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Radical Addition of 2-Iodoalkanamide or 2-Iodoalkanoic Acid to Alkenols Using a Water-Soluble Radical Initiator in Water. A Facile Synthesis of γ-Lactones

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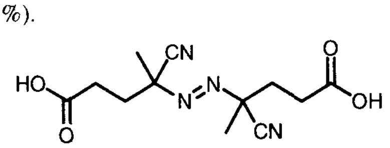
Abstract: Heating a mixture of 2-iodoacetamide and 5-hexen-1-ol in water at 75 °C in the presence of a water-soluble radical initiator, 4,4'-azobis(4-cyanopentanoic acid), provided γ-(4-hydroxybutyl)-γ-lactone in 95% yield. The use of 2-iodoacetic acid in place of 2-iodoacetamide also gave the same γ-lactone in 93% yield. © 1998 Elsevier Science Ltd. All rights reserved.

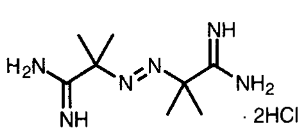
Keywords: Cyclisation; Lactonisation; Radicals and radical reactions; Solvents and solvent effects

Recently, processes using a less toxic solvent or no solvent have been required in the design of new synthetic methods from the ecological point of view. Water might be the best among many kinds of solvents. In the last decade, there has been increasing recognition that organic reactions carried out in aqueous media may offer advantages over those occurring in organic solvents.[1] However, methods for carbon-carbon bond formation based on a radical process in aqueous media have been limited.[2] Thus, we started our study on radical addition reaction in water mediated by a water-soluble radical initiator. Here we describe that (1) the addition of PhSH to alkene or alkyne proceeds smoothly to give the corresponding adducts, (2) atom transfer cyclization of *N*,*N*-diallyl-2-iodoacetamide affords lactams in excellent yields, and (3) the addition of 2-iodoacetamide to alkenol gives γ-lactones in good yields.

We chose the following two radical initiators,[3] [4,4'-azobis(4-cyanopentanoic acid) (**1a**, $t_{1/2}$ = 10 h, 69 °C in H_2O) and 2,2'-azobis(2-methylpropanamidine) dihydrochloride (**1b**, $t_{1/2}$ = 10 h, 56 °C in H_2O)], which are soluble in water. At first, we examined radical addition of benzenethiol to carbon-carbon multiple bonds. Heating a mixture of *N*-acetyldiallylamine (**2**, 1.0 mmol) and benzenethiol (1.5 mmol) in water (10 mL) at 60 °C in the presence of **1b** (0.3 mmol) for 2 h provided *N*-acetylpyrrolidine derivative **3** in 96% yield. In a similar fashion, treatment of diallylic ether **4** with benzenethiol in the presence of **1a** at 75 °C gave tetrahydrofuran derivative **5** in 75% yield. The reaction of 3-butyn-1-ol (**6**) with PhSH at 60 °C in the presence of **1b** afforded 4-(phenylthio)-3-buten-1-ol (**7**) in 80% yield in addition to 3,4-bis(phenylthio)-1-butanol (**8**) (8%).

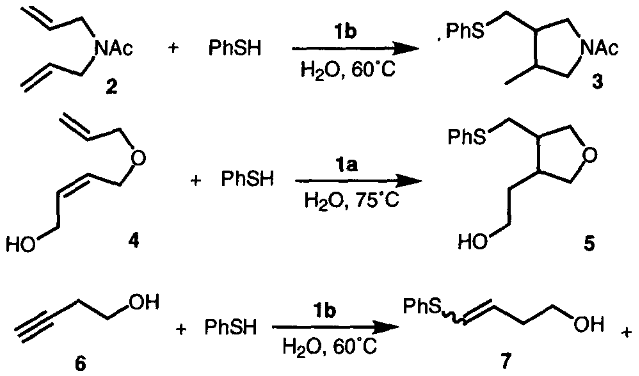


1a



1b

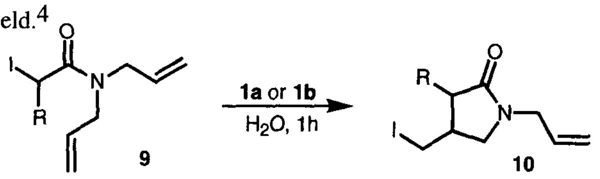
PII: S0040-4039(98)02391-0



96% (*c*/*t* or *t*/*c* = 65/35)

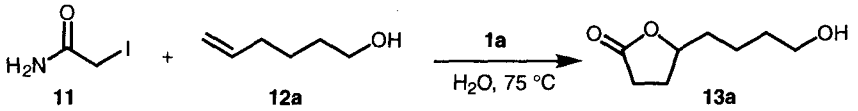
75% (*c*/*t* or *t*/*c* = 60/40)

