Kinugasa Reaction under Click Chemistry Conditions

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Abstract: Various monocyclic β-lactams, both *cis* and *trans*, have been successfully prepared via Kinugasa reaction mimicking the click chemistry conditions.

Key word: Kinugasa reaction, nitrone, β-lactam, click chemistry

Amongst the various heterocyclic ring systems, β-lactams are possibly one of the best-known and most widely investigated.[1] This is primarily due to their antibacterial activity, which has so far quite successfully withstood the onslaught of resistant bacterial infections (e.g. Augmentin) and their ability to act as synthetic intermediates.[2] Ever since the discovery of β-lactams, organic chemists have unraveled various strategies for the synthesis of the strained 4-membered 2-azetidinone ring. Among these, Kinugasa reaction,[3] involving a Cu(I)-catalyzed cycloaddition between a nitrone and a terminal acetylene has been largely neglected. It is only due to recent reports from Fu's[4] as well as our[5] laboratories that this reaction caught the attention of the scientific community.[6] The usual way of carrying out Kinugasa reaction is to add the solution of a nitrone in acetonitrile or DMF to an in situ generated Cu(I) acetylide (acetonitrile or DMF). In the original paper, Kinugasa and Hasimoto[3] used pyridine as the solvent. The mechanism as proposed by Ding and Irwin[7] involves the 1,3-dipolar cycloaddition between the metal acetylide and the nitrone to form the isoxazoline which then collapses to the β-lactam. The alkyne–nitrone cycloaddition which would normally occur under refluxing conditions takes place at room temperature (or even at 0 °C) in the presence of Cu(I). Recently, a new concept called click chemistry[8] has been developed to generate what are known as click chemistry products, involving the high-yielding cyclization of terminal alkyne and azide at room temperature in the presence of Cu(I). The latter was generated via reduction of $CuSO_4$ by sodium ascorbate. The proposed mechanism of click chemistry[9] is strikingly similar to what has been proposed for Kinugasa reaction. The logical conclusion that can be immediately drawn is that perhaps the Kinugasa reaction would work under similar conditions. Tang et al.[10] have earlier reported the use of Cu(II) perchlorate to carry out the Kinugasa reaction. These authors used the acetylide to reduce Cu(II) to Cu(I). The use of ascorbate is simpler and more convenient. In this paper, we reveal our success in synthesizing various monocyclic β-lactams in moderate to good yields mimicking click chemistry conditions. In some cases, the click chemistry conditions resulted in improved yield.

The Kinugasa reaction is occasionally accompanied by side products. The main side reaction is the oxidative dimerization of the terminal acetylene (Glaser coupling)[11] and the formation of exomethylene β-lactam with propargyl alcohol.[5e] The dimerization is due to the presence of Cu(II) which often contaminates Cu(I) or might have been generated during the course of the reaction. By carrying out the reaction in a reductive atmosphere (in the presence of ascorbic acid), such dimerization can be prevented. This may also ensure the use of Cu(I) in catalytic amount. With all these facts in mind, as an initial experiment, the various alkynes were dissolved in DMF along with Et_3N at 0 °C. The solution was then added to an aqueous solution of $CuSO_4$ (1 equiv) which was pretreated with sodium ascorbate (2 equiv) for 30 minutes. The various nitrones[12] dissolved in DMF were added to the reaction mixture. The reaction was complete in about 16–25 hours after which it was worked up and the *cis* and *trans* β-lactams were isolated by silica gel chromatography.[13] The reaction gave almost similar results if $CuSO_4$ was replaced with $Cu(OAc)_2$. The presence of L-ascorbate is an absolute necessity, as the reaction did not work in its absence, thus ruling out the involvement of Cu(II) in Kinugasa reaction. The reaction was free from dimeric acetylenic products, as was expected. The diastereoselectivity, however, remained unchanged. The results are shown in Table 1. Regarding the choice of the solvent, DMF can be replaced with other solvents like acetonitrile, *tert*-butanol or water (Scheme 1). However, amongst the four solvent systems, acetonitrile–water (2:1) (condition B) gave the best result in terms of yield. The diastereoselectivity was almost the same as was observed with other solvent systems. The click conditions worked really well with propargyl nucleobases; the β-lactam nucleobase chimeric molecules could be obtained in up to 75% yield (Table 2). In this case, because of solubility, DMF–water combination (condition A) had to be employed (Scheme 2).

