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A Novel and Efficient Methodology for the C–C Bond Forming Radical Cyclization of Hydrophobic Substrates in Water

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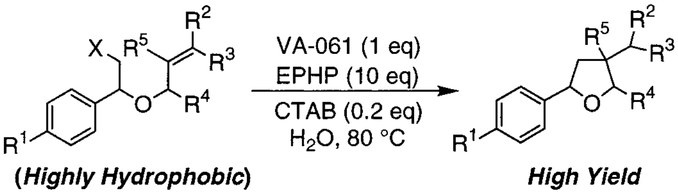
ABSTRACT



The combination of water-soluble radical initiator 2,2′-azobis[2-(2-imidazolin-2-yl)propane] (VA-061), water-soluble chain carrier 1-ethylpiperidine hypophosphite (EPHP), and surfactant cetyltrimethylammonium bromide (CTAB) was found to be the most suitable condition for effective radical cyclization in water for a variety of hydrophobic substrates.

Water has many potential advantages as a solvent for organic reactions from the vantage point of its cost, safety, and environmental concern.[1] Recently, some attempts to achieve organic reactions in aqueous media have been performed, and consequently some successful examples have appeared in the literature.[2] The development of an efficient and convenient synthetic methodology to accomplish C−C bond formation in water is of paramount significance because of heightened importance in green chemistry.

An intramolecular radical cyclization in water has been reported by Oshima et al.[3] using β-iodocarbonyl compounds as the substrate; however, increasing hydrophobicity of the substrate tended to decrease the reactivity. Naito et al.[4] recently reported a radical addition reaction in water by the use of highly polar imine compounds, which can dissolve easily in water. Some remarkable results along these lines have been reported by Culbertson and Porter.[5] In all these reports, advantage has been taken of the hydrophilicity of the respective substrates, which renders their easy solubility in water, thereby facilitating a smooth C−C bond formation.

To the best of our knowledge, only isolated reports restricted to some specific substrates are available for the C−C bond forming radical reactions of hydrophobic substrates in water. A general methodology for the C−C bond forming radical reaction in water is highly desirable. In this context, we wish to report the preliminary results of an unprecedented C−C bond forming radical reaction of

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hydrophobic substrates in water using a novel and efficient radical reaction system. Our strategy is based on the use of a combination of a water-soluble radical initiator 2,2′-azobis-[2-(2-imidazolin-2-yl)propane] (VA-061),[6] water-soluble chain carrier 1-ethylpiperidine hypophosphite (EPHP),[7] and surfactant cetyltrimethylammonium bromide (CTAB).[8]

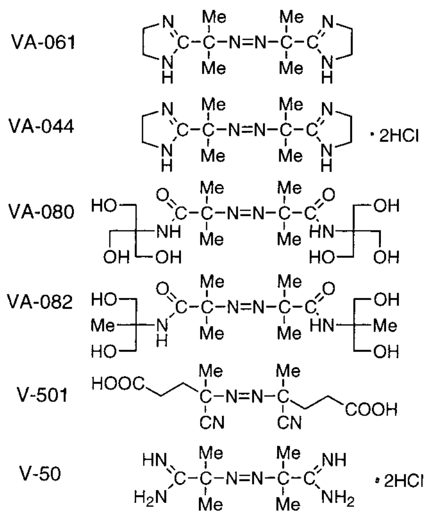
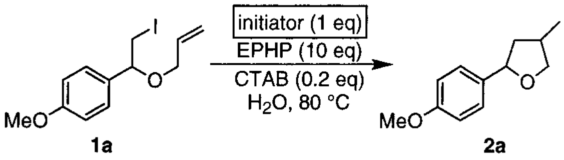


Figure 1. Water-Soluble Radical Initiators

Table 1. Radical Cyclization Reaction Using Various Initiators

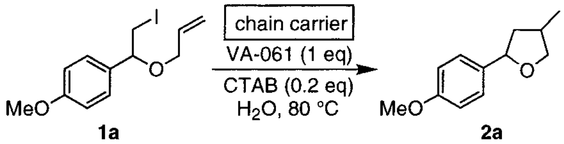


entry	initiator	time (h)	yield (*trans*:*cis*)[a]
1	**VA-061**	**2**	**98% (55:45)**
2	VA-044	2.5	95% (50:50)
3	VA-080	5	76% (50:50)
4	VA-082	24	71% (50:50)
5	V-501	24	72% (51:49)
6	V-50	4	92% (51:49)
7	AIBN	24	19% (57:43) [56%][b]
8[c]	Et_3B	24	50% (67:33) [46%][b]

[a] The ratios were determined by ^1H NMR. [b] Recovered starting material. [c] Room temperature.

