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Microwave-assisted ethylene–alkyne cross-metathesis: synthesis of chiral 2-(*N*-1-acetyl-1-arylmethyl)-1,3-butadienes

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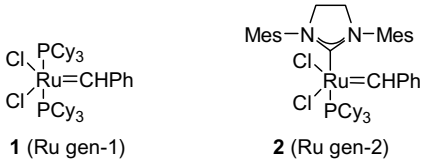
Abstract—Chiral 1-arylpropargyl amides, which are resistant to undergoing ethylene–alkyne cross-metathesis at atmospheric pressure, were reacted under microwave irradiation to afford enantiomerically enriched 2-(*N*-1-acetyl-1-arylmethyl)-1,3-butadienes within a few minutes. Enantiomerically enriched amides underwent ethylene–alkyne cross-metathesis with retention of configuration at the propargylic/allylic position. A series of chiral 2-(*N*-1-acetyl-1-arylmethyl)-1,3-butadienes were synthesised with ee ⩾95%; these latter compounds could be used as building blocks for the synthesis of new antifungal and antiaromatase agents.

1. Introduction

Enyne metathesis (EYM) is a bond reorganisation of an alkene and an alkyne to give a 1,3-diene. It has been used in both intramolecular and intermolecular applications.[1] Intramolecular examples of alkyne–alkene metathesis (enyne RCM) are well documented in the literature.[2–4] Intermolecular enyne metathesis has seen fewer synthetic applications because it has additional difficulties when compared to the unimolecular one. Recently, Mori et al.[5a–c] and Diver et al.[5d–f] developed an approach to 1,3-butadienes by ethylene–alkyne cross-metathesis using the first and second-generation Grubbs' catalyst (Fig. 1).

2. Results and discussion

In the context of our synthetic and molecular modelling studies on racemic and enantiomerically pure new antifungal and antiaromatase agents[6] and in view of our previous studies related to the synthesis of chiral synthons of high enantiomeric purity useful for the preparation of bioactive compounds in a non-racemic form,[7] we turned our attention to the synthesis of enantiomerically enriched 2-(*N*-1-acetyl-1-arylmethyl)-1,3-butadienes **7** as building blocks for the stereoselective synthesis of compounds related to bifonazole **3**, letrazole **4** and more complex antifungal azole derivatives such as **5** (Fig. 2).[6a,b]



1 (Ru gen-1) **2** (Ru gen-2)

Figure 1.

Diene **7** was transformed via a Diels–Alder reaction, followed by an oxidation–cyclisation, into **6**. Compound **7** was obtained in enantiomerically enriched form from chiral 1-arylpropargyl amides **8** via ethylene–alkyne cross-metathesis reaction (Scheme 1).

Only a few cases of enyne cross-metathesis with NH-amides have been reported in the literature,[8] in particular it has been reported that secondary acetamides and pivaloylamides undergo cross-metathesis with low yield also in the presence of high Grubbs' catalyst loading. In some cases, the metathesis reactions are problematic, since the catalyst may be inhibited by the complex formation properties of amines and amides, in the specific case of amides, the catalyst may become inhibited by intramolecular interaction with the carbonyl group.[1d] Recently, Smulik and Diver investigated the ethylene metathesis for 1-substituted-propargyl alcohols, these substrates reacted poorly in ethylene–alkyne cross-metathesis. In order to circumvent this problem, a high

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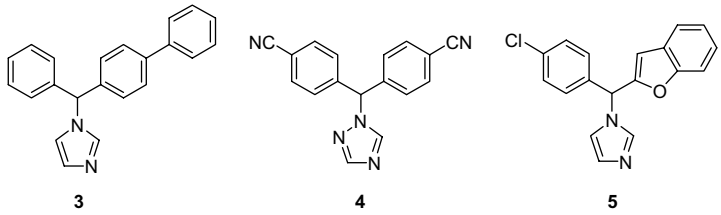
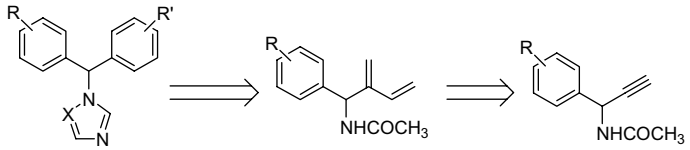


3 4 5

Figure 2.



6 7 8

X = CH, N

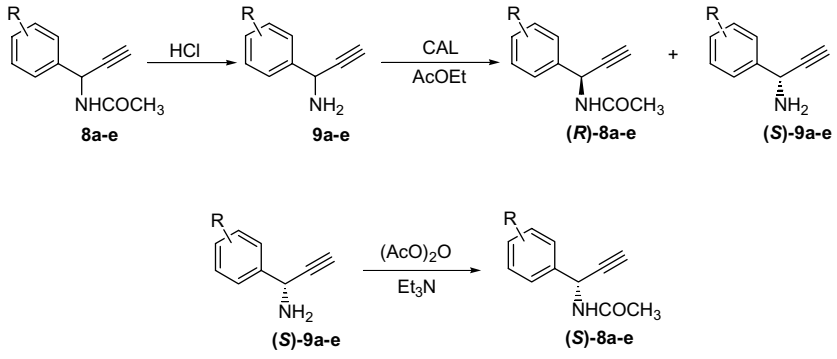
Scheme 1.