With water as the only solvent, the reaction worked less efficiently in terms of yield and duration (usually 30 h) (see Table 1, entries 12 and 13). The use of organic solvent only led to poor yield (<10%) of the products. The reaction can also be accomplished with less catalyst [Cu(II)] loading without sacrificing the yield. The catalyst loading could be decreased down to 10 mol% (Table 3). Below this amount, the reaction became sluggish and gave poor yield.

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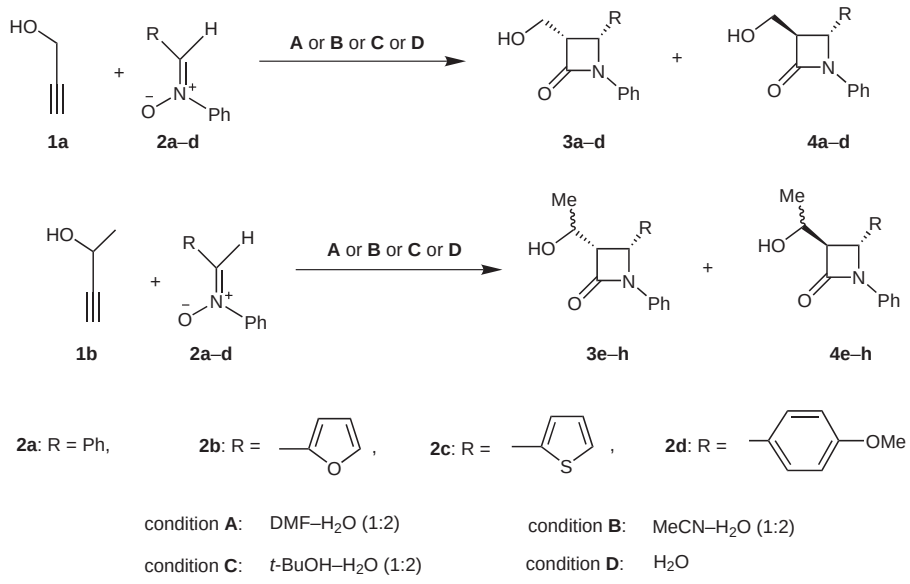
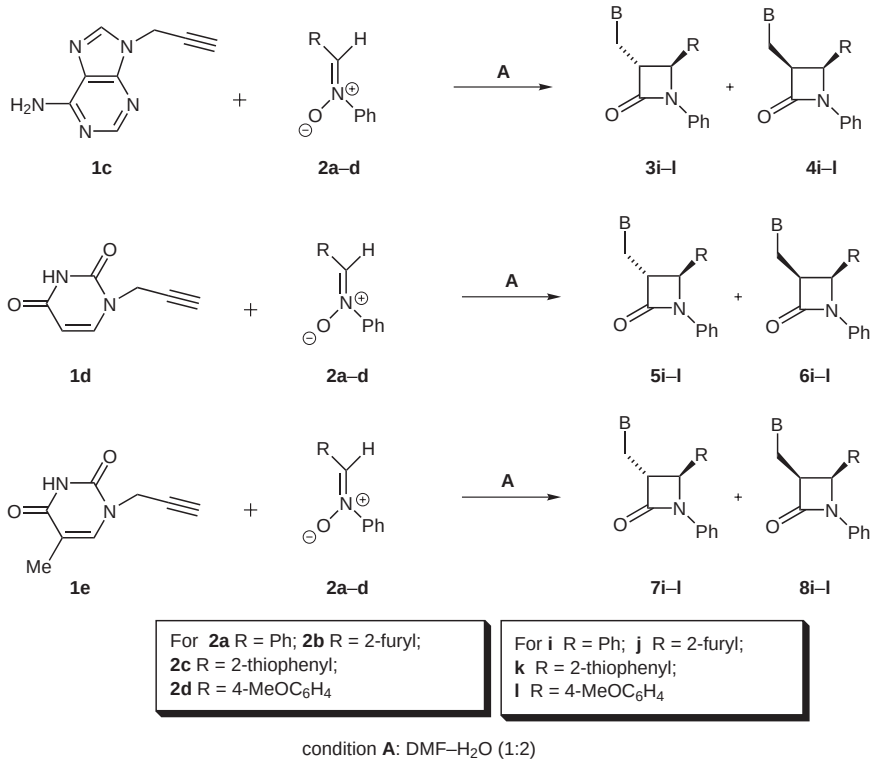


