New Click Chemistry: Click Polymerization via 1,3-Dipolar Addition of Homo-ditopic Aromatic Nitrile Oxides Formed In Situ

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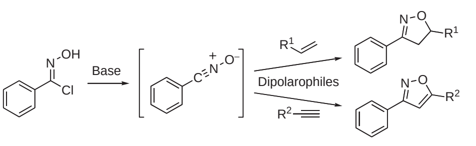
New click chemistry is demonstrated. Click polymerization proceeded via 1,3-dipolar polycycloaddition of homo-ditopic nitrile oxides to bifunctional terminal olefinic and acetylenic monomers as dipolarophiles. Molecular sieves (MS 4A) served as an efficient promoter for the polymerization to afford polyisoxazolines and polyisoxazoles in high yields.

Recent sophisticated supramolecular and macromolecular architectures strongly require viable means of powerful, highly reliable, and selective reactions. For this purpose, click chemistry,[1] exploiting the Huisgen dipolar cycloaddition of azides and alkynes, has generated particular interest.[2] Click reactions have been actually utilized in a variety of synthetic processes for supramolecules and macromolecules. However, problems of safety with the azide moiety concerning toxicity and explosiveness lead to several limitations to the use.[3] Recognizing these issues, we became intrigued by the potential usefulness of nitrile *N*-oxide as a 1,3-dipole, which allows efficient [2 + 3]cycloaddition reaction with not only alkenes but also alkynes to selectively give isoxazoline and isoxazole.[4,5] These hetero-rings are versatile scaffolds for various derivatives, because they enable simple conversion to useful functional groups; aldol, diketone, γ-aminoalcohol, and so on. Nitrile *N*-oxides, however, have not been employed to click chemistry yet.

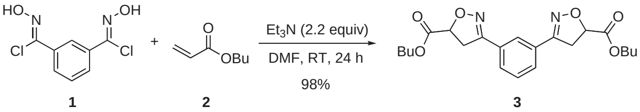
Herein, we wish to describe affirmative answers for the utility and productivity of new click chemistry exploiting nitrile *N*-oxide, as demonstrated by the polycycloaddition reaction of homo-ditopic aromatic nitrile *N*-oxide to various bifunctional terminal olefins and acetylenes as dipolarophiles, according to a MS 4A promoted protocol.

Scheme 1 shows the fundamental reaction scheme of the "click chemistry" utilizing aromatic hydroxamoyl chloride as the precursor of reactive aromatic nitrile *N*-oxide. Prior to the polymerization, a click reaction using benzene-1,3-dicarbohydroximoyl dichloride (**1**) and butyl acrylate (**2**) was carried out as shown in Scheme 2. The addition product 1,3-bis(3-isoxazolinyl)benzene **3** was obtained in a high yield as a single diastereomer, certainly suggesting the possibility of efficient polymerization.

Table 1 summarizes the results of "click polymerization" via polycycloaddition of **1** to a bifunctional acrylate **4** mainly to find the effect of base. While base-free condition[6–8] (Entry 1) proved inferior to base-promoted conditions, we found that a variety of bases effectively promoted the desired polymerization in moderate yields (Entries 2–5). In hopes of efficiently accelerating the polymerization, we sought to identify a more active base working without any side reaction. After considerable efforts, this goal was achieved by the addition of MS 4A as a suitable base as well as a dehydrating agent (Entries 6–9).[9–11] Polyisoxazoline poly-**5** was obtained in 99% yield by polymerization at 80 °C for 1 d in the presence of 344 mg of MS 4A (vs. 0.22 mmol of **4**), giving preferentially one regioisomer (Entry 7, M_n 9100, M_w 14900, and $M_\mathrm{w}/M_\mathrm{n}$ 1.6 by GPC).[12] In the present MS 4A-containing system, higher temperature and prolonged reaction time resulted in the decrease of yield and the lowering in molecular weight, probably due to retrocycloaddition (Entries 8 and 9).



Scheme 1. Click reaction exploiting nitrile *N*-oxide and olefin or acetylene.



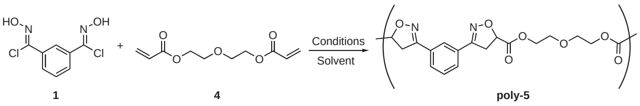
Scheme 2. Reaction of bifunctional nitrile *N*-oxide **1** and butyl acrylate (**2**).

