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Stereoselective synthesis of tri- and tetrasubstituted oxepanes via *n*-Bu_3SnH mediated *7-endo-trig* vinyl radical cyclisation

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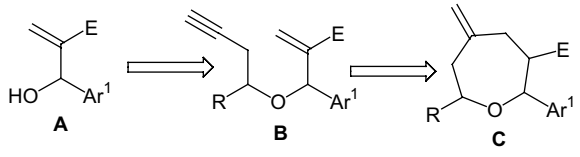
Abstract—A stereoselective *7-endo-trig* cyclisation of homopropargyl and phenyl homopropargyl derivatives of Baylis–Hillman adducts using *n*-Bu_3SnH/AIBN mediated vinyl radical cyclisation affords tri- and tetrasubstituted oxepanes, respectively, in good yields.

1. Introduction

Amongst various carbon–carbon bond forming reactions, the Baylis–Hillman reaction is important, giving rise to densely functionalised molecules and is considered to be atom economic. Highly functionalised Baylis–Hillman adducts have been used as starting materials for various stereoselective preparations of functionalised intermediates and in natural product synthesis.[1] Seven-membered oxacycles are structural fragments of a variety of bioactive natural products,[2] besides their use in pharmacological applications.[3] Examples of their occurrence in Nature range from the monocyclic compounds zoapatanol, isolaurepinnacin and rogiolenyne to the highly complex ciguatoxin.[4] The presence of these units in complex molecules make them challenging synthetic targets, thus resulting in the development of a number of synthetic methods.[5] The number of methods for the construction of seven-membered oxacycles has steadily increased.[6] Tin radical mediated cyclisation has been developed as a potential method for preparing various types of cyclic compounds via intramolecular carbon–carbon bond-forming processes.[7] There are few examples in the literature for the construction of seven-membered ring systems by a tin hydride-mediated *7-endo-trig* cyclisation strategy.[8] Recently, we reported the vinyl radical cyclisation of isomerised Baylis–Hillman propargyl and homopropargyl derivatives for the synthesis of functionalised tetrahydrofuran and tetrahydropyran ring systems, respectively.[9c,d] In continuation of our research on the use of Baylis–Hillman adducts for the synthesis of functionalised oxacycles,[9] we envisaged that substituted oxepane rings could be synthesised stereoselectively from simple homopropargyl derivatives and phenyl homopropargyl derivatives of the Baylis–Hillman adducts. Radical addition reactions of Baylis–Hillman adducts have been carried out to investigate the 1,2-stereoinduction during the H-abstraction[10] step; thereby the stereochemistry of the products could be predicted and all such reactions were found to be intermolecular radical addition reactions. We intended to synthesise tri- and tetrasubstituted oxepanes from *O*-homopropargyl Baylis–Hillman derivatives and to study the 1,2-stereoinduction in the H-abstraction step[11] of the tin hydride-mediated vinyl radical cyclisation.

2. Results and discussion

The synthetic strategy is depicted in Scheme 1, thus, radical cyclisation of homopropargyl and aryl homopropargyl derivatives **B** would provide oxepanes **C**. The



Scheme 1. Synthetic strategy.

Keywords: *7-endo-trig*; Vinyl radical; Baylis–Hillman adduct; Oxepanes; *n*-Butyltin hydride.
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derivatives **B** could be synthesised from Baylis–Hillman adducts **A** by heating with the corresponding homopropargyl alcohol in the presence of eco-friendly Montmorillonite-K10 clay[9c] as catalyst, under neat conditions. They can also be prepared from bromide derivatives of Baylis–Hillman adducts with homopropargyl alcohol using bromide as the leaving group.[12]

The synthesis of trisubstituted oxepanes is outlined in Scheme 2. The Baylis–Hillman adducts were prepared according to the literature procedure.[13] The *O*-alkylation of Baylis–Hillman adducts **1a–f** with homopropargyl alcohol under clay-catalytic conditions[9c] afforded the key intermediates **2a–f** in moderate yields (Scheme 2, Table 1). Adducts bearing a nitrile group at the activated position, **2d–f**, were not isolated in pure form since they could not be separated from minor isomerised products. Hence, after passing through a silica gel column, the mixture was subjected to radical cyclisation and the pure compounds **3d–f** were isolated after column chromatography. Radical cyclisation of compound **2a** was carried out with 1.5 equiv of tri-*n*-butyltin hydride and a catalytic amount of AIBN in benzene at reflux for 12 h under an inert atmosphere to afford the crude stannylated compound, which was protiodestannylated in dichloromethane with pyridinium *p*-toluenesulfonate (PPTS) to give 2,3,5-trisubstituted oxepane **3a** in good yield (Scheme 2, Table 1). To show the generality of this reaction, we examined the cyclisations of homopropargyl derivatives **2b–f** all of which furnished the desired cyclised products **3b–f** in good yields. The results are summarised in Table 1. All new compounds were characterised by IR, ^{1}H and ^{13}C NMR, DEPT-135, 2D H–H COSY, X–H COSY and HRMS data.