We presumed that a surfactant is essential to solubilize the hydrophobic substrate in water, and with this in mind we examined the radical cyclization of **1a** using various water-soluble azo-type initiators (Figure 1)[6] in the presence of water-soluble chain carrier (EPHP) and catalytic amount of CTAB as the first chosen surfactant. The reaction did not go to completion when the typical radical initiator AIBN was used (Table 1, entry 7). While using Et_3B,[9] a known radical initiator at low temperature, the yield of the desired product was found to be low (Table 1, entry 8). On the other hand, water-soluble initiators were found to be quite effective in promoting the intramolecular cyclization of **1a**. Remarkably, VA-061 was found to be the most suitable initiator under these conditions (Table 1, entry 1), and thus the use of VA-061 was explored further.

Table 2. Effect of Various Chain Carrier



entry	chain carrier	time (h)	yield (*trans*:*cis*)[a]
1	none	24	no reaction
2	EPHP (10 equiv)	2	98% (55:45)
3	H_3PO_2 (10 equiv) + $NaHCO_3$ (10 equiv)	6	84% (78:22)
4	NaH_2PO_2 (10 equiv)	24	58% (78:22) [8%][b]
5[c]	$(TMS)_3SiH$ (2 equiv)	0.5	94% (67:33)

[a] The ratios were determined by ^1H NMR. [b] Recovered starting material. [c] VA-061 (0.5 equiv) was used.

We next optimized for an expedient chain carrier for our system containing VA-061 and CTAB (Table 2). Although the radical cyclization of **1a** did not proceed at all in the absence of chain carriers, we found that the addition of water-soluble chain carriers afforded the expected cyclization product in high yield within a short time. After screening a series of chain carriers such as EPHP, tris(trimethylsilyl)silane [$(TMS)_3SiH$],[10] etc., we found that EPHP suits our system the best. When $(TMS)_3SiH$ was used as the chain

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(6) The water-soluble azo-type radical initiators used in our studies are available from Wako Pure Chemical Industries, Ltd. Osaka, Japan. The use of azo-type radical initiator (V-70) working at room temperature was reported by us: Kita, Y.; Sano, A.; Yamaguchi, T.; Oka, M.; Gotanda, K.; Matsugi, M. *Tetrahedron Lett.* **1997**, *38*, 3549. Kita, Y.; Gotanda, K.; Murata, K.; Suemura, M.; Sano, A.; Yamaguchi, T.; Oka, M.; Matsugi, M. *Org. Process Res. Dev.* **1998**, *2*, 250. Kita, Y.; Gotanda, K.; Ohira, C.; Suemura, M.; Sano, A.; Matsugi, M. *J. Org. Chem.* **1999**, *64*, 6928 and references therein.

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(8) (a) *Catalysis in Micellar and Macromolecular Systems*; Fendler J. H., Ed.; Academic Press: New York, 1998. (b) Tascioglu S. *Tetrahedron* **1996**, *52*, 11113. (c) Tohma, H.; Takizawa, S.; Watanabe, H.; Kita, Y. *Tetrahedron Lett.* **1998**, *39*, 4547. (d) Tohma, H.; Takizawa, S.; Watanabe, H.; Fukuoka, Y.; Maegawa, T.; Kita, Y. *J. Org. Chem.* **1999**, *64*, 3519.

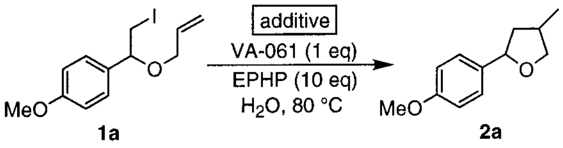
(9) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 403.

(10) (a) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188. (b) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3072.

carrier, the target product was obtained in good yield within a short period of time; however, it required a tedious procedure for the isolation of the desired product from the byproduct derived from $(TMS)_3SiH$.

We next investigated the additive effect of surfactants in radical reactions in water. The characteristic effect of some surfactants or phase transfer catalysts in radical cyclization is apparent from Table 3. From these observations, we found that CTAB is the most efficient additive for the radical cyclization of **1a** from the viewpoint of its rate acceleration effect (Table 3, entry 2). In the absence of the additive, the reaction did not go to completion until 24 h (Table 3, entry 1). Thus, we discovered that the combination of VA-061, EPHP, and CTAB is the most appropriate condition for radical reactions in water for these substrates. It is worthy to note that the concentration of CTAB used in our reactions is within the range of micelle formation and therefore the possibility of a micellar reaction cannot be ruled out. However, at present, we do not have sufficient evidence to prove this aspect.

Table 3. Effect of Various Surfactants



1a **2a**

entry	additive (0.2 equiv)	time (h)	yield (*trans*:*cis*)[a]
1	none	24	64% (74:26) [24%][b]
2	CTAB	2	98% (55:45)
2	SDS[c]	3.5	98% (51:49)
4	Triton X-100[d]	4	98% (62:38)
5	$Et_4N^+Br^-$	24	85% (65:35) [7%][b]

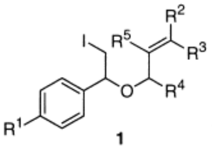
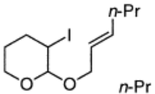
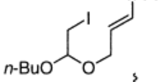
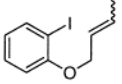
[a] The ratios were determined by ^1H NMR. [b] Recovered starting material. [c] SDS: sodium dodecyl sulfate. [d] Triton X-100: polyoxyethylene(10) isooctylphenyl ether.