Scheme 1 Kinugasa reaction under click chemistry conditions



Scheme 2 Synthesis of β-lactam nucleobase chimera under click conditions

In summary we have successfully synthesized various monocyclic β-lactams as *cis* and *trans* forms via Kinugasa reaction mimicking click chemistry conditions.

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Table 1 Kinugasa Reaction under Click Conditions

Entry	Alkyne	Nitrone	Condition	*cis*/*trans* Ratio	Combined yield (%)
1	**1a**	**2a**	A	2:1	55
2	**1a**	**2a**	B	2:1	64
3	**1a**	**2b**	A	3:2	48
4	**1a**	**2b**	B	2:1	60
5	**1a**	**2c**	B	2:1	60
6	**1a**	**2d**	B	2:1	62
7	**1b**	**2a**	B	3:2	65
8	**1b**	**2b**	B	3:2	60
9	**1b**	**2c**	B	2:1	61
10	**1b**	**2d**	B	3:2	65
11	**1a**	**2a**	C	2:1	55
12	**1a**	**2a**	D	2:1	52
13	**1b**	**2a**	D	2:1	53

Table 2 Preparation of β-Lactam Nucleobase Chimeric Molecules

Entry	Alkyne/ nitrone	Condition	*cis*/*trans* Ratio	Total yield (%)	Reported yield[5e] (%)
1	**1c**/**2a**	A	1:1	71	64
2	**1c**/**2b**	A	1:1	70	–
3	**1c**/**2c**	A	2:1	72	–
4	**1c**/**2d**	A	1:1	75	–
5	**1d**/**2a**	A	2:1	75	60
6	**1d**/**2b**	A	2:1	71	–
7	**1d**/**2c**	A	1:1	73	–
8	**1d**/**2d**	A	1:1	75	–
9	**1e**/**2a**	A	2:1	73	60
10	**1e**/**2b**	A	1:1	70	–
11	**1e**/**2c**	A	2:1	73	–
12	**1e**/**2d**	A	2:1	75	–

Table 3 Effect of Catalyst Loading

Entry	Alkyne	Nitrone	Catalyst (mol%)	*cis*/*trans* Ratio	Yield (%)
1	**1a**	**2a**	$CuSO_4 \cdot 5H_2O$ (50)	2:1	62
2	**1a**	**2a**	$CuSO_4 \cdot 5H_2O$ (40)	2:1	62
3	**1a**	**2a**	$CuSO_4 \cdot 5H_2O$ (10)	2:1	60
4	**1a**	**2a**	$Cu(OAc)_2 \cdot H_2O$ (50)	2:1	67
5	**1a**	**2a**	$Cu(OAc)_2 \cdot H_2O$ (10)	2:1	67

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(12) (a) All the nitrones were prepared according to the procedure described in: Bhattacharya, G. *PhD Thesis*; Indian Institute of Technology: Kharagpur, India, **1997**. (b) However, a general method of preparation is given below along with the spectroscopic data of some representative compounds:
To a solution of EtOH (30 mL) and H_2O (20 mL) nitrobenzene or *p*-methoxynitrobenzene (50 mmol), benzaldehyde (or *p*-methoxybenzaldehyde or furfural or thienyl aldehyde; 50 mmol) and Zn dust (5 gm) were placed. The mixture was stirred at 5 °C. AcOH (30 mL) was slowly added in a span of 20 min. The reaction mixture was stirred for an additional 1.5 h at –5 °C. The mixture was filtered and the residue was washed with EtOAc. The filtrate was concentrated to 10 mL. H_2O was added and the products were extracted with EtOAc. The organic layer was washed with $NaHCO_3$, brine and dried over Na_2SO_4. The solvent was evaporated under vacuo and the crude mass was subjected to silica gel column chromatography. The products were eluted with hexane–EtOAc mixture.
Compound 2a: ^{1}H NMR: δ = 7.39–7.52 (m, 6 H), 7.71–7.81 (m, 2 H), 7.90 (s, 1 H), 8.33–8.42 (m, 2 H).
Compound 2b: ^{1}H NMR: δ = 6.62 (dd, *J* = 1.3 Hz, 3.2 Hz, 1 H), 7.39–7.44 (m, 3 H), 7.57 (d, *J* = 3.6 Hz, 1 H), 7.78–7.81 (m, 2 H), 8.0 (d, *J* = 3.3 Hz, 1 H), 8.14 (s, 1 H).
Compound 2c: ^{1}H NMR: δ = 7.15 (dd, *J* = 4.0, 4.8 Hz, 1 H), 7.39–7.56 (m, 5 H), 7.76–7.81 (m, 2 H), 8.46 (s, 1 H).

