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Diastereoselective Synthesis of Carbapenams via Kinugasa Reaction

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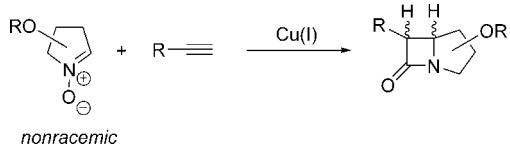
Received June 5, 2008

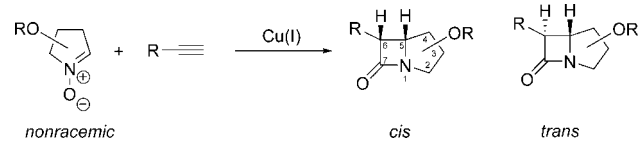


A facile approach to carbapenams via Kinugasa reaction between terminal copper acetylides and nonracemic cyclic nitrones derived from malic and tartaric acid is reported. The stereochemical preferences observed in these reactions are explained. The reaction provides an entry to the carbapenams basic skeleton.

The β-lactam antibiotics represent the most powerful tool against the bacterial infections. Owing to their attractive biological activity, the synthesis and properties of mono- and polycyclic systems containing the β-lactam ring have been extensively investigated.[1] The history of β-lactams goes back to 1907 when Staudinger discovered the imine-ketene cycloaddition.[2] To date, a number of methodologies for the β-lactam ring construction in both diastereoselective and enantioselective manner have been developed.[3] Some of these methods have also found application in syntheses of the non-β-lactam compounds.[3]

In 1972 Kinugasa and Hashimoto reported a convergent route to β-lactams through the reaction between copper phenyl acetylides and nitrones.[4] Four years later, Ding and Irwin proposed the mechanism of the Kinugasa reaction, which involved the 1,3-dipolar cycloaddition and subsequent rearrangement of the intermediate isoxazoline.[5] Later on, Miura and co-workers developed a first catalytic version of this reaction with a substoichiometric amount of CuI.[6] The same authors reported also a first asymmetric version of the Kinugasa reaction using chiral bisoxazoline ligands.[6] In following years, the extended asymmetric versions of the Kinugasa reaction have been proposed by groups of Basak,[7] Fu,[8] Tang,[9]and Guiry.[10]

SCHEME 1



In previous attempts, mostly the acyclic nitrones have been tested.[5−10] Only a limited number of examples of the use of cyclic 1,3-dipole have been reported to date. These tend to offer, however, a poor yield of the bicyclic β-lactams.[5] In connection with our interest in the synthesis of β-lactams,[11] as well as in the 1,3-dipolar cycloadditions involving cyclic nitrones,[12] we decided to investigate, for the first time, a general and a highly stereoselective approach to the construction of the carbapenams basic skeleton, using Cu(I)-mediated cycloaddition of nonracemic nitrones and simple acetylenes (Scheme 1).

In this Note, we report our preliminary studies on the Kinugasa reaction involving cyclic nitrones **1**−**3** and simple, terminal acetylenes **4a**−**f**. Both nitrones **1** and **2** are readily available from *S*-malic acid,[13] whereas nitrone **3** is derived from L-tartaric acid.[13]

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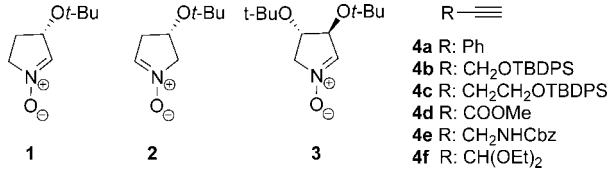
10.1021/jo801212q CCC: $40.75
Published on Web 08/08/2008



The reaction of nitrone **1** with phenylacetylene gave two bicyclic products **5a** and **6a** in a ratio of about 85:15, respectively. The configuration of both compounds was assigned by the NMR spectra and NOE experiments. For **5a**, the configuration assignment was confirmed by the X-ray crystal structure analysis.[14] Our initial experiments were carried out in degassed MeCN using 1 equiv of Et_3N and 1 equiv of CuI. Unfortunately, the yield of the reaction did not exceed 56% even after 20 h. Further extension of the reaction time led to the increase of the amount of the 5,6-*trans* product **6b** only (Table 1, entry 2). The replacement of the triethylamine by a bulky amine (Table 1, entries 3 and 4) resulted in an increase of the diasteroselectivity up to 96% but simultaneously decreased the overall reaction yield. The use of other amines such as pyridine or *N*,*N*,*N*′,*N*′-tetramethylethylenediamine did not improve the reaction outcome (Table 1, entries 5 and 6).

The careful analysis of the reaction revealed that the cyclic nitrone readily undergoes the Cu(I)-mediated deoxygenation. This process is well-known in literature.[15] The rate of the side reaction is similar to that of the cycloaddition, which explains the poor yield of the β-lactam. Moreover, the fast decomposition of the nitrone and simultaneous deactivation of copper eliminated the possibility to carry out the catalytic version of the reaction. In an experiment with 10 mol % of CuI, only a trace of products was detected. It was found that the addition of hydrazine monohydrate (20 mol %) to the reaction mixture stopped the deoxygenation process and allowed a significant increase of the yield.[16] At the same time we observed, however, a decrease of the stereoselectivity (Table 1, entries 7 and 8). The replacement of triethylamine by hydrazine resulted in decrease of both the yield and the diastereoselectivity.

