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Microwave assisted free radical cyclisation of alkenyl and alkynyl isocyanides with thiols

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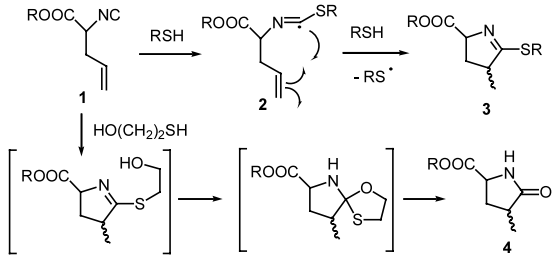
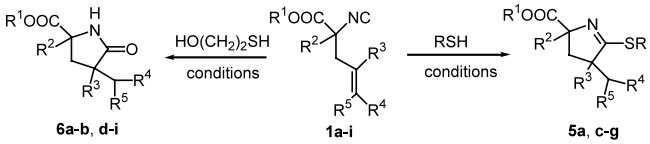
Abstract—Alkenyl and alkynyl isocyanides were synthesised and then reacted, using microwave flash-heating technology, with thiophenol, 2-mercaptoethanol and ethanethiol, in the presence of a radical initiator, to give highly functionalised pyrrolines and pyroglutamates. Direct comparison with results obtained using traditional heating techniques showed the advantage of using the microwave technology in terms of faster reactions and better yields. © 2003 Published by Elsevier Science Ltd.

The rapidly growing field of combinatorial chemistry has precipitated the development of new technologies aimed at improving the efficiency of performing chemical reactions. The microwave technique provides such a method. It's efficiency in dramatically accelerating reaction rates has recently been proven in several different fields of synthetic organic chemistry,[1,2] but only a few examples of radical reactions have been reported.[3] We now report that flash-heating by microwave irradiation promotes rapid thiol-mediated radical cyclisations of alkenyl and alkynyl isonitriles to give highly functionalised pyrrolines and pyroglutamates (Scheme 1).[4,5] The usefulness of this technique is exemplified by comparison with traditional thermal heating techniques. In a typical reaction a thiyl radical ($RS^{\bullet}$) adds to an alkenyl isocyanide **1**, generating a thioimidoyl radical **2** which undergoes 5-*exo* cyclisation and subsequent hydrogen atom abstraction affords *cis*- and *trans*-pyrrolines **3**. When 2-mercaptoethanol is used *cis*- and *trans*-pyroglutamates **4** are obtained, through the intermediacy of a cyclic derivative which undergoes hydrolysis during the reaction (Scheme 1). Alkenyl isocyanides **1a–i** (Scheme 2) were synthesised in a few steps from simple starting materials. Compounds **1a–e** were obtained by *C*-alkylation of commercially available ethyl isocyanoacetate[6,7] and **1f–i** by derivatisation of glycine through the corresponding *N*-formyl derivatives,[8] dehydration[4] to the isocyanides and then alkylation using standard methods.

Free radical cyclisations of isocyanides **1a–i** with benzenethiol, ethanethiol and 2-mercaptoethanol were performed using traditional thermal heating techniques and microwave flash-heating[9] (Scheme 2 and Table 1). Cyclisation of the isocyanides, **1a** and **1g**, gave the *cis*- and *trans*-pyrrolines **5a** and **5g** in satisfactory yields, 60



Scheme 1. Thiol-mediated radical cyclisation mechanism.



a	R^1 = Et	R^2= R^3 = R^4 = R^5 = H		
b	R^1 = Et	R^2 = $CH_2CH{=}CH_2$	R^3 = R^4 = R^5 = H	
c	R^1 = Et	R^2 = R^4 = R^5 = H	R^3 = Me	
d	R^1 = Et	R^2 = $CH_2CCH_3{=}CH_2$	R^3 = Me	R^4 = R^5 = H
e	R^1 = Et	R^2 = R^3 = H	R^4 = R^5 = Me	
f	R^1 = PMB	R^2 = R^3 = R^4 = R^5 = H		
g	R^1 = Bn	R^2 = R^3 = R^5 = H	R^4 = Ph	
h	R^1 = Bn	R^2 = R^4 = R^5 = H	R^3 = Me	
i	R^1 = Bn	R^2 = $CH_2CCH_3{=}CH_2$	R^3= Me	R^4 = R^5 = H

Scheme 2. Thiol-mediated radical cyclisations of alkenyl isocyanides.