(13) **General Procedure**: To a solution of $CuSO_4 \cdot 5H_2O$ (1 mmol) in degassed H_2O (10 mL), sodium ascorbate (2 mmol) was added and the mixture was stirred for 30 min at r.t. (solution X). In another flask, to a solution of propargyl alcohol–3-butyn-2-ol–propargyl nucleobase (2 mmol) in DMF–MeCN (3 mL) under argon at 0 °C, Et_3N (2 mmol) was added and the mixture was stirred for 30 min (solution Y). Solution Y was added dropwise to the solution X at r.t. after which a 2 mL DMF or MeCN solution of the nitrones[12] **2a**–**2d** (1 mmol) was added slowly over 10 min. The reaction was stirred at r.t. for 16–25 h. It was then diluted with H_2O and filtered through celite. The celite bed was washed with EtOAc. The combined filtrate and washings were extracted with EtOAc. The organic layer was washed with NH_4Cl, H_2O and brine and dried over Na_2SO_4 and evaporated. The residue, obtained after evaporation, upon chromatography afforded a mixture of *trans* and *cis* diastereomers.[15] These were easily separated by conventional chromatography over silica gel using hexane–EtOAc (2:1) as eluent. The various hydroxymethyl β-lactams [combined mixture of *cis* (**3e**–**h**) and *trans* (**4e**–**h**) products] could be oxidized to a single *trans* ketone by Dess–Martin oxidation[14] in quantitative yield.

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(c) For the new compounds, the spectral data are given below:

β-Lactam 8j: ^{1}H NMR: δ = 1.85 (s, 3 H), 3.90 (dd, *J* = 7.6, 14.4 Hz, 1 H), 3.98 (dd, *J* = 7.6, 14.4 Hz, 1 H), 4.14 (m, 1 H), 5.26 (d, *J* = 5.6 Hz, 1 H), 6.50 (br s, 2 H), 7.08–7.48 (m, 7 H), 8.64 (br s, 1 H). ^{13}C NMR: δ = 12.18, 45.51, 50.95, 52.54, 110.41, 111.16, 111.26, 116.77, 124.45, 129.13, 137.09, 140.79, 143.60, 147.73, 150.60, 164.02, 164.29. MS (ES): *m*/*z* = 368 [MH^+], 390 [MNa^+].
β-Lactam 7j: ^{1}H NMR: δ = 1.84 (s, 3 H), 3.76 (m, 1 H), 4.15 (dd, *J* = 5.6, 14.8 Hz, 1 H), 4.29 (dd, *J* = 6.6, 14.6 Hz, 1 H), 5.09 (d, *J* = 2.4 Hz, 1 H), 6.35 (d, *J* = 2.8 Hz, 1 H), 6.50 (m, 1 H), 7.06–7.48 (m, 7 H), 9.06 (br s, 1 H). ^{13}C NMR: δ = 12.23, 45.75, 52.48, 55.86, 110.31, 110.71, 111.32, 116.88, 124.46, 129.10, 137.10, 140.62, 143.43, 148.71, 151.59, 164.08, 164.61. MS (ES): *m*/*z* = 368 [MH^+], 390 [MNa^+].
β-Lactam 8k: ^{1}H NMR: δ = 1.82 (s, 3 H), 3.82–3.94 (m, 2 H), 4.13 (m, 1 H), 5.55 (d, *J* = 5.6 Hz, 1 H), 6.36 (s, 1 H), 6.99–7.40 (m, 8 H), 8.45 (br s, 1 H). ^{13}C NMR: δ = 14.13, 24.83, 31.92, 45.64, 52.84, 53.38, 117.16, 124.55, 126.42, 127.18, 127.96, 129.43, 138.51, 140.99, 150.86, 164.31, 164.42. MS (ES): *m*/*z* = 384 [MH^+], 406 [MNa^+].
β-Lactam 7k: ^{1}H NMR: δ = 1.90 (s, 3 H), 3.51 (m, 1 H), 4.10 (dd, *J* = 4.8, 14.8 Hz, 1 H), 4.35 (dd, *J* = 7.2, 14.8 Hz, 1 H), 5.30 (br s, 1 H), 6.92–7.61 (m, 9 H), 8.59 (br s, 1 H). ^{13}C NMR: δ = 12.31, 22.69, 28.94, 46.01, 55.40, 60.49, 111.59, 117.29, 124.62, 126.09, 127.19, 127.41, 136.82, 140.31, 151.51, 164.32, 164.49. MS (ES): *m*/*z* = 384 [MH^+], 406 [MNa^+].
β-Lactam 4k: ^{1}H NMR (DMSO-d_6): δ = 4.18 (dd, *J* = 8.2, 13.8 Hz, 1 H), 4.35–4.46 (m, 2 H), 5.80 (d, *J* = 5.2 Hz, 1 H), 7.09–7.60 (m, 9 H), 8.12 (s, 1 H). ^{13}C NMR (DMSO-d_6): δ = 41.04, 56.27, 58.17, 116.78, 123.87, 125.91, 127.09, 128.37, 128.93, 129.17, 137.03, 137.17, 140.78, 149.49, 152.57, 155.95, 164.08. MS (ES): *m*/*z* = 377 [MH^+], 399 [MNa^+].
β-Lactam 3k: ^{1}H NMR: δ = 3.49 (m, 1 H), 4.72 (d, *J* = 6.0 Hz, 2 H), 5.45 (br s, 1 H), 5.74 (br s, 2 H), 6.91–7.37 (m, 8 H), 7.93 (s, 1 H), 8.44 (s, 1 H). ^{13}C NMR: δ = 52.71, 54.49, 60.18, 117.70, 124.12, 126.44, 126.46, 127.74, 127.84, 128.71, 136.91, 137.26, 140.85, 149.55, 152.60, 164.23, 165.00. MS (ES): *m*/*z* = 377 [MH^+], 399 [MNa^+].
β-Lactam 4l: ^{1}H NMR (DMSO-d_6): δ = 3.75 (s, 3 H), 3.97 (dd, *J* = 8.0, 14.4 Hz, 1 H), 4.20 (dd, *J* = 8.0, 14.4 Hz, 1 H), 4.39 (m, 1 H), 5.50 (d, *J* = 6.0 Hz, 1 H), 7.03–7.37 (m, 10 H), 8.08 (s, 1 H). ^{13}C NMR (DMSO-d_6): δ = 39.96, 55.23, 58.58, 59.70, 114.57, 119.28, 120.29, 124.92, 128.11, 128.99, 129.43, 136.95, 141.02, 149.71, 153.15, 155.69, 159.84, 164.03. MS (ES): *m*/*z* = 401 [MH^+], 423 [MNa^+].
β-Lactam 3l: ^{1}H NMR: δ = 3.52 (m, 1 H), 3.84 (s, 3 H), 4.73 (app d, *J* = 6.0 Hz, 2 H), 4.97 (br s, 1 H), 6.02 (br s, 2 H), 7.00–7.43 (m, 9 H), 7.95 (s, 1 H), 8.42 (s, 1 H). ^{13}C NMR: δ = 40.99, 52.73, 55.31, 56.88, 114.70, 117.91, 124.28, 126.51, 127.06, 128.11, 129.33, 133.43, 136.95, 140.02, 141.72, 152.72, 160.10, 164.25. MS (ES): *m*/*z* = 401 [MH^+], 423 [MNa^+].