Having optimized the reaction conditions, we attempted to test the scope of this reaction (Table 2). The use of other acetylenes **4b**−**f** provided products with a high diastereoselectivity but rather a poor yield (Table 2). In all cases, the *anti*-approach to the *t*-BuO was observed and the 5,6-*cis* penams **5a**−**f** were obtained as a major component. For acetylenes **4b**, **4c**, and **4e** only a trace amount of 5,6-*trans* products was observed in the NMR spectra and HPLC but they were not isolated. The ethyl propiolate **4d** gave only the *trans*-product **6d**, which underwent a rapid decomposition, probably by the β-elimination process.[17]

In case of acetylenes having silyl (**4b**−**c**) or Cbz (**4e**) protections, addition of hydrazine monohydrate to the reaction mixture decreased the reaction yield. For compounds **4b**, **4c**, and **4e** a hydrazine-mediated deprotection of hydroxyl or amine group was also observed. Similar results were also observed when the anhydrous hydrazine was used.

(14) Complete crystallographic data for the structural analysis of **5a** have been deposited with Cambridge Data Center, CCDC 686539.

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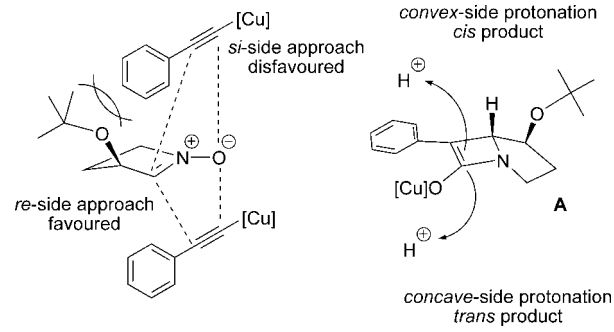
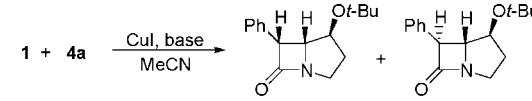


FIGURE 1

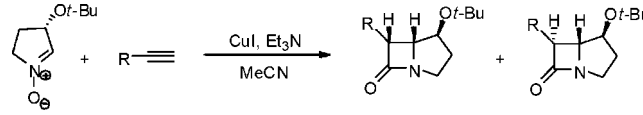
TABLE 1. Effect of Base and Additives on the Kinugasa Reaction



entry	amine[a]	time [h]	yield [%]	*cis*:*trans*[b]
1	Et_3N	20	56	85:15
2	Et_3N	48	58	52:48
3	*i*-Pr_2NEt	20	38	98:2
4	(*c*-$C_6H_{11})_2NMe$	21	50	95:5
5	pyridine	22	10	54:46
6	TMEDA	20	26	55:45
7	Et_3N	24	80[c]	74:26
8	Et_3N	48	70[c]	60:40
9	$NH_2NH_2 \cdot H_2O$	21	58	70:30

[a] Standard condition: nitrone (2 equiv), acetylene (1 equiv), base (1 equiv), CuI (1 equiv) in MeCN. [b] According to HPLC. [c] With 20 mol % of $NH_2NH_2 \cdot H_2O$.

TABLE 2. Reaction of Nitrone 1 with Acetylenes 4a−f[a]

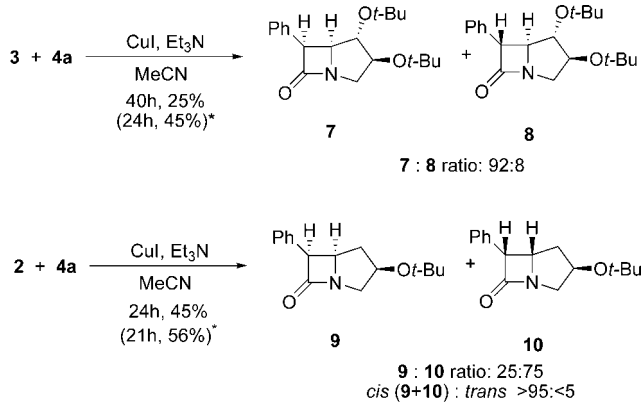


entry	R		time [h]	**5**:**6** ratio	yield [%]
1	Ph	**4a**	20	85:15	56
2[b]	Ph	**4a**	24	74:26	80
3	$CH_2OTBDPS$	**4b**	20	>95:<5	33
4[b]	$CH_2OTBDPS$	**4b**	22	>95: <5	15
5	$CH_2CH_2OTBDPS$	**4c**	23	>95: <5	32
6[b]	$CH_2CH_2OTBDPS$	**4c**	23	>95:<5	10
7[c]	$CH_2CH_2OTBDPS$	**4c**	23	>95:<5	15
8	COOEt	**4d**	24	0:100	10[d]
9	CH_2NHCbz	**4e**	23	>95:<5	36
10[b]	CH_2NHCbz	**4e**	22	>95:<5	13
11	$CH(OEt)_2$	**4f**	22	85:15	72
12[b]	$CH(OEt)_2$	**4f**	23	83:17	44

