ORGANIC LETTERS

2000
Vol. 2, No. 8
1077−1079

A Trans-Stereoselective Synthesis of 3-Halo-4-alkyl(aryl)-NH-azetidin-2-ones

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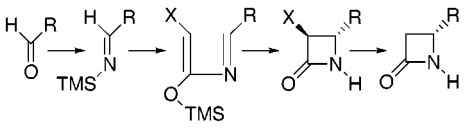
Received February 7, 2000

ABSTRACT



Conrotatory ring closure of 1-halo-3-aza-4-alkyl-1,3-dienes in refluxing toluene gives rise to 3-halo-4-aryl-2-azetidinones in satisfactory yields. Dehalogenation of the resulting β-lactams by tris(trimethylsilyl)silane furnished 3-unsubstituted azetidinones, valuable intermediates in the synthesis of biologically active compounds.

The utilization of 2-aza-1,3-dienes for preparation of the β-lactam ring was explored by our group.[1] In this paper we report a trans-stereoselective synthesis of 3-halo-4-arylazetidin-2-ones and 3-halo-4-[1-(triialkylsilyloxy)alkyl]azetidin-2-ones.

α-Halo-β-lactams are versatile synthons in constructing a wide variety of functionalized lactams.[2] Major transformations directed at the C_α-halogen center include reduction, metalation, alkylation, and replacement by azide. Notable routes to α-halo-β-lactams are cycloaddition of haloketenes to imine[3] and thermal decomposition of [*N*-(dihaloacetyl)-piperidinyl]phenyl mercury.[4] More recently, a nickel-promoted cyclization route,[5] a catalytic Hunsdiecker,[6] and a synthesis of 3-halo-β-lactams from α,β-unsaturated *N*-sulfonamides[7] have been reported. New procedures for the synthesis of 3-halo-4-substituted-β-lactams are welcomed since these compounds allow a faster and easier synthesis of substituted β-lactams, which are known to be useful compounds with potential applications as β-lactamases or inhibitors of 3-hydroxy-3-methyl glutarate coenzyme A synthase, human leukocyte elastase, poliovirus, and human rhinovirus C3-proteinase.[8]

Following our published general protocol on the synthesis of the β-lactam ring using a two-step Staudinger reaction,[9] we synthesized azadiene **4** starting from *N*-(trimethylsilyl)-arylmethanimine **2**[10,11] and α-haloacetyl chloride **3** in the presence of TEA as base.[12] Identification of **4** and the relative stereochemical assignments were obtained by ^{1}H NMR

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(9) For an up-to-date review on [2 + 2] cycloadditions of imines and ketenes, see: Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223. See also: Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993; pp 295−368.

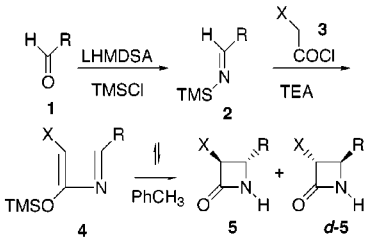
(10) For the synthesis and chemistry of *N*-silyl imines see: Panunzio, M.; Zarantonello, P. *Org. Process Res. Dev.* **1998**, *2*, 49

(11) For [2 + 2] cycloaddition of *N*-silyl imines and ketenes, see also: Bennet, D. M.; Okamoto, I.; Danheiser. R. L. *Org. Lett.* **1999**, *1*, 641.

10.1021/ol005633x CCC: $19.00
Published on Web 03/30/2000

spectra. Refluxing **4** in toluene overnight resulted in the formation of *trans*-β-lactam **5** as single stereoisomer (J_{3-4} = 1.5−2.5 Hz) (Scheme 1 and Table 1). The presence of

Scheme 1

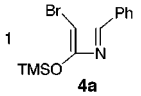
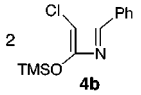
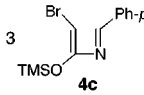
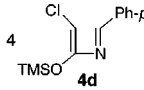
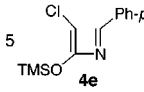
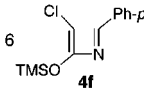


X=Cl, Br
R=Ph, p-Cl-Ph, p-NO_2-Ph, p-MeO-Ph
-CH(OTIPS)CH_3, -CH(OTBDMS)CH_3;
-CH(OTBDMS)CH_2CH_3
-CH(OTIPS)$CH(CH_3)_2$, -CH(OTBDMS)$C(CH_3)_3$,
-CH(OTIPS)Ph, -CH(OTBDMS)Ph

EWG or EDG in the para-position of the aromatic ring of the imine substituents does not have any effect on the stereochemical outcome of the reaction (Table 1, entries 3−6). As a matter of fact no cis-stereoisomer was detected in the crude reaction mixture.