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Table 1. Radical cyclisations of isocyanides **1a–i** with thiophenol, 2-mercaptoethanol and ethanethiol

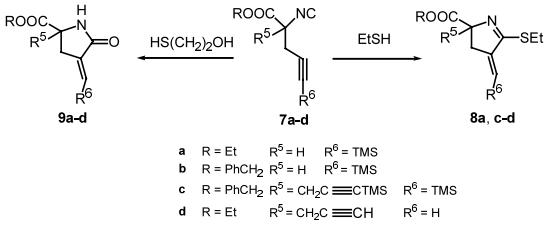
Entry	Isocyanide	Thiol	Conditions[a]	Product	Yield[b] (%)	*cis*/*trans*[c]
1	**1a**	PhSH	AIBN,[10] 110°C, 1 h	**5a**	60	1:1
2	**1a**	PhSH	AIBN, μω, 130°C, 5 min	**5a**	75	1.1:1
3	**1a**	$HS(C_2H_4)OH$	AIBN, 40°C, 1.5 h	**6a**	88	1:1
4	**1a**	$HS(C_2H_4)OH$	AIBN, μω, 130°C, 5 min	**6a**	99	1:1
5	**1b**	$HS(C_2H_4)OH$	AIBN, 40°C, 7 h	**6b**	96	1.2:1
6	**1b**	$HS(C_2H_4)OH$	AIBN, μω, 130°C, 5 min	**6b**	98	2:1
7	**1c**	EtSH	ACN,[10] μω, 130°C, 5 min	**5c**	47	–
8	**1d**	$HS(C_2H_4)OH$	ACN, μω, 130°C, 5 min	**6d**	61	–
9	**1d**	EtSH	ACN, μω, 130°C, 5 min	**5d**	51	–
10	**1e**	EtSH	ACN, μω, 130°C, 5 min	**5e**	80	1.4:1
11	**1e**	$HS(C_2H_4)OH$	ACN, μω, 130°C, 5 min	**6e**	94	1.3:1
12	**1f**	$HS(C_2H_4)OH$	AIBN, 40°C, 12 h	**6f**	85	1.1:1
13	**1f**	$HS(C_2H_4)OH$	AIBN, μω, 130°C, 5 min	**6f**	96	1:1
14	**1f**	EtSH	AIBN, μω, 130°C, 5 min	**5f**	63	1.1:1
15	**1g**	EtSH	ACN, 110°C, 5 h	**5g**	40	1:1
16	**1g**	EtSH	ACN, μω, 130°C, 5 min	**5g**	78	1.2:1
17	**1g**	$HS(C_2H_4)OH$	ACN, μω, 130°C, 5 min	**6g**	76	1.3:1
18	**1h**	$HS(C_2H_4)OH$	AIBN, μω, 130°C, 5 min	**6h**	64	–
19	**1i**	$HS(C_2H_4)OH$	AIBN, μω, 130°C, 5 min	**6i**	82	–
20	**1a**	PhSH	μω, 130°C, 10 min	**5a**	58	1:1
21	**1a**	$HS(C_2H_4)OH$	μω, 130°C, 10 min	**6a**	70	1:1
22	**1b**	$HS(C_2H_4)OH$	μω, 130°C, 10 min	**6b**	85	1.4:1
23	**1f**	$HS(C_2H_4)OH$	μω, 130°C, 10 min	**6f**	91[d]	–

[a] All reactions were performed using 2.0 equiv. of thiol (except entries 20–23, where 4.0 equiv. were used) in dry degassed toluene and 0.2 equiv. of radical initiator.
[b] Isolated yield after chromatography.
[c] Determined by NMR.
[d] Calculated by HPLC by comparison with a standard.

and 40%, respectively, under thermal conditions (entries 1 and 15, Table 1).