[a] Standard condition: nitrone (1.3 mmol), acetylene (1 mmol), Et_3N (1 mmol), CuI (1 mmol), MeCN (3 mL). [b] In the presence of 20 mol % $NH_2NH_2 \cdot H_2O$. [c] In the presence of 20 mol % anhydrous NH_2NH_2 and 1 equiv anhydrous K_2CO_3. [d] Product undergoes fast decomposition.

It should be pointed out that the stereochemical outcome of the Kinugasa reaction is controlled by the initial cycloaddition step leading to the isoxazoline intermediate. The cycloaddition step determines the configuration at the bridgehead carbon atom. Two possible approaches of acetylide to the nitrone are depicted in Figure 1. The approach of acetylide to the *si* side of the nitrone (*syn* to *t*-BuO) is disfavored due to the steric interactions. The lack of steric hindrance for the nitrone *re* side makes the

SCHEME 2



* in presence of 20 mol % NH_2NH_2-H_2O

approach from that direction more favorable. Owing to that, the cycloaddition step proceeded with a high diastereoselectivity, and only products with a *cis* arrangement of the *t*-BuO group and the bridgehead proton were obtained. According to the mechanism proposed by Fu,[8] subsequently the rearrangement of the enolate **A** to β-lactams **5/6** occurs (Figure 2). The protonation of the less shielded side (convex) of the double bond leads to the 5,6-*cis* β-lactams, whereas the protonation of the more shielded concave side gives thermodynamically more stable 5,6-*trans* products. This explains very well a high diastereoselectivity of the reaction with acetylenes bearing a bulky group, or when the reaction is carried out in the presence of hindered amines. The basic conditions of the reaction cause epimerization at the C-6 carbon atom upon extension of the reaction time, which resulted in marked decrease of the 5,6-*cis/trans* selectivity (**5**:**6** ratio).

The introduction of a second *t*-BuO group to the nitrone (**3**) did not affect the stereochemical outcome of the cycloaddition step, and the 5,6-*cis* penam (**7**) was formed as a major product. The shift of the *t*-BuO group from C-3 to C-4 of the nitrone moiety (**2**), however, did change the observed diastereoselectivity significantly (Scheme 2).

Due to the lack of steric interactions, both nitrone faces are accessible, and the approach of acetylide to the nitrone **2** may occur from both sides. The decreased facial selectivity led to the formation of two 5,6-*cis* products **9** and **10** in ratio of 1:3, respectively. The increased content of **10** indicates that the *anti*-approach of acetylide with respect to the 3-*t*-BuO group in the nitrone is more favorable than the *syn*-approach (Scheme 2).

We have presented the stereoselective synthesis of carbapenams via Kinugasa reaction involving readily available cyclic nitrones. As it has been shown, the diastereoselectivity of the reaction, which is controlled by the 3-*tert*-butoxy group of nitrone, is high, and the 5,6-*cis* carbapenam is a major product. The 5,6-*cis*/*trans* ratio depends on the structure of acetylene as well as the type of amine used. Due to the nitrones' deoxygenation process mediated by Cu(I), the products were obtained in a poor yield. It was found, however, that in some cases the addition of hydrazine to the reaction mixture stopped this side reaction and consequently allowed increase of the reaction yield. Owing to the presence of the *tert*-butyl-protected hydroxyl group in the five-membered ring and a variety of substituents at C-6 of the penam skeleton, further transformations of adducts or introduction of new substituents is possible.

Experimental Section

Reaction of Nitrones with Acetylenes. General Method. To a suspension of CuI (1 mmol) in dry, degassed acetonitile (3 mL) were added triethylamine (1 mmol) and hydrazine monohydrate (0.2 mmol) under nitrogen. After cooling to 0 °C acetylene **4** was added (1 mmol). The mixture was stirred for 10 min, and then a solution of nitrone (2 mmol) in acetonitrile was added slowly at 0 °C. After next 30 min the mixture was warmed up and stirred at room temperature under nitrogen. The progress of the reaction was monitored by TLC. At the end, buffer solution (pH 7) and ethyl acetate were added. The aqueous layer was washed with ethyl acetate, and the combined organic layers were dried over anhydrous sodium sulfate. After removal of solvent, the residue was purified by column chromatography.

Acknowledgment. Authors are grateful to Prof. Grzegorz Mlostoń (University of Łódź, Poland) for fruitful discussion and advices. Financial support for this work was provided through the Polish Ministry of Science and Higher Education, grant PBZ-KBN-126/T09/08/2004.

Supporting Information Available: Experimental procedures, characterization data of compounds **5a**−**c**, **5e, f**, **6a, f**, **7**, **9** and **10** and crystallographic information file of **5a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801212Q