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DES as a Green Solvent to Prepare 1,2-bis-Organylseleno alkenes. Scope and Limitations

Eric F. Lopes, Lóren C. Gonçalves, Julio C.G. Vinueza, Raquel G. Jacob, Gelson Perin, Claudio Santi, Eder J. Lenardão

PII:	\$0040-4039(15)30291-4
DOI:	http://dx.doi.org/10.1016/j.tetlet.2015.10.095
Reference:	TETL 46924
To appear in:	Tetrahedron Letters
Received Date:	9 October 2015
Accepted Date:	28 October 2015



Please cite this article as: Lopes, E.F., Gonçalves, L.C., Vinueza, J.C.G., Jacob, R.G., Perin, G., Santi, C., Lenardão, E.J., DES as a Green Solvent to Prepare 1,2-bis-Organylseleno alkenes. Scope and Limitations, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.10.095

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Graphical Abstract

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DES as a Green Solvent to Prepare 1,2-bis- Organylseleno alkenes. Scope and Limitations	Leave this area blank for abstract info.
Eric F. Lopes, Lóren C. Gonçalves, Julio C. G. Vinueza, Raquel G. Jacob, Gelson Perin, Claudio Santi and Eder J. Lenard	dão*
$R^{1} \xrightarrow{R^{1} = R^{1}} R^{1} \xrightarrow{R^{2}SeSeR^{2}} \xrightarrow{R^{2}SeSeR^{2}} R^{1}$ only product R ¹ NaBH ₄ , 90 °C, N ₂ NaB	$R = H \qquad R \qquad SeR^{2} \qquad R \qquad SeR^{2}$ $CI/urea 1:2 \qquad R^{2}Se \qquad + \qquad R \qquad SeR^{2}$ $H_{4}, 90 \ ^{\circ}C, N_{2}$
$R^1 = C_6 H_5$, $CH_2 OH$ $R^2 = aryl, butyl$	R = aryl, alkyl, cyclohexenyl



Tetrahedron Letters journal homepage: www.elsevier.com

DES as a Green Solvent to Prepare 1,2-bis-Organylseleno alkenes. Scope and Limitations

Eric F. Lopes,^a Lóren C. Gonçalves,^a Julio C. G. Vinueza,^a Raquel G. Jacob,^a Gelson Perin,^a Claudio Santi^b and Eder J. Lenardão^{a,}*

^a Laboratório de Síntese Orgânica Limpa - LASOL - CCQFA - Universidade Federal de Pelotas - UFPel - P.O. Box 354 - 96010-900, Pelotas, RS, Brazil, ^b Dipartimento di Scienze Farmaceutiche, Group of Catalysis and Green Chemistry, Università degli Studi di Perugia, Perugia, Italy.

ARTICLE INFO

Received in revised form

Organoselenium Compounds

Article history: Received

Available online

Green Chemistry Bis-chalcogen Alkenes Deep Eutectic Solvent

Accepted

Keywords.

Alkynes

ABSTRACT

We describe here our results on the use of choline chloride/urea 1:2 as a deep eutectic solvent (DES) in the synthesis of vinyl selenides. A good selectivity for the (*E*)-1,2-bis-organylseleno alkenes was observed starting from terminal alkynes and diaryl or dibutyl diselenides in the presence of NaBH₄. The reaction of 1,3-butadiynes with diphenyl diselenide afforded exclusively the respective mono-selenylated (*Z*)-alkenynes. Diphenyl ditelluride reacted with phenylacetylene and 1,4-diphenyl-but-1-en-3-yne affording (*Z*)-phenyltelluro alkenes in good yields.