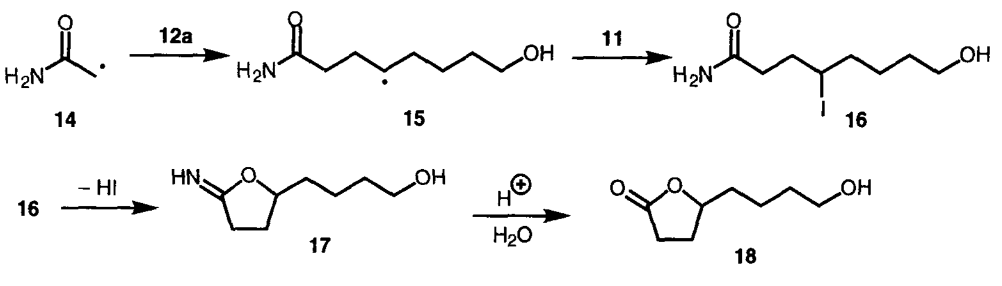
This radical reaction could be successfully applied to the atom transfer radical cyclization of 2-iodoacetamide **9**. Heating a mixture of *N*,*N*-diallyl-2-iodoacetamide (**9a**, 1.0 mmol) and **1a** or **1b** (0.3 mmol) at 75 °C or 60 °C in water (30 mL) for 1 h provided γ-lactam **10a** in 80 % or 99% yield, respectively. The reaction of **9b** in the presence of **1a** or **1b** also afforded the corresponding lactam **10b** in 95% (32/68) or 85% (31/69) yield.[4]



9a: R = H
9b: R = CH_3

Next, we focused on the reaction of 2-iodoacetamide with alkenol. The addition of 2-iodoacetamide (**11**) to alkenol **12** afforded γ-lactone **13** in high yields. For instance, the reaction of 2-iodoacetamide (**11**) with 5-hexen-1-ol (**12a**) in the presence of **1a** at 75 °C for 16 h provided γ-(4-hydroxybutyl)-γ-lactone **13a** in an isolated yield of 95%.[5] The typical examples are shown in Table 1.[6] The reaction proceeds as follows: Radical **14** derived from **11** should add readily to the alkenyl terminal carbon of alkenol **12a** to provide **15**. The iodine atom transfer reaction between the radical **15** and **11** would afford 4-iodo-8-hydroxyoctanamide **16** and regenerate **14**. The compound **16** could cyclize to γ-lactone **18** via **17** under the reaction conditions[7] due to the well-known ionic lactonization[8,9] of 4-iodoalkanamide.





The addition to alkenol containing an internal double bond such as 2-buten-1-ol did not take place. 1-

Dodecene was recovered completely after heating at 75 °C in water containing 2-iodoacetamide and **1a** because of the insolubility of 1-dodecene in water.

Not only 2-iodoacetamide but 2-iodoacetic acid also provided γ-lactones in the reaction with alkenol in water at 75 °C in the presence of water-soluble radical initiator **1a**. The representative results are also summarized in Table 1. 2-Iodoacetic acid (**19a**) was added to 4-penten-1-ol (**12b**) to give tetrahydrofuran derivative **21** in 40% yield in addition to γ-lactone **22** (54%). The former compound **21** was obtained by an intramolecular etherification of the iodine transfer product **20**.

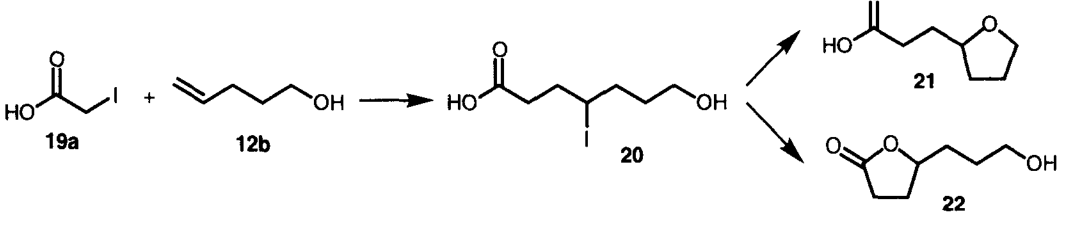
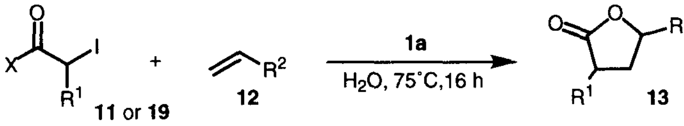
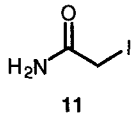
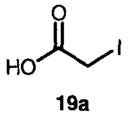
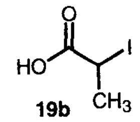


Table 1. γ-Lactone Synthesis by Tandem Radical-Ionic Reaction between 2-Iodoacetamide or 2-Iodoacetic Acid and Alkenol[a]