pressure of ethylene (60 psi) was used.[5d,e] Metathesis reactions were carried out at room temperature or at slightly elevated temperature, sometimes requiring several hours to achieve full conversion. Due to our previous experience in the field of microwave-assisted organic reactions,[9] we decided to circumvent the problem of long reaction time and high pressure of ethylene, by carrying out the ethylene–alkyne metathesis reaction under microwave irradiation.[10] While several examples of microwave-assisted diene ring closing metathesis and diyne ring closing metathesis have been reported, to the best of our knowledge, no microwave-assisted intermolecular EYM has been described.[11]

Herein, we report the synthesis of enantiomerically enriched 2-(*N*-1-acetyl-1-arylmethyl)-1,3-butadienes, important building blocks for synthesis of potential biologically active compounds, via microwave-assisted EYM between chiral 1-arylpropargyl amides and ethylene.

Racemic 1-arylpropargyl amides **8a**–**e** were prepared according to our previous work via a Ritter reaction of the corresponding propargyl alcohols, obtained by the addition of ethynylmagnesiumbromide to the appropriate aldehydes.[7] Enantiomerically pure 1-arylpropargyl acetamides (*R*)-**8a**–**e** were prepared by stereoselective amidation using acyl transfer reactions catalysed by *Candida antarctica* lipase (CAL) of racemic 1-arylpropargylamines **9a**–**e**,[7] obtained after acidic hydrolysis of racemic **8a**–**e**. Enantiomerically pure amines (*S*)-**9a**–**e** were converted into the corresponding enantiopure acetamides (*S*)-**8a**–**e** by acetylation with acetic anhydride in the presence of triethylamine with a retention of configuration at the propargylic position (Scheme 2 and Table 1).

We initially investigated the reaction of 1-phenylpropargylamide (*R*)-**8a** with ethylene at 1 atm using different solvents and different temperatures. First- and second-generation Grubbs' catalysts were used in different loadings but in not one case were traces of diene (*R*)-**7a** detected. Hence, we decided to investigate the reactivity of (*R*)-**8a** with ethylene under microwave irradiation.[11] Microwave irradiation produces efficient internal heating; this leads to a dramatic rate enhancement of the metathesis reaction and to an increased catalyst lifetime by the elimination of wall effects.[12] The results of the ethylene–alkyne metathesis of (*R*)-**8a** under microwave irradiation are summarised in Table 2. By carrying out the reaction in a closed vessel saturated with ethylene, in toluene at 80 °C with 5 mol % of **2** for



8a-e 9a-e (*R*)-8a-e (*S*)-9a-e (*S*)-9a-e (*S*)-8a-e

Scheme 2.

Table 1. Chiral 1-arylpropargyl amides

	R	ee[a] (%)	$[\alpha]_D^{20}$[b]
(*R*)-**8a**	4-H	98	+61
(*R*)-**8b**	4-F	98	+51
(*R*)-**8c**	4-Cl	98	+81
(*R*)-**8d**	3-F	98	+59
(*R*)-**8e**	3-Me	98	+58
(*S*)-**8a**	4-H	98	−60
(*S*)-**8b**	4-F	98	−52
(*S*)-**8c**	4-Cl	97	−78
(*S*)-**8d**	3-F	98	−59
(*S*)-**8e**	3-Me	97	−57

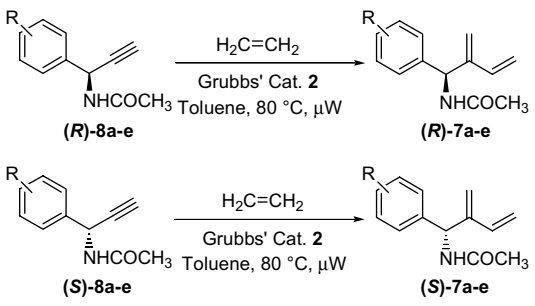
[a] Determined by chiral HPLC–MS using an (*S*,*S*)-Whelk-O1 column (50% water–methanol, 0.8 ml/min, UV-254).
[b] Measured in $CHCl_3$ solution (*c* 1.0).

Table 2. Reaction of (*R*)-**8a** with ethylene under microwave irradiation

Entry	Solvent	**2** (mol %)	*T* (°C)	Time (min)	Yield[a] (%)
1	Toluene	5	80	2 × 10	NR
2	Toluene	10	80	2 × 5	NC
3	Toluene	10	80	2 × 10	45
4	DCE	10	80	2 × 10	42

NR = no reaction; NC = not completed.
[a] Referred to isolated and purified materials.