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The synthesis and reactivity of organoselenium compounds is described in a number of books and reviews.¹ Since the discover that some selenium-containing small molecules possess GPxmimicking activity, acting as anti-oxidant,^{2,3} the search for new bioactive Se-based molecules and selective methods to prepare them have exponentially increased. More recently, 1,2-bisorganylseleno alkenes have aroused the interest of chemists and biochemists due to their pharmacological properties; more specifically, some of them presented excellent antinociceptive and antioxidant activities (Figure 1).⁴ The bis-selenylation of alkynes is the most straightforward and atom-economic way to prepare 1,2-bis-organylseleno alkenes.^{1e} This reaction can be performed using radical selenium species⁵ or diorganyl diselenides in the presence of a transition metal,⁶ such as palladium and furnishes selectively the Z-isomer. The use of heavy metals and high temperature, besides the toxicity and hazard associated with the use of volatile organic solvents (VOCs) are some drawbacks of these protocols, which are incompatible with the green requirements of the modern chemical and pharmaceutical industry.⁷

Recently, improvements have been proposed by $us^{4b,8}$ and others^{4a,9} on the selective and clean synthesis of (*E*)-1,2-bisorganylchalcogen alkenes. These new approaches include the use of environmentally benign catalysts (FeCl₃^{4a} or CuI/Zn^{4b}), green solvents (glycerol,^{8a} ionic liquid⁹) or even solvent-free conditions under microwave irradiation.^{8b} Despite the greenness of these

protocols, some of them present limitations in the scope, e.g., are restrict to internal alkynes and aromatic diselenides. Thus, the search for new synthetic routes to these valuable chalcogen derivatives in a green and selective way is deeply interesting.



Figure 1. (*E*)-1,2-Bis-arylseleno alkenes with antioxidant and analgesic-like (antinociceptive) properties.⁴

Very recently, the use of deep eutectic solvents (DES) has been explored in organic synthesis as a green alternative to VOCs and fluorinated ionic liquids (ILs). DES are usually composed by a quaternary ammonium salt and a hydrogen bond donor (HBD) and are usually named as third generation or advanced ILs (Figure 2).¹⁰ The possibility of using cheap, biodegradable precursors, combined with several green features (negligible volatility, high polarity, versatility), make DES a greener solvent than the 'classical' ILs. The physical-chemical properties of DES can be tuneable and are dependent of the stoichiometric ratio and the identity of the ammonium salt and the HBD parts.^{10d} One of the most studied DES is the choline chloride (ChCl):urea 1:2 mixture, which has been successfully used as a solvent in cross-

^{*}Corresponding author. Tel./fax: +55 5332757533,

e-mail: lenardao@ufpel.edu.br

coupling, 11 click (CuAAC) synthesis, 12 hydrogenation 13 and dehydration reactions. 14



Figure 2. Deep Eutectic Solvents (DES) used in this study.

Thought the versatility and green features of DES combined with the synthetic and biological attributes of 1,2-bisorganylseleno alkenes and vinyl chalcogenides, we decided to explore the use of a 1:2 mixture of choline chloride (ChCl) and urea as a solvent in the synthesis of vinyl selenides and the results are presented here (Scheme 1).

Scheme 1. General purpose.

Aiming to define the best protocol to the hydrochalcogenation of terminal alkynes 1 with diorganyl dichalcogenides 2 using DES as the reaction medium, different reducing systems were tested to prepare the nucleophilic species of selenium in situ. Initially, we chose phenylacetylene 1a (1.0 mmol) and diphenyl diselenide 2a (0.5 mmol) as model substrates to define the best reaction conditions (Table 1). We started by using thiourea dioxide in the presence of 13% aq. NaOH (TUD/NaOH)¹⁵ as the reducing agent to cleave the Se-Se bond in 2a and anhydrous ChCl:urea 1:2 (DES A, 1.5 mL) as the reaction medium. Due to the viscosity of the solvent, the reactions were performed at 90 °C, to facilitate the homogenization of the reaction mixture. By using these conditions, the only product observed after 2 h under N_2 was (Z)- β -phenylselenostyrene **5a** in 61% yield (Table 1, entry 1). This result encouraged us to extend the reaction time aiming to promote the insertion of a second moiety of PhSe, as in the (E)-1,2-bis-phenylseleno styrene **3a**. The reaction progress was followed by TLC and after 22 h we observed the formation of a mixture of the desired compound 3a, the (Z)-isomer 4a and the mono-selenide 5a in 67% overall yield and a ratio 3a:4a:5a of 18:76:6 (Table 1, entry 2).