The regiochemistry of the isoxazoline moiety of poly-**5** was determined as that illustrated in Table 1 by the NOESY correlation observed between the isoxazoline methylene protons and the aromatic protons.

As for the versatility of monomers of this click polymerization, terephthalohydroximoyl dichloride instead of **1** and a variety of bifunctional terminal olefinic and acetylenic monomers could be employed, as shown in Tables 2 and 3.

Dimethacrylate **7**, bisphthalimide **9**, and 1,5-hexadiene (**11**) with **1** underwent clean polycycloadditions (Entries 2–4).[13] The polyaddition to alkynes such as bispropiolate **13**, *p*-diethynyl-

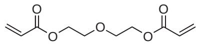
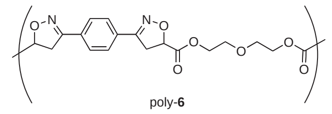
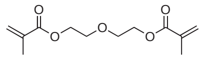
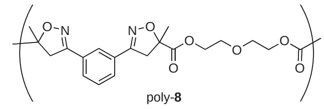
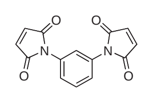
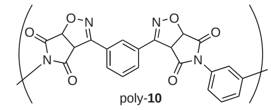
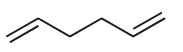
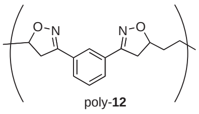
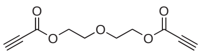
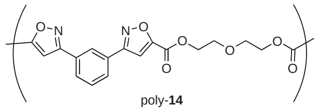
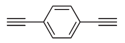
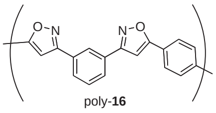
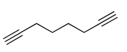
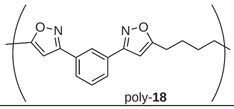
Table 1. "Click polymerization" in terms of the effect of base



Entry	Base	Solvent	Temp/°C	Time/d	M_n[a]	M_w[a]	$M_\mathrm{w}/M_\mathrm{n}$[a]	Yield/%
1	—	Toluene	120	1	3700	5500	1.5	24
2[b]	NaOH	CH_2Cl_2/H_2O	rt	1	3400	4600	1.3	99
3	Et_3N	DMF	rt	1	4200	5700	1.4	60
4	KF	DMF	rt	1	4600	6500	1.4	60
5	KF	DMF	rt	5	5300	7800	1.5	67
6	MS 4A	DMF	rt	7	6000	8600	1.4	90
7	MS 4A	DMF	80	1	9100	14900	1.6	99
8	MS 4A	DMF	80	8	6000	8600	1.4	86
9	MS 4A	DMF	100	1	6700	10100	1.5	89

[a] Estimated by GPC based on polystyrene standards. [b] Polymerization reaction was carried out with NaOH (2.5 equiv) in the presence of TBAB (5 mol %).

Table 2. Syntheses of polyisoxazoles and polyisoxazolines by MS 4A-promoted polycycloaddition

Entry	Dipolarophile	Products	Yield/%
1[a]	 **4**	 poly-**6**	99
2	 **7**	 poly-**8**	99
3	 **9**	 poly-**10**	99
4	 **11**	 poly-**12**	81
5	 **13**	 poly-**14**	99
6	 **15**	 poly-**16**	99
7	 **17**	 poly-**18**	80

[a]Terephthalohydroxamoly chloride was used as a precursor of bifunctional nitrile oxide.

Table 3. Molecular weight and thermal properties of polyisoxazolines and polyisoxazoles

Entry	Products	M_n[a]	M_w[a]	M_w/M_n[a]	T_g/°C	T_{d5}/°C	T_{d10}/°C
1	poly-**5**	9100	14900	1.6	73.6	253	260
2	poly-**6**	3300	4900	1.5	75.9	266	279
3	poly-**8**	4200	5400	1.3	57.8	268	278
4	poly-**10**	4700[b]	—[c]	—[c]	—[c]	296	306
5	poly-**12**	4400	7000	1.6	145.3	241	269
6	poly-**14**	1500	1900	1.3	64.3	283	303
7	poly-**16**	1200	2400	2.0	—[c]	—[c]	—[c]
8	poly-**18**	2200	2800	1.3	58.8	289	336