20 min (two runs of 10 min) (entry 1), no traces of diene (*R*)-**7a** were detected and (*R*)-**8a** was fully recovered. With a higher catalyst loading (10 mol % of **2**) after 10 min (two runs of 5 min), HPLC–MS analysis of the crude mixture revealed the formation of (*R*)-**7a** and of a small amount of (*R*)-**8a** (entry 2). Longer reaction times resulted in better yields; no traces of (*R*)-**8a** could be detected (entry 3). After work-up with dimethylsulfoxide (DMSO),[13] to remove ruthenium by-products generated during the metathesis and purification by chromatography of the crude mixture, (*R*)-**7a** was recovered in 45% yield.[14,15] With the intention of improving the yield, we studied the effects of higher catalyst loading and higher temperatures, but all our efforts proved unsuccessful. The reaction of (*R*)-**8a** with ethylene in dichloroethane, a solvent non-transparent to microwaves, was investigated, but no improvement in the yield was observed (entry 4). On the basis of these data, the conditions reported in entry 2 were chosen to synthesise a series of substituted enantioenriched 2-(*N*-1-acetyl-1-phenylmethyl)-1,3-butadienes (*R*)-**7a**–**e** and (*S*)-**7a**–**e** (Scheme 3). The dienyl derivatives (*R*)-**7a**–**e** and



Scheme 3.

(*S*)-**7a**–**e** were determined to have ⩾95% ee by HPLC.[16] The enantiomeric excesses are reported in Table 3 as well as the yields, the specific rotation and the HPLC retention times.

Table 3. Enantioenriched 2-substituted butadienes

R		ee[a]	Yield[b] (%)	$[\alpha]_D^{20}(c)$[c]	HPLC t_R[a] (min)
4-H	(*R*)-**7a**	96	45	+34 (0.8)	56.6
4-F	(*R*)-**7b**	97	64	+36 (1.0)	67.2
4-Cl	(*R*)-**7c**	95	70	+69 (1.0)	52.4
3-F	(*R*)-**7d**	96	55	+20 (0.6)	67.8
3-Me	(*R*)-**7e**	95	48	+35 (0.7)	39.4
4-H	(*S*)-**7a**	95	44	−30 (0.8)	58.9
4-F	(*S*)-**7b**	96	62	−32 (1.0)	84.9
4-Cl	(*S*)-**7c**	95	68	−65 (0.4)	59.4
3-F	(*S*)-**7d**	95	54	−18 (0.6)	72.4
3-Me	(*S*)-**7e**	96	49	−37 (0.7)	42.1

[a] Determined by chiral HPLC–MS using an (*S*,*S*)-Whelk-O1 column (50% water–methanol, 0.8 ml/min, UV-254).
[b] Referred to isolated and purified materials.
[c] Measured in $CHCl_3$ solution.

3. Conclusion

In conclusion, a new methodology for the synthesis of enantioenriched 2-substituted butadienes has been developed. It has been shown that chiral 1-arylpropargyl amides do not undergo cross-metathesis with ethylene at atmospheric pressure; microwave irradiation is essential to afford chiral 2-substituted butadienes within a few minutes. Enantiomerically enriched alkynes underwent ethylene cross-metathesis with retention of configuration at the propargylic/allylic position, making this method suitable for preparing enantiomerically enriched dienes. This method is currently being used to prepare new potential biologically active derivatives of general structure **6**.

Acknowledgements

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14. Characterisation of compound **7a**: oil. ^{1}H NMR ($CDCl_3$): δ 7.47–7.26 (5H, m, Ph), 6.39–6.24 (1H, dd, $J = 17.7$ Hz, $J = 11.5$ Hz, CC*H*CH_2), 5.89 (1H, d, $J = 7.9$ Hz, C*H*N), 5.81 (1H, br d, $J = 7.9$ Hz, N*H*), 5.31 (1H, s, CCH_2), 5.19 (1H, d, $J = 17.7$ Hz, CCHCH_2), 5.09 (1H, s, CCH_2), 5.05 (1H, d, $J = 11.5$ Hz, CCHCH_2), 2.00 (3H, s, CH_3). IR (KBr): 1674, 1492 cm^{-1}. Electrospray MS *m*/*z*: 202 (M^+), 224 (M+Na).
15. General procedure for the synthesis of (*R*)-**7a**. Into an oven-dried pressure vessel equipped with a magnetic stirrer under argon, a solution of (*R*)-*N*-1-acetyl-1-aryl-propynylamine (*R*)-**8a** (0.6 mmol) in 4 ml of dry toluene was added. Grubbs' catalyst second-generation (10 mol %) was then added and the mixture submitted to an ethylene atmosphere under stirring. The vessel was introduced into the microwave oven and heated at 80 °C twice for 10 min under microwave irradiation. Dimethylsulfoxide (DMSO) (50 equiv) was added and the reaction mixture left under stirring for 12 h. The solvent was then removed in vacuo to afford a dark brown oil that was purified by flash chromatography (Et_2O–petroleum ether, 2:1) to give (*R*)-**7a** as a clear oil.
16. Enantiomeric excesses of chiral (*R*)-**7a**–**e** and (*S*)-**7a**–**e** were determined by HPLC–MS using an (*S*,*S*)-Whelk-O1 column (50% water–methanol, 0.8 ml/min, UV-254).