Aiming to improve the selectivity for the (E)-1,2bis(phenylseleno)styrene **3a**, different eutectic mixtures were tested (Table 1, entries 3-5) and the best yield of **3a** using TUD/NaOH was obtained when ChCl/oxalic acid (DES C) was used as the solvent (65% yield after 22 h, ratio **3a**:**4a** = 89:11; Table 1, entry 4). Because we are interested in new uses of glycerol as a bio-based and renewable feedstock, the reaction was also tested using this solvent, but the selectivity to the desired (E)-1,2-bis-phenylseleno styrene **3a** was inferior to that using DES (Table 1, entry 6 vs. 4). ChCl:urea was then fixed as the solvent and the reducing agent was changed to aqueous hypophosphorous acid (0.5 mL, 50% w/w).¹⁶ In this case, the diphenyl diselenide was totally consumed after 1 h to afford a mixture of mono- and 1,2-bis-phenylseleno alkenes **5a**, **3a** and **4a**, with large predominance of **5a** (Table 1, entry 7).

For our delight, when NaBH₄ was used as reducing agent, the desired (*E*)-1,2-bis-phenylseleno styrene **3a** was obtained in excellent yield and selectivity after 1 h at 90 °C under N₂, among a small amount of the (*Z*)-isomer **4a** (94% yield, **3a:4a** ratio= 91:9; Table 1, entry 8). This result is superior both in terms of total yield and selectivity compared to the use of other green

including glycerol^{8a} and solvents, the ionic liquid [bmim][BF₄]¹⁷ (Table 1, entries 9 and 10). Additional assays were performed to verify the effect of time, temperature and stoichiometric ratio of the reagents in the yield and selectivity of the reaction. Thus, for example, it was observed a slight increase in the selectivity to 3a when stoichiometric amounts of phenylacetylene 1a and PhSe)₂ 2a were used, even if the yield resulted to be slightly lower (Table 1, entry 11), indicating that an excess of alkyne is necessary. It was observed also that increasing the reaction time did not improve the final yield while decreased the selectivity, with the formation also of the monoselenylated alkene 5a (Table 1, entry 12). The temperature and the N₂ atmosphere had also a crucial influence in the reaction, and the yields were drastically diminished when the reaction was performed at 60 °C or in an open flask (Table 1, entries 13 and 14). The presence of water in the reaction mixture (0.5 mL) had a negative effect, reducing both, the selectivity and the yield of the reaction (Table 1, entry 15), indicating that the removal of water from the DES or their precursors is a critical point to be considered. Finally, the effect of energy source was evaluated and it was observed that both microwaves and ultrasound are not suitable to this reaction, once only modest yields and low selectivity were observed using them (Table 1, entries 16 and 17).

Table 1. Optimization of the reaction conditions.^a

					Ph
	H	reducing age	nt PhSe	F	hSe SePh
	+ ~ ⁵⁰ 5	Se solvent	- Ph	SePh +	4a
	1a 2	90 °C, N ₂ 2a		3a	Ph SePh
					5a
Entry 1 2	Reducing	Solvent	Time	Yield	ratio of
	agent ^b	Solvent	Time	$(\%)^{c}$	3a 4a 5a
1	TUD/NaOH	DES A	2 h	61	0 0 100
2	TUD/NaOH	DES A	22 h	67	18 76 6
3	TUD/NaOH	DES B	22 h	85	42 14 44
4	TUD/NaOH	DES C	22 h	65	89 11 0
5	TUD/NaOH	DES D	22 h	43	79 12 9
6^{d}	TUD/NaOH	Glycerol	2 h	85	60 10 30
7	aq. H ₃ PO ₂	DES A	1 h	98	34 3 63
8	$NaBH_4$	DES A	1 h	94	91 9 0
9	$NaBH_4$	Glycerol ^{8a}	1 h	75	77 23 0
10	NaBH ₄	[bmim][BF ₄] ¹⁷	3 h	85	26 0 74
11^{e}	$NaBH_4$	DES A	3 h	82	96 4 0
12	$NaBH_4$	DES A	6 h	88	76 10 14
13 ^f	$NaBH_4$	DES A	1 h	39	26 28 46
14^{g}	NaBH ₄	DES A	1 h	60	57 7 36
15 ^h	NaBH ₄	DES A	1 h	38	58 8 34
16^{i}	$NaBH_4$	DES A	40 min	79	91 7 2
17 ^j	$NaBH_4$	DES A	20 min	49	51 12 37