The 1,2-stereoinduction during H-abstraction leads to the aryl and ester groups being in a *cis* orientation in order to reduce steric interactions. The relative stereochemistry of the oxepane **3a** was established by NOE irradiation studies. Irradiation of H_a at δ 4.6 enhanced the resonance corresponding to H_b at δ 2.85 by 1.6%. Similarly, for compound **3f**, irradiation of H_a enhanced the signal corresponding to H_b by 3.2%. This indicated that they were *cis* to one another. Hence, the relative stereochemistry of the substituents is assigned as shown in Figure 1.

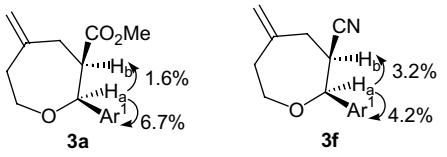
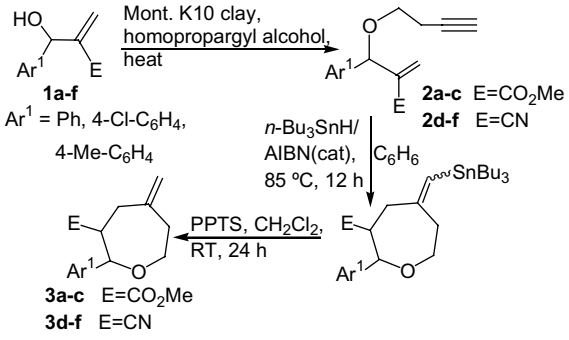
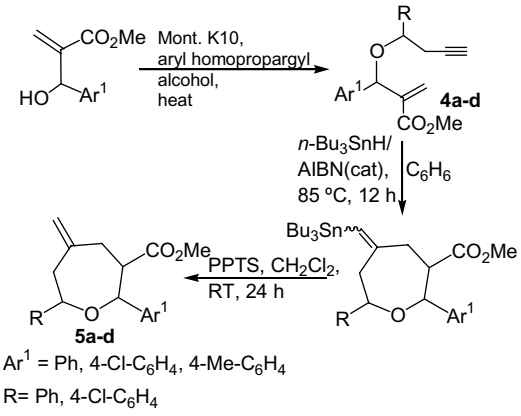


Figure 1. NOE correlations in trisubstituted oxepanes **3a** and **3f**.

In order to synthesise tetrasubstituted oxepanes, we prepared phenyl substituted homopropargyl alcohols from their corresponding aldehydes.[14] The phenyl substituted *O*-homopropargyl derivatives **4a–d** were synthesised following the procedure reported for compounds **2a–f**. Radical cyclisation of **4a** with 1.5 equiv of tri-*n*-butyltin hydride and a catalytic amount of AIBN in benzene at reflux for 12 h afforded a crude stannylated compound which was protiodestannylated, without purification, with PPTS to give 2,3,5,6-tetrasubstituted oxepane **5a** in good yield (Scheme 3, Table 2). The cyclisations of **4b–d** all furnished the desired cyclised products **5b–d** in good yields. The results are summarised in Table 2. All new compounds were characterised by IR, ^{1}H and ^{13}C NMR, DEPT-135, 2D H–H COSY, X–H COSY and HRMS data.



Scheme 2. Synthesis of trisubstituted oxepanes.



Scheme 3. Synthesis of tetrasubstituted oxepanes.

Table 1. Synthesis of trisubstituted oxepanes **3a–f**

Entry	Ar^1	E	Enyne ether	Yield (%)	Oxepane	Yield (%)
1	Ph	CO_2Me	**2a**	34	**3a**	58
2	4-Cl-C_6H_4	CO_2Me	**2b**	37	**3b**	61
3	4-Me-C_6H_4	CO_2Me	**2c**	36	**3c**	63
4	Ph	CN	**2d**	45[a]	**3d**	57
5	4-Cl-C_6H_4	CN	**2e**	48[a]	**3e**	48
6	4-Me-C_6H_4	CN	**2f**	44[a]	**3f**	58

[a] Combined yield with isomerised compounds.

Table 2. Synthesis of tetrasubstituted oxepanes **5a–d**

Entry	Ar^1	R	Enyne ether	Yield (%)	Oxepane	Yield (%)
1	Ph	Ph	**4a**	34	**5a**	62
2	4-Me-C_6H_4	Ph	**4b**	37	**5b**	57
3	4-Cl-C_6H_4	Ph	**4c**	36	**5c**	55
4	Ph	4-Cl-C_6H_4	**4d**	45	**5d**	51

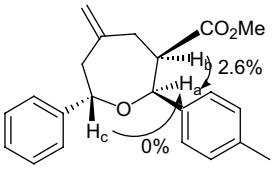


Figure 2. NOE correlations in tetrasubstituted oxepane **5d**.