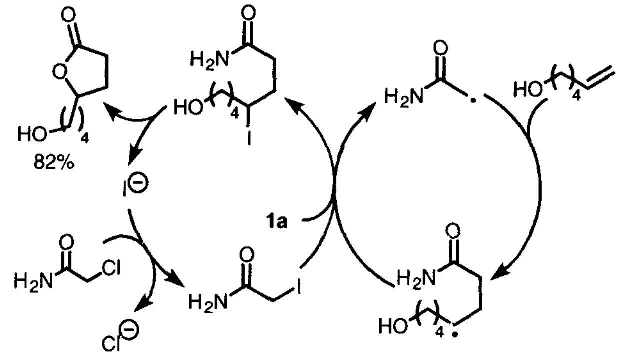
2-Iodocarbonyl Compound	Alkenol R^2	Product (%)	2-Iodocarbonyl Compound	Alkenol R^2	Product (%)
 **11**	$(CH_2)_4OH$	95	 **19a**	$(CH_2)_4OH$	93
	$(CH_2)_3OH$	85		$(CH_2)_2OH$	95
	$(CH_2)_2OH$	91[b]		CH_2OH	76
	CH_2OH	88[b]		$(CH_2)_2COOH$	100[c]
	$CH_2OCH_2CH_2O$*i*-Pr	84	 **19b**	$(CH_2)_4OH$	86 (55/45)
	$(CH_2)_2COOH$	94[c]			

a) 2-Iodoacetamide or 2-iodoacetic acid (1.0 mmol), alkenol (1.5 mmol), and 4,4'-azobis(4-cyanopentanoic acid) (0.5 mmol) were employed unless otherwise noted. b) Three equivalents of alkenol were employed. c) The product was isolated as allyl ester after treatment with allyl bromide in the presence of K_2CO_3 in acetone.

Iodide was liberated in the transformation of **16** into **18**. Thus, it was anticipated that the use of 2-chloroacetamide instead of the iodoamide **11** would provide the lactone **18** by the addition of a catalytic amount of sodium iodide. We have indeed found that the radical-ionic tandem reaction of 2-chloroacetamide with 5-hexen-1-ol (**12a**) in the presence of a catalytic amount of NaI proceeds smoothly as shown in Scheme

1. Heating a mixture of 2-chloroacetamide (1.0 mmol), 5-hexen-1-ol (1.5 mmol), and NaI (0.5 mmol)[10] in water (10 mL) at 75 °C for 16 h in the presence of radical initiator **1a** (0.5 mmol) provided γ-lactone **18** in 82% yield.

Scheme 1



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References and Notes

1. (a) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley & Sons, Inc.: New York, 1997; (b) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023–2035; (c) Grieco, P. A. *Organic Synthesis in Water* ; Blackie Academic & Professional, London, 1998.
2. Minisci, F. *Synthesis* **1973**, 1-24; Yamazaki, O.; Togo, H.; Nogami, G.; Yokoyama, M. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2519–2523; Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, in press.
3. Recent examples using water-soluble initiator in polymer chemistry: Morgan, J. D.; Lusvardi, K. M.; Kaler, E. W. *Macromol.* **1997**, *30*, 1897–1905; Encinas, M. V.; Lissi, E. A.; Martinez, C. *Eur. Polym. J.* **1996**, *32*, 1151–1154; Badey, B.; Boullanger, P.; Delair, T.; Cros, P.; Domard, A.; Pichot, C. *Macromol. Chem . Phys.* **1996**, *197*, 3711–3728; Baday, B.; Boullanger, P.; Domard, A.; Cros, P.; Delair, T.; Pichot, C. *Macromol. Chem . Phys.* **1997**, *198*, 945–957; Aoki, S.; Morimoto, Y. *Colloid Polym. Sci.* **1995**, *273*, 733–739.
4. Allyl 2-iodoacetate gave the desired γ-lactone in only 38% yield upon heating at 60 °C in H_2O for 10 h in the presence of **1b**. In addition to the γ-lactone, a complex mixture containing acids, which were generated by hydrolysis of the ester group, was obtained.
5. Radical additions of alkyl 2-haloalkanoates to alkenes initiated by electron transfer from copper in solvent-free systems have been reported. Metzger, J. O.; Mahler, R.; Francke, G. *Liebigs. Ann./Recueil* **1997**, 2303–2313.
6. Representative experiment for preparation of γ-lactone: A water-soluble radical initiator **1** (0.5 mmol) was added to a solution of 2-iodoacetamide (1.0 mmol) and 5-hexen-1-ol (1.5 mmol) in water (10 mL). The mixture was heated at 75 °C for 16 h. The product was extracted with ethyl acetate (20 mL x 2). The combined organic layers were washed with water, and then dried and concentrated. The residue was purified by silica gel column chromatography to give γ-lactone in 95% yield.
7. The solution became acidic as the reaction proceeded.
8. Stirling, C. J. M. *J. Chem. Soc.* **1960**, 255–262; Zaugg, H. E.; Michaels, R. J. *J. Org. Chem.* **1963**, *28*, 1801–1805.
9. Radical atom transfer reactions followed by irreversible ionic reactions have been reported. Curran, D. P.; Ko, S.-B. *Tetrahedron Lett.* **1998**, *39*, 6629–6632; Joung, M. J.; Ahn, J. H.; Lee, D. W.; Yoon, N. M. *J. Org. Chem.* **1998**, *63*, 2755–2757; Nagahara, K.; Ryu, I.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1997**, *119*, 5465–5466.
10. Reducing the amount of NaI (0.2 mmol) resulted in formation of γ-lactone **18** in only 39% yield.