^a Reactions are performed using diphenyl diselenide **2a** (0.15 mmol) and reducing agent in 1.5 mL of solvent at 90 °C under N₂ atmosphere. After the generation the benzeneselenolate anion (30 min), phenylacetylene **1a** (0.3 mmol) was added. ^b TUD/NaOH = a mixture of thiourea dioxide (0.3 mmol) in 13% aq. NaOH (0.5 mL). ^c Determined by GC/MS and ¹H NMR of the crude reaction mixture. ^d 4.0 mL of glycerol was used as solvent. ^e Stoichiometric amounts of **1a** and **2a** (0.3 mmol) were used. ^f The reaction was performed at 60 °C. ^g The reaction mixture. ⁱ An ultrasound probe was used instead an oil bath. ^j The reaction was irradiated with microwaves instead using an oil bath.

With the best conditions in hands,¹⁸ we selected different alkynes and diselenides to speculate on the generality of the reaction in the preparation of (*E*)-1,2-bis-organylseleno alkenes **3** (Table 2). As it can be seen in Table 2, starting from terminal alkynes **1** the DES/NaBH₄ system can be successfully used to prepare selectively (*E*)-1,2-bis-organylseleno alkenes in most of cases. For example, 4-ethynyl anisole **1b** reacted with diphenyl diselenide **2a** to afford after 2 h a mixture of (*E*)-1,2-bis-phenylseleno-4-methoxystyrene **3b** and (*Z*)-2-phenylseleno-4-methoxystyrene **5b** in 77% overall yield and a **3b:5b** ratio =

83:17 (Table 2, entry 2). The mono and bis-selenylated alkenes are easily separable by column chromatography. The presence of two methoxyl groups in the aromatic ring of the arylalkyne, as in **3c**, caused an increase in the amount of the respective (*Z*)-vinyl selenide **5c** and a mixture of (*E*)-1,2-bis-phenylseleno-3,5-(dimethoxy)styrene **3c** and (*Z*)-(2-phenylseleno)3,5-(dimethoxy)styrene **5c** was obtained in 80% yield after 1 h, with a **3c:5c** ratio= 47:53 (Table 2, entry 3).