[a]Estimated by GPC based on polystyrene standards. [b]Determined from the integral ratio of terminal protons in ^{1}H NMR spectrum. [c]Not estimated.

benzene (**15**), and 1,7-octadiyne (**17**) also proceeded well to afford polyisoxazoles,[12] although the molecular weight was low, due to the low solubility of the polyisoxazoles which were precipitated during the polymerization.[14]

In conclusion, this paper has demonstrated new click chemistry utilizing nitrile *N*-oxide as a 1,3-dipolar molecule coupled with olefinic and acetylenic compounds, especially from viewpoint of macromolecular synthesis. The use of MS 4A to promote the polycycloaddition is notable for both the mild reaction conditions and simple procedure and work-up. This protocol of new click chemistry can be characterized by (i) nonexplosive materials, (ii) versatility in both 1,3-dipolar molecule and dipolarophile, (iii) C–C bond formation, (iv) easy work-up, (v) absence of catalyst, and (vi) easy transformation of the isoxazoline and isoxazole moieties, all of which enable access to high-performance materials. Further broad applications of this click chemistry are currently in progress.

References and Notes

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2 For selected reports of polymerization exploiting ditopic azido group, see: a) D. J. V. C. van Steenis, O. R. P. David, G. P. F. van Strijdonck, J. H. van Maarseveen, J. N. H. Reek, *Chem. Commun.* **2005**, 4333. b) D. D. Diaz, K. Rajagopal, E. Strable, J. Schneider, M. G. Finn, *J. Am. Chem. Soc.* **2006**, *128*, 6056.

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6 Y. Iwakura, K. Uno, S.-J. Hong, T. Hongu, *Polym. J.* **1970**, *2*, 36.

7 For a selected report about polyisoxazolines and polyisoxazoles, see: S.-J. Hong, *Polymer* **1973**, *14*, 286.

8 The major side pathway was a dimerization of nitrile oxide to give a furoxane, which afforded a swelled gel, due most likely to the crosslinking reaction of furoxane and propagation end.

9 For a review of molecular sieve promoted reactions, see: S. E. Sen, S. M. Smith, K. A. Sullivan, *Tetrahedron* **1999**, *55*, 12657.

10 For related reports about MS 4A promoted cycloadditon of nirile *N*-oxide, see: a) J. N. Kim, E. K. Ryu, *Heterocycles* **1990**, *31*, 1693. b) U. Pindur, M. Haber, *Heterocycles* **1991**, *32*, 1463. c) T. Matsuura, J. W. Bode, Y. Hachisu, K. Suzuki, *Synlett* **2003**, 1746.

11 MS 4A have the general formula $Na_2O \cdot Al_2O_3 \cdot xSiO_2 \cdot yH_2O$.

12 Polymerization. Both benzene-1,3- and 1,4-dicarbohydroximoyl dichloride were prepared according the literatures.[3] A typical experimental procedure for the reaction of benzene-1,3-dicarbohydroximoyl dichloride (**1**) and bisacrylate **4**: To a solution of **1** (50.0 mg, 0.215 mmol) and **6** (46.0 mg, 0.215 mmol) in DMF (0.43 mL) was added non-activated MS 4A (344 mg) at room temperature. The resulting slurry was stirred at room temperature for 30 min and at 80 °C for 1 d. The resulting mixture dissolved in $CHCl_3$ was filtrated and the filtrate was precipitated into MeOH. The precipitates were filtered, dried in vacuo to give polyisoxazoline poly-**5** (84.3 mg, 99% yield) as colorless powder: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (brd, 1H), 7.59 (brd, 2H), 7.31 (brd, 1H), 5.13 (brd, 2H), 4.23 (brd, 4H), 3.64 (brd, 4H), 3.56 (brd, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0 (2C), 155.7 (2C), 129.3 (2C), 129.2 (1C), 128.7 (2C), 125.2 (1C), 78.2 (2C), 68.7 (2C), 64.7 (2C), 38.7 (2C); IR (NaCl): 3062, 2962, 1745, 1261, 1203, 900 cm^{-1}.

13 Structural assignments of polymers were based on the NOESY correlations. The NOE observed between the isoxazoline methylene protons or isoxazole methyne protons and the aromatic proton at the ortho position was diagnostic, in each case.

14 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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