposure of the allylic bromodiazoacetates to rhodium(II) catalysts induced an intramolecular cyclopropanation and gave cyclopropyl bromolactones in yields that were low to good, depending on the substitution pattern.

Key words: cyclization, diazo compounds, fused ring system, rhodium, catalysis, carbenoids

Electrophilic rhodium(II) carbenoids are useful and versatile intermediates in organic synthesis. These highly reactive species participate in a wide range of carbon–carbon and carbon–heteroatom bond-forming reactions.[1] The most frequently encountered rhodium(II) carbenoid precursors are diazo compounds. Diazoacetates are the most widely studied class of diazo compounds and are widely used in organic synthesis.[2] We previously developed a novel and highly efficient procedure for the synthesis of halogenated analogues of ethyl diazoacetate (Scheme 1).[3]

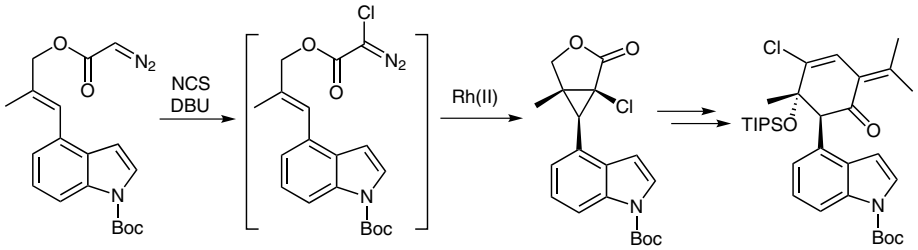


Scheme 1 Preparation of halogenated analogues of ethyl diazoacetate

Treatment of commercially available ethyl diazoacetate with a small excess of 1,8-diazabicyclo[5.4.0]undec-7-ene and an *N*-halosuccinimide results in quantitative conversion into the corresponding halogenated analogue in less than five minutes. We previously investigated the use of the resulting halodiazoacetates in rhodium(II)-catalyzed intermolecular cyclopropanation,[3] C–H insertion, and Si–H insertion reactions.[4] The mechanisms of the intermolecular cyclopropanation reactions[5] and the intermolecular C–H insertion reactions[6] have also been investigated by density functional theory calculations. The use of halodiazoacetates in carbenoid reactions represents a novel approach to the selective introduction of halogens.[7] Whereas intermolecular reactions with halodiazoacetates have been well studied, there are no published reports of any systematic investigation of the intramolecular cyclopropanation reactions of halodiazoacetates. However, there is one report of an intramolecular cyclopropanation of a chlorodiazoacetate that demonstrates the usefulness of this intramolecular reaction. Zhang and Tang used electrophilic chlorination to produce an indole-derived chlorodiazoacetate that underwent subsequent intramolecular cyclopropanation as a key step in their total synthesis of the cyclohexanone core of the biologically very interesting welwitindolinone C series of compounds (Scheme 2).[8]

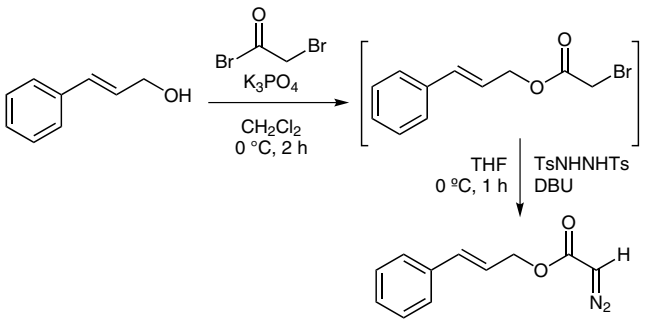
Here we describe a systematic study of the synthesis of a range of allylic bromodiazoacetates and their subsequent intramolecular cyclopropanation reactions in the presence of rhodium(II) catalysts.

Various ways of synthesizing diazo compounds have recently been reviewed.[9] In the search for an efficient synthesis of allylic diazoacetates from allylic alcohols, we screened several of the known methods, and we found the procedure developed by Toma and co-workers[10] to be the best for our purposes. We chose to optimize the reaction conditions by using cinnamyl alcohol as the substrate (Scheme 3).