When electron-withdrawing groups are present in the arylalkyne, a longer time was necessary to complete the reaction. Thus, 1-chloro-4-ethynylbenzene 1d reacted with PhSeSePh 2a for 4 h to afford a mixture of the respective (E)-1,2bisphenylseleno alkene **3d** and the (Z)-vinyl selenide **5d** in 69% yield and a 3d:5d ratio = 65:35. Surprising, the only product from the reaction between 4-ethynyl benzonitrile 1e and 2a was (Z)-(2-phenylseleno)4-(cyano)styrene 5d, isolated in 56% yield after 5 h (Table 2, entry 5). 1-Dodecyne 1f and the conjugated enyne 1-ethynylcyclohex-1-ene 1g reacted with diphenyl diselenide 2a to afford exclusively the respective (E)-1,2-bisphenylseleno-alkenes 3f and 3g in 66 and 74% yields after 24 and 7 h respectively (Table 2, entries 6-7). These are very interesting findings, once monoalkyl-substituted alkynes have a low reactivity and poor selectivity in selenylation reactions in the absence of a transition metal catalyst.1e The reaction was also explored using diverse diaryl diselenides, containing electrondonnor and electron-attractor groups in the aromatic ring (Table 2, entries 8-10). It was observed that electron-rich diselenides 2b and 2c favored the formation of the respective (E)-1,2-bisarylseleno alkene, but with a decrease in selectivity and yields compared to diphenyl diselenide 2a (Table 2, entries 8-9 vs entry 1). The presence of electron-withdrawing groups in the diaryl diselenide 2d however, decreases the rate of the reaction and the amount of the respective (E)-1,2-bis-arylseleno alkene 3j was diminished compared to the monoselenylated alkene 5j (Table 2, entry 10). Dibutyl diselenide 2e was also submitted to the reaction with phenylacetylene **1a** under our conditions and after 2 h it afforded selectively (E)-1,2-bis-butylseleno styrene **3k**, together with (Z)-2-butylselenostyrene 5k in 82% yield and a **3k:5k** ratio = 82:18 (Table 2, entry 11). Aiming to prepare highly functionalized vinyl chalcogenides, we decided to extend the DES-based method to the 1,3-butadyines 1h and 1i. Despite the low reactivity of internal alkynes to the reaction with selenolate, the presence of a second, conjugated triple bond favors the reaction. Thus, 1,4-diphenyl-but-1-en-3-yne 1h reacted with diphenyl diselenide 2a to afford, after 12 h, the respective (Z)-1phenylseleno-1,4-diphenyl-but-1-en-3-yne 51 as the only product in 89% yield (Table 2, entry 12). Similarly, the dimer of propargyl alcohol 1i afforded after 5 h of reaction only (Z)-1,6dihydroxy-1-phenylseleno-hex-1-en-3-yne 5m in 73% yield (Table 2, entry 13). The DES was also a good solvent to promote the cleavage of the Te-Te bond of diphenyl ditelluride 2f with NaBH₄ and the subsequent hydroteluration of alkynes, affording (Z)-vinyl tellurides in reasonable yields (Table 2, entries 14-15). Vinyl tellurides are very useful precursors of alkenyl synthons in organic synthesis. They can be easily converted to vinyl anions by transmetalation with alkyl lithium¹⁹ or cyanocuprates,²⁰ for example, or directly coupled with terminal alkynes to afford enediynes.²¹ In all these reactions, the configuration of the double bond in the vinyl telluride is preserved, so the development of methods to access this class of compounds is pertinent. It was observed that diphenyl ditelluride 2f was less reactive under our optimized conditions, affording the respective adducts in lower yields compared to the selenium analog 2a. The difference in reactivity reflected in the different products in the case of the with phenylacetylene 1a, with the reaction (Z)-2phenyltellurostyrene **5n** being the only product after reaction for 5 h (Table 2, entries 14 *vs* 1). When 1,4-diphenyl-but-1-en-3yne **1h** was the starting material, the expected (*Z*)-1phenyltelluro-1,4-diphenyl-but-1-en-3-yne **5o** was obtained in 42% yield after 15 h (Table 2, entry 15).

To examine the involvement of a radical mechanism in the reaction, phenylacetylene **1a** and diphenyldiselenide **2a** were reacted in the presence of hydroquinone, a radical inhibitor. By using 5 mol% of hydroquinone, a mixture of **3a**, **4a** and **5a** was obtained in 68% yield and a **3a**:**4a**:**5a** ratio of 69:12:19 after 2 h at 90 °C. When an equimolar amount of hydroquinone was used, was used, after 3 h, the selenium derivatives were obtained in 76% yield and with a **3a**:**4a**:**5a** ratio of 62:6:32. In both reactions, unreacted diphenyl diselenide was recovered. These findings indicate that the reaction occurs in part by a radical mechanism,²² once the yield of the 1,2-bis-phenylseleno alkene is reduced in the presence of the radical scavenger, nevertheless ionic intermediates could also be involved.²³



Scheme 2. A plausible mechanism for the reaction.

A plausible explanation for the formation of bis- and monochalcogen alkenes is depicted in Scheme 2 for the reaction between phenylacetylene **1a** and diorganyl diselenide **2**. In the formation of the (E)-1,2-bis-organylseleno-alkene **3** a transition state like **I** could be involved, with concomitant addition of the selenolate to the terminal carbon and the capture of a second organylselanyl group by the incipient negative charge formed in the internal carbon of the new double bond (path A). In the formation of the (Z)-organylseleno alkene **5**, a transition state like **II**, involving the donation of a hydrogen from the solvent, could be part in the reaction (path B).

In conclusion, the DES ChCl:urea (1:2) combined with NaBH₄ was used for the first time in the selective synthesis of (E)-1,2bis-organylseleno alkenes starting from terminal alkynes and diorganyl diselenides. This reaction system presents interesting peculiarities, including the possibility to use alkyl and alkenyl monosubstituted alkynes in a very efficient way, what is not possible using other so-called green solvents.