The relative stereochemistry of the tetrasubstituted oxepane **5d** was established by NOE irradiation studies. Irradiation of H_b at δ 2.9 enhanced the signal corresponding to H_a at δ 4.9 by 2.6%. However, irradiation of the H_c proton at δ 4.81 did not show any signal enhancement of protons H_a and H_b. Hence, the relative stereochemistry of the substituents in compound **5d** is assigned as shown in Figure 2.

3. Conclusion

In conclusion, we have demonstrated a short route for the construction of functionalised tri- and tetra-substituted oxepanes starting from Baylis–Hillman adducts by a tin mediated vinyl radical cyclisation as the key step. Further studies to apply this strategy in the synthesis of natural products are underway in our laboratory.

4. Typical experimental procedure for radical cyclisation and protiodestannylation

A mixture of propargyl ether **3a** derived from the Baylis–Hillman adduct **1a** (1 mmol), 1.5 equiv of freshly prepared tri-*n*-butyltin hydride (1.5 mmol) and 5 mg of AIBN in dry benzene (25 mL) was heated at reflux under an inert atmosphere until complete disappearance of the starting material (TLC ca. 12 h). The solvent was then removed under reduced pressure. The crude cyclised stannylated product in dichloromethane (10 mL) was stirred with PPTS (2 equiv) for 24 h at rt. The mixture was diluted with dichloromethane and washed with water and brine. The organic layer was separated and dried (Na_2SO_4) and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography using gradient elution (hexane, hexane/EtOAc) to afford the pure cyclised product.

5. Spectral data for selected compounds

5.1. Methyl 3-(but-3-yn-1-yloxy)-2-methylene-3-phenylpropanoate: 2a

IR (CH_2Cl_2): 3294, 2953, 1722, 1635 cm^{-1}; ^1H NMR ($CDCl_3$, 300.1 MHz): δ 1.89 (t, J = 2.5 Hz, 1H), 2.43 (dt, 2H, J = 6.9, 2.3 Hz), 3.47 (dt, 1H, J = 15.8, 6.9 Hz), 3.55 (dt, 1H, J = 15.8, 6.9 Hz), 3.68 (s, 3H), 5.24 (s, 1H), 5.92 (s, 1H), 6.28 (s, 1H), 7.34 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.00, 51.71, 67.29, 69.46, 79.34, 81.12, 125.02, 127.58, 127.96, 128.34, 139.55, 141.32, 165.99. HRMS-EI: Calcd for $C_{15}H_{16}O_3$: 244.1099. Found: 244.1087.

5.2. Methyl 5-methylene-2-phenyl oxepane-3-carboxylate: 3a

IR (CH_2Cl_2): 2949, 1737, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 300.1 MHz): δ 2.47 (d, 1H, J = 15 Hz), 2.61–2.67 (m, 3H), 2.84–2.87 (m, 1H), 3.44 (s, 3H), 3.70–3.72 (m, 1H), 4.09–4.14 (m, 1H), 4.69 (d, 1H, J = 8.8 Hz), 4.89 (s, 2H), 7.19–7.26 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.78, 38.87, 51.51, 54.20, 70.28, 85.08, 114.60, 126.62, 127.84, 128.38, 141.97, 145.34, 173.57. HRMS-EI: Calcd for $C_{15}H_{18}O_3$: 246.1256. Found: 246.1248.

5.3. 5-Methylene-2-(4-methylphenyl) oxepane-3-carbonitrile: 3f

IR (CH_2Cl_2): 2928, 2237, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300.1 MHz): δ 2.35 (s, 3H), 2.53–2.86 (m, 4H), 3.08–3.12 (m, 1H), 3.64–3.68 (m, 1H), 4.22–4.26 (m, 1H), 4.53 (s, 1H), 5.05 (s, 2H), 7.14 (d, 2H, J = 7.9 Hz), 7.24 (d, 2H, J = 7.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.07, 37.86, 37.92, 40.22, 70.41, 82.59, 116.59, 118.37, 125.43, 128.98, 136.66, 137.51, 141.96. HRMS-EI: Calcd for $C_{15}H_{17}NO$: 227.1310. Found: 227.1301.

5.4. Methyl 5-methylene-7-phenyl-2-(4-methylphenyl) oxepane-3-carboxylate: 5b

^1H NMR: δ 2.30 (s, 3H), 2.54–2.66 (dd, 1H, J = 14.7, 10.8 Hz), 2.78 (d, 2H, J = 7.1 Hz), 2.81–2.87 (dd, 1H, J = 14.7, 3.7 Hz), 2.99 (m, 1H), 3.54 (s, 3H), 4.81–4.86 (dd, 1H, 10.8, 3.7 Hz), 4.93 (m, 3H), 7.06 (d, 2H, J = 7.9 Hz), 7.18–7.32 (m, 7H). ^{13}C NMR: 21.19, 37.26, 46.88, 51.64, 54.66, 82.40, 84.03, 115.27, 125.51, 126.29, 127.07, 128.22, 128.97, 137.19, 139.35, 143.29, 144.50, 173.95. HRMS-EI: Calcd for $C_{22}H_{24}O_3$: 336.1725. Found: 336.1715.

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