Scheme 2 Zhang and Tang's electrophilic α-diazoacetate chlorination and subsequent intramolecular cyclopropanation[8]

SYNLETT 2014, 25, 0221–0224
Advanced online publication: 02.12.2013
DOI: 10.1055/s-0033-1340170; Art ID: ST-2013-D0877-L



Scheme 3 Synthesis of cinnamyl diazoacetate

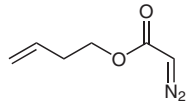
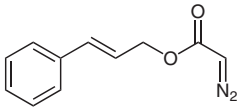
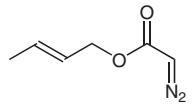
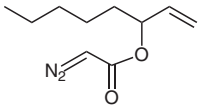
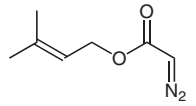
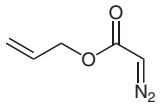
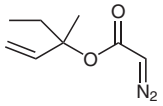
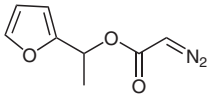
We modified the literature procedure slightly, and found that the yield increased substantially when we changed the base from potassium carbonate to potassium phosphate and extended the reaction time from ten minutes to two hours. Furthermore, excess *N*,*N*′-ditosylhydrazine, present after the workup, co-eluted with the product during column chromatography. This problem in purifying the product was solved by washing the organic phase with 0.1 M aqueous sodium hydroxide before performing the chromatographic purification. By using the optimized reaction conditions, we synthesized a series of allylic diazoacetates from commercially available allylic alcohols (Table 1).

With primary and secondary allylic alcohols, the yields were generally high; however, the reaction became more sluggish and gave a lower yield when a tertiary allylic alcohol was used as the substrate.

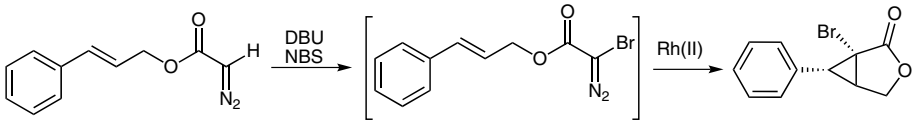
We used cinnamyl diazoacetate as a substrate to optimize the reaction conditions for the synthesis of the desired allylic bromodiazoacetates and for the subsequent intramolecular cyclopropanation reaction (Scheme 4).

We began by using our previously developed procedure for the bromination of ethyl diazoacetate (Scheme 1).[3] The halogenated analogues of ethyl diazoacetate are unstable when neat and handled at room temperature, but they can be conveniently handled in solution at 0 °C. We therefore expected that cinnamyl bromodiazoacetate would have similar thermal stability. The cinnamyl bromodiazoacetate was kept in solution at 0 °C during workup and purification, and the solution was used directly in the next step. The yield was measured over two steps for the isolated cyclopropyl bromolactone. We varied several of the reaction conditions, such as the catalyst, temperature, addition rate, order of addition, and concentration to optimize the reaction conditions, and we used an aqueous sodium thiosulfate ($Na_2S_2O_3$) workup instead of silica gel plug filtration. The highest isolated yield in the catalyst-screening process was 62%, obtained with tetrakis(1-{[4-alkyl(C_{11}–C_{13})phenyl]sulfonyl}-(2*S*)-pyrrolidinecarboxylate)dirhodium(II) [Rh_2(*S*-DOSP)$_4$], which gave an average 80% yield for the bromination and intramolecular cyclopropanation steps. However, the enantioselectivity of the bromocyclopropane was only 4%, which made us choose the best nonchiral catalyst, bis{rhodium[3,3'-(1,3-phenylene)bis(2,2-dimethylpropanoic acid)]} [Rh_2(esp)$_2$],[11] for our systematic study. This was also found to be the best catalyst in Zhang and Tang's study.[8] In a control experiment, we exposed cinnamyl diazoacetate to Rh_2(esp)$_2$, under otherwise identical conditions to those used for cinnamyl bromodiazoacetate, and we observed rapid decomposition of the diazo compound; however, the crude product mixture did not contain any

Table 1 Yields of Allylic Diazoacetates from Allylic Alcohols and Bromoacetyl Bromide

Allylic diazoacetate	Yield[a] (%)
	99
	82
	76
	75
	65
	60
	58
	36

[a] Isolated yield after silica gel chromatography.

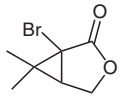
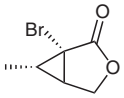
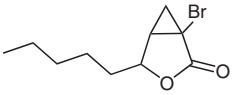
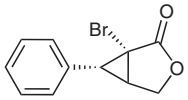
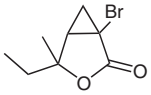
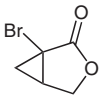
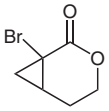
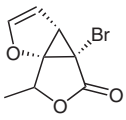


Scheme 4 Synthesis of cinnamyl bromodiazoacetate

bicyclic lactone formed by intramolecular cyclopropanation.