The utility and generality of this method was confirmed by applying it to a series of hydrophobic substrates (**1a**−**j**). In all cases, the intramolecular cyclization proceeded with high efficiency and yield (Table 4). Notable is the fact that the reaction showed low reactivity when no surfactant (CTAB) was used.

To test the scope and limitations of our methodology, we subsequently investigated the radical cyclization strategy to yield pyrrolidines, which are often present in natural products. The allylamine **1k** was subjected to the radical reaction conditions in water at 80 °C, which afforded the corresponding pyrrolidine **2k** in 90% yield. Similar results are summarized in Table 5. The attempted synthesis of the unprotected amines to use as substrates in radical cyclization met with unacceptable yields, probably as a result of the inherent instability associated with these compounds. Thus, we established that our method is also effective for the radical cyclization in water to afford pyrrolidines (Table 5, entry 2). As expected, in the absence of the surfactant, the reaction proceeded with decrease in reactivity (Table 5, entries 1 and 3). The following experimental results using a more hydro-

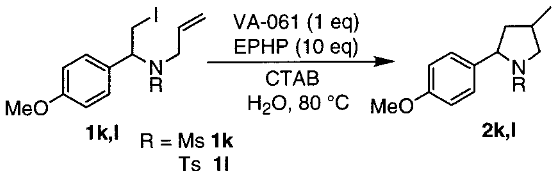
Table 4. Radical Cyclization Reaction Using VA-061, EPHP, and CTAB

$$\textbf{Substrate} \xrightarrow[\substack{\text{CTAB (0.2 eq)} \\ H_2O\text{, 80 °C}}]{\substack{\text{VA-061 (1 eq)} \\ \text{EPHP (10 eq)}}} \textbf{Product}$$

entry	substrate		R^1	R^2	R^3	R^4	R^5	time (h)	product	yield (*trans:cis*)[a]
1	 **1**	**1a**	MeO	H	H	H	H	2	**2a**	98% (55:45) [64% (74:26)][b]
2		**1b**	MeO	Me	H	H	H	4	**2b**	88% (66:34) [53% (62:38)][b]
3		**1c**	MeO	Me	Me	H	H	3	**2c**	94% (61:39)
4		**1d**	MeO	H	H	H	Me	4	**2d**	86%
5		**1e**	MeO	H	- $(CH_2)_3$ -		H	3	**2e**	94%[c]
6		**1f**	MeO	CO_2Et	H	H	H	2	**2f**	96% (75:25)
7		**1g**	H	H	H	H	H	2	**2g**	87% (78:22)
8[d]		**1h**						0.5	**2h**	98%[e] [21%][f]
9[g]		**1i**						2	**2i**	99% (74:26) [9% (67:33)][b]
10[h]		**1j**						18	**2j**	64% [22%][b]

[a] The ratios were determined by ^1H NMR. [b] When CTAB was not used; reaction time, 24 h. [c] Obtained as a mixture of *endo* and *exo* (53:47). [d] VA-061 (0.5 equiv) was used. [e] Obtained as a mixture of *endo* and *exo* (76:24). [f] Obtained as a mixture of *endo* and *exo* (75:25) when CTAB was not used; reaction time, 0.5 h. [g] $NaHCO_3$ (10 equiv) was added. [h] VA-061 (1.5 equiv) was used.

Table 5. Application to Other Hydrophobic Substrates



entry	R	CTAB (equiv)	time (h)	yield (*cis*:*trans*)[a]
1	Ms	none	24	90% (72:28)
2	Ms	0.2	8	99% (72:28)
3	Ts	none	24	8% (53:47) [23%][b]
4	Ts	0.2	24	46% (75:25) [21%][b]
5	Ts	1	24	65% (75:25) [14%][b]
6	Ts	2	6	87% (75:25)

[a] The ratios were determined by ^{1}H NMR. [b] Recovered starting material.

phobic substrate (**1l**) supported the apparent effectiveness of the surfactant CTAB (Table 5, entries 4−6). Thus by tuning the amount of CTAB, the reactivity can be greatly enhanced.

In conclusion, we have discovered that a combination of VA-061, EPHP, and CTAB is an ideal reaction system to accomplish radical cyclization in water. This method is an elegant way to achieve C−C bond forming radical reactions in water for various hydrophobic substrates. Further application of this methodology is currently under active investigation in our laboratories.

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Supporting Information Available: Experimental procedures and characterization for all compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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