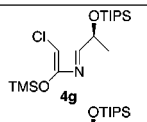
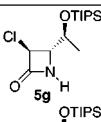
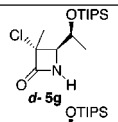
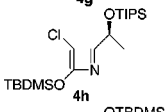
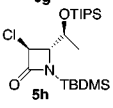
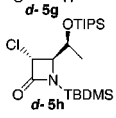
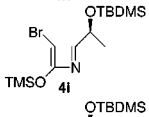
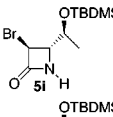
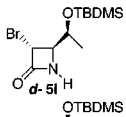
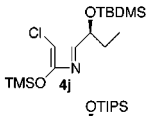
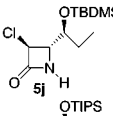
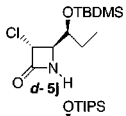
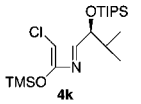
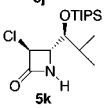
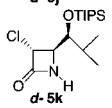
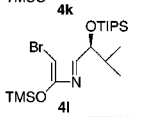
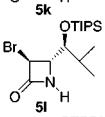
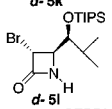
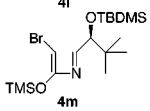
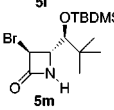
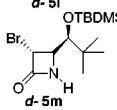
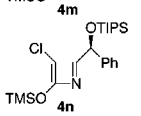
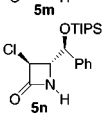
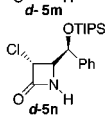
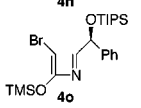
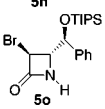
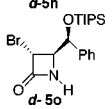
Application of this protocol to *N*-trimethylsilyl alkyl imines **2** containing a stereogenic center in the imine moiety once again results in the formation of the sole *trans*-azetidinones **5** and ***d*-5** through the azadiene **4**. Of the four possible stereoisomers only the two trans-isomers were obtained (Scheme 1 and Table 2). The ratio of the isomers were determined by ^{1}H NMR spectroscopy, and separation of the

Table 1. Synthesis of Azetidinones **5**

Entry	Azadiene	β-Lactams[a]	Yield
1	 **4a**	 **5a**	40
2	 **4b**	 **5b**	37
3	 **4c**	 **5c**	35
4	 **4d**	 **5d**	31
5	 **4e**	 **5e**	45
6	 **4f**	 **5f**	55

a: Racemic mixture. For the sake of simplicity only one enantiomer has been reported.

Table 2. Synthesis of Azetidinones **5** and *d*-**5**

Entry	Azadiene	β-Lactams	Yield	Ratio **5**/*d*- **5**
1	 **4g**	 **5g**	 ***d*- 5g**	55	50/50
2	 **4h**	 **5h**	 ***d*- 5h**	65	52/48
3	 **4i**	 **5i**	 ***d*- 5i**	43	50/50
4	 **4j**	 **5j**	 ***d*- 5j**	28	56/44
5	 **4k**	 **5k**	 ***d*- 5k**	69	66/34
6	 **4l**	 **5l**	 ***d*- 5l**	53	52/48
7	 **4m**	 **5m**	 ***d*- 5m**	32	72/28
8	 **4n**	 **5n**	 ***d*-5n**	37	39/61
9	 **4o**	 **5o**	 ***d*- 5o**	46	33/67
10	**4p**	**5p**	***d*- 5p**	39	50/50

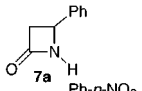
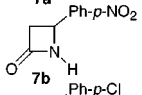
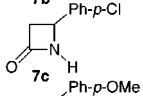
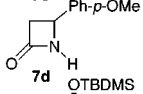
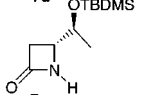
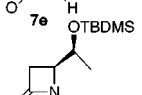
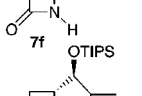
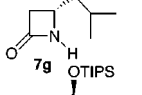
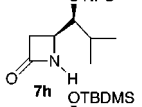
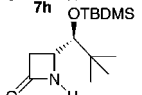
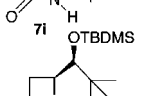
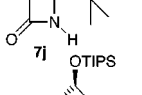
products by flash chromatography on silica gel yielded the pure isomers. The trans-configuration was established by ^{1}H NMR spectroscopy, and the relative configuration of the β-lactams was determined by comparison with previously prepared similar compounds. No particularly appreciable effect was obtained on the facial stereochemical outcome when changing the steric requirement of the trialkylsilyl groups directly linked to the enolic oxygen as well as to the ethereal oxygen (Table 2, entries 2, 3, 9, and 10).