Acknowledgments

We are grateful to CNPq and FAPERGS and Dipartimento di Scienze Farmaceutiche- Università degli Studi di Perugia "Fondo per il sostegno della Ricerca di Base 2015" for the financial support. Eder J. Lenardão is Bolsista CAPES - Processo No. BEX 6391/14-1. This research was undertaken as part of the scientific activity of the international multidisciplinary "SeS Redox and Catalysis" network.

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18. General procedure for the addition reaction: To a round-bottomed flask containing a solution of the diorganyl dichalcogenide 2 (0.5 mmol) in the deep eutectic solvent (ChCl:urea 1:2, 1.5 mL) under N₂ atmosphere, sodium borohydride (0.023g, 0.6 mmol) was added and the mixture stirred for 30 min at 90 °C. After that time, the alkyne 1 (1.0 mmol) was added and the reaction mixture was stirred at 90 °C for the time indicated in Table 2 (followed by TLC and GC). After that time, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (20.0 mL) and washed with saturated aqueous NH₄Cl (3x 20.0 mL). The organic phase was separated, dried over MgSO₄ and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using hexanes or a mixture of ethyl acetate/hexanes as the eluent. Detailed experimental procedure and spectral data of products **3** and **5** are listed in the Supplementary data.

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Table 2. Synthesis of 1,2-bis-chalcogen alkenes (3 and 4) and vinyl chalcogenides 5.^a

	R		ChCl/urea 1:2 R SeR ² R R ¹	R	SeR ²	
		1 2	NaBH ₄ , 90 °C, N ₂ (<i>E</i>)- 3 (<i>Z</i>)- 4	² + H	R ¹ (Z)- 5	
Entry	alkyne 1	R ² SeSeR ² 2	Products	Time (h)	Yield (%) ^{b,[ref]}	Ratio ^c 3 : 4 : 5
1	<u>الم</u>	Se Se Za	Se -	1	94 ^[8b]	93 : 7 : 0
2	H ₃ CO-	2a	CH_{3O} CH_{3O} CH_{3O} $+$ Se Se Se Se Se Se Se Se	2	77 [24]	83 : 0 : 17
3	H ₃ CO H ₃ CO 1c	2a	$H_{3}CO - Se - S$	1	80 [25]	47 : 0 : 53
4	CI	2a	Cl Se Se Se Se Se Se Se Se	4	69 ^[4b]	65 : 0 : 35
5	NC-	2a		5	56	0 : 0 : 100
6	₩ ₈ 1f	2a	Se-Co Se 3f	24	66 ^[9a]	100 : 0 : 0
7	(2a	Se-Se 3g	7	74	100 : 0 : 0
8	1a	Se Se Se	Se- 	2	74 ^[8b]	59 : 41 : 0
9	la	H ₃ CO Se Se Se 2c	$H_3CO - Se - Se - OCH_3 + H_3CO - Se - Se - OCH_3 + H_3CO - Se - Se - Se - OCH_3$	7	58 ^[4b]	86 : 14 : 0
10	Ia	F ₃ C Se Se CF ₃	$CF_3 \xrightarrow{CF_3} Se \xrightarrow{CF_3} + \xrightarrow{CF_3} Se \xrightarrow{CF_3} $	3	79 ^[4b]	67 : 0 : 33
11	1a	Se 2e	Se	2	82 [5,26]	82 : 0 : 18
12	() 	2a	Se-	12	89 ^[27]	0 : 0 : 100
13	HO	2a	HO Se 5m OH	5	73 [27]	0 : 0 : 100

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6			Tetrahedron Letters			
14	1a	Te Te Te	Te- 5n	5	68 [28]	0 : 0 : 100
15	1h	2f		15	42 [19]	0 : 0 : 100
^a All the	reactions were	carried out with alkyne 1 (0.6 mmol) a	and diarylchalcogenides 2 (0.6 mmol) 1.5 mL of	f DES at 90 °C und	der N2 atmosp	here. ^b Yield afte
purificatio	on by column chr	romatography. ^c Determined by GC/M	S of the crude reaction mixture and confirmed a	fter isolation of pu	re products.	
					2	
		Q				
	6					