We then exposed the allylic diazoacetates listed in Table 1 to *N*-bromosuccinimide and 1,8-diazabicyclo[5.4.0]undec-7-ene in dichloromethane at 0 °C. When bromination was complete (about 5 min), we changed the solvent to toluene and we used $Rh_2(esp)_2$ as the catalyst for the intramolecular cyclopropanation step, keeping the temperature at 0 °C. The $Rh_2(esp)_2$-catalyzed decomposition of the bromodiazoacetates was complete within a few seconds. The results from our systematic study are shown in Table 2. The reported yields are for both the bromination and the intramolecular cyclopropanation steps; combined yields of up to 68% were obtained for the best substrates.

Table 2 Yields of Bicyclic Bromolactones

Bicyclic bromolactone	Yield[a]
	68
	64
	44[b]
	44
	29[c]
	18
	15
	–

[a] Isolated yield for two steps determined by silica gel chromatography.
[b] dr = 2:1 (by ^{1}H NMR).
[c] dr = 3:1 (by ^{1}H NMR).

The general trend with respect to the yield appears to follow the substitution pattern on the olefin. Substrates with a terminal olefin group gave the lowest yields, the substrate with a terminal *gem*-disubstituted olefin group gave the highest yield (68%), and substrates with disubstituted olefins gave moderate yields. The yields for the chlorination and subsequent intramolecular cyclopropanation reported in Zhang and Tangs's study[8] were 50–60% and correspond well with those obtained in our study.

In summary, we have developed an efficient synthetic protocol[12] for the synthesis of allylic bromodiazoacetates and cyclopropyl bromolactones. The allylic bromodiazoacetates are thermally unstable at room temperature, but can be conveniently handled in solution at 0 °C. Exposure of the allylic bromodiazoacetates to birhodium(II) catalysts induced a very rapid intramolecular cyclopropanation. The yields for the $Rh_2(esp)_2$-catalyzed intramolecular cyclopropanation of the allylic bromodiazoacetates varied from low to good, but were considerably lower than those for intermolecular cyclopropanation of styrene with halogenated analogues of ethyl diazoacetate.[3] It is apparent that there is an unexplored potential for further development of the catalyst with respect to both the yield and enantiomeric induction in the intramolecular cyclopropanation reaction. Further studies on the reactivity and stability of halodiazoacetates, halodiazoamides, and halodiazophosphonates are in progress and will be reported in due course.

Acknowledgment

Financial support by the Chemistry Department, University of Oslo is gratefully acknowledged. We would like to thank Mr. Osamu Sekiguchi for his assistance with mass spectrometric analyses.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **Cyclopropyl Bromolactones; General Procedure**
DBU (1.3 equiv) and NBS (1.2 equiv) were added sequentially to a solution of the allylic diazoacetate (1.0 equiv) in CH_2Cl_2 (5.0 mL/mmol diazo substrate) at 0 °C, and the solution was stirred for 15 min. The solution was then washed with 20% aq $Na_2S_2O_3$ (6 × 6 mL/mmol diazo substrate), and the aqueous phases were extracted with CH_2Cl_2 (6.0 ml/mmol diazo substrate) at 0 °C. The organic

phases were combined, dried ($MgSO_4$), and filtered through a plug of silica gel, with elution by CH_2Cl_2 cooled to 0 °C. The filtered soln was diluted with toluene (10 mL/mmol diazo substrate) and the CH_2Cl_2 was removed in vacuo at 0 °C. To the rapidly stirred toluene solution of the resulting allylic bromodiazoacetate at 0 °C under N_2 was added a solution of $Rh_2(esp)_2$ (1 mol%) in toluene (2 mL/mmol diazo substrate), and the resulting mixture was stirred for 15–25 min. The solvent was removed in vacuo, and the crude product was purified by flash chromatography (silica gel).

1-Bromo-6-phenyl-3-oxabicyclo[3.1.0]hexane-2-one
White solid; 96.6 mg (44% yield); mp 117–118 °C; R_f = 0.33 (20% EtOAc–hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.58 (d, *J* = 5.1 Hz, 1 H), 2.87 (ddd, *J* = 0.6, 4.7, 5.1 Hz, 1 H), 4.39 (dd, *J* = 0.6, 9.6 Hz, 1 H), 4.59 (dd, *J* = 4.7, 9.6 Hz, 1 H), 7.17–7.40 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.6, 34.2, 35.8, 68.5, 128.1, 128.5, 128.7, 132.9, 172.1. MS (EI): *m/z* (%) = 254/252 (0.5/0.5) [M^+], 174 (25), 173 (100), 145 (34), 128 (30), 115/117 (85/85), 91 (37). HRMS: *m/z* calcd for $C_{11}H_9O_2Br$: 251.9779; found 251.9786 (Δ 2.5 ppm).