A useful modification of the so-obtained β-lactams has been achieved with a new dehalogenation procedure by means of the recently developed tris(trimethylsilyl)silane.[13] Treatment of α-haloazetidinone **5** in toluene with commercially available tris(trimethylsilyl)silane **6** (100 °C, 2 h) in the presence of AIBN furnished the 3-unsubstituted azetidinones **7** in good yields (Scheme 2 and Table 3).

Scheme 2

5 **7**

Table 3. Synthesis of Azetidinones **7**

Entry	Starting	Product	Yield
1	**5a**	 **7a**	79
2	**5c**	 **7b**	74
3	**5e**	 **7c**	85
4	**5f**	 **7d**	67
5	**5i**	 **7e**	78
6	***d*-5i**	 **7f**	65
7	**5l**	 **7g**	86
8	***d*-5l**	 **7h**	70
9	**5m**	 **7i**	73
10	***d*-5m**	 **7j**	69
11	**5o**	 **7k**	70
12	***d*-5o**	 **7l**	74

The resulting 3-unsubstituted azetidinones may be used as useful intermediates for the synthesis of carbapenem antibiotics as well as Monobactams inhibiting the human cytomegalovirus protease.[14] Work in this direction is ongoing.

In this paper we have reported a new application of our two-step protocol for the synthesis of azetidinone ring by [2 + 2] reaction. Although the final yields are not very high (the yields in azetidinone reported are based on the starting aldehydes), they can be considered satisfactory taking into account the three-step process. The isolation and stereochemical identification of the neutral intermediates **4** and the elaboration[15] of 3-haloazetidinones to 3-unsubstituted azetidinone by a new dehalogenation procedure confers an extra interest to this contribution.

Acknowledgment. This work was supported by the Progetto Strategico "Applicazioni Industriali della Tecnologie delle Microonde-CNR Rome". Thanks are due to Biosearch Italia S.p.A. for financial suppport.

Supporting Information Available: Experimental procedures, characterization data, and ^{1}H NMR spectra for azadienes, and cycloaddition and reduced products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL005633X

(12) Synthesis and applications of azadiene in HDA reaction have been studied extensively by Ghosez and co-workers. See: (a) Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617. (b) Ghosez, L.; Jnoff, E.; Beaudegnies, R.; Bayard, P.; Sainte, P. *Tetrahedron* **1999**, *55*, 3387. (c) Ntirampebura, D.; Ghosez, L. *Tetrahedron Lett.* **1999**, *40*, 7079. (d) Ghosez, L. *Pure Appl. Chem.* **1996**, *68*, 15. (e) Ghosez, L.; Bayard, P.; Nshimyumukiza, P.; Gouverneur, V.; Sainte, F.; Beaudegnies, R.; Rivera, M.; Frisque-Hesbain, A. M.; Wynants, C. *Tetrahedron* **1995**, *51*, 11021 and references therein cited. See also: (a) Bongini, A.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *J. Org. Chem.* **1997**, *62*, 8911. (b) Panunzio, M.; Villa, M.; Missio, A.; Rossi, T. Seneci, P. *Tetrahedron Lett.* **1998**, *39*, 6585. (c) Bandini, E.; Martelli, G.; Spunta, G.; Bongini, A.; Panunzio, M.; Piersanti, G. *Tetrahedron: Asymmetry* **1997**, *8*, 3717. (d) Bandini, E.; Bongini, A.; Martelli, G.; Panunzio, M.; Piersanti, G.; Spunta, G. *Tetrahedron: Asymmetry* **1999**, *10*, 1445. (e) Bandini, E.; Martelli, G.; Spunta, G.; Bongini, A.; Panunzio, M. *Synlett* **1999**, 1735.

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(15) The stereochemical assignments were deduced by NOE experiments.