When microwave flash-heating was used the products were obtained in higher yields (75 and 78%, respectively, entries 2 and 16, Table 1), in only 5 min. Similarly microwave assisted cyclisations of more substituted alkenyl isocyanides with ethanethiol afforded pyrrolines **5c–f** in good yields (entries 7, 9, 10 and 14, Table 1). When 2-mercaptoethanol was used *cis*- and *trans*-pyroglutamates **6a–b** and **6d–f** were obtained in excellent yields (entries 3–6, 8, 11–13 and 17–19, Table 1), both with thermal and microwave conditions. The microwave reactions afforded slightly better yields and were completed in much shorter times. Cyclisations were also attempted using benzenethiol and 2-mercaptoethanol in the absence of radical initiator. Isocyanides **1a–b** and **1f** all cyclised in good yield using this method (Table 1, entries 20–23), although the reaction time had to be increased to 10 min with 4 equiv. of thiol. The obtained yields were lower than with the radical initiator but still comparable to thermal methods.

When alkynyl radical traps were used (isocyanides **7a–d**), the reaction followed a similar pattern to that of alkenyl isocyanides, as shown in Scheme 3. Under standard thermal conditions, cyclisation of alkynyl isocyanides **7a**, **7c** and **7d**, using 2-mercaptoethanol, gave surprisingly poor yields of the corresponding pyroglutamates **9a**, **9c** and **9d** (entries 2, 6 and 8, Table 2), whereas with microwave flash-heating good yields were



Scheme 3. Thiol-mediated free radical cyclisation of alkynyl isocyanides.

obtained (entries 3, 7, and 9, Table 2). High yields of pyrrolines (**8a**, **8c** and **8d**) were also obtained using ethanethiol under thermal and microwave assisted conditions.

In conclusion pyrrolines and pyroglutamates of type **5**, **6**, **8** and **9** have been synthesised in good to excellent yields employing microwave flash-heating technology. Reaction times were dramatically reduced and cyclisations of alkynyl isocyanides **7**, which gave poor results under standard thermal conditions, were improved.

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Table 2. Radical cyclisations of alkynyl isocyanides **7a–d** with ethanethiol and 2-mercaptoethanol[a]

Entry	Isocyanide	Thiol	Conditions	Product	Yield[b] (%)
1	**7a**	EtSH	ACN,[10] μω, 130°C, 5 min	**8a**	86
2	**7a**	$HS(C_2H_4)OH$	ACN, 110°C, 7.5 h	**9a**	Traces
3	**7b**	$HS(C_2H_4)OH$	ACN, μω, 130°C, 5 min	**9b**	72
4	**7c**	EtSH	ACN, 110°C, 3 h	**8c**	73
6	**7c**	$HS(C_2H_4)OH$	ACN, 110°C, 2.5 h	**9c**	35
7	**7c**	$HS(C_2H_4)OH$	ACN, μω, 130°C, 5 min	**9c**	73
8	**7d**	$HS(C_2H_4)OH$	ACN, 80°C, 6 h	**9d**	37
9	**7d**	$HS(C_2H_4)OH$	ACN, μω, 130°C, 5 min	**9d**	60
10	**7d**	EtSH	ACN μω, 130°C, 5 min	**8d**	40

[a] All reactions were performed using 2.0 equiv. of thiol in dry degassed toluene and AIBN or ACN (0.2 equiv.) as radical initiator.
[b] Isolated yield after chromatography.

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8. Wade, H.; Scanlan, T. S. *J. Am. Chem. Soc.* **1999**, *121*, 1434–1443.
9. All microwave reactions were performed using the Smith Synthesiser™.
10. AIBN: *N*,*N*′-azobisisobutyronitrile; ACN: *N*,*N*′-cyclohexylcarbonitrile.