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ScienceDirect
Tetrahedron 62 (2006) 11652–11656
Tetrahedron

Fast and efficient preparation of Baylis–Hillman-derived (*E*)-allylic azides and related compounds in aqueous medium

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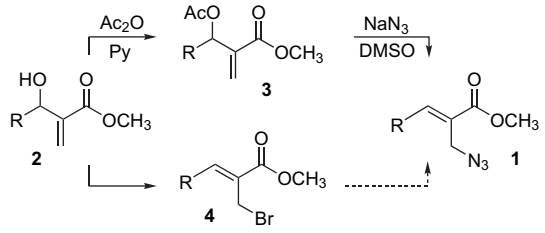
Received 24 July 2006; revised 14 September 2006; accepted 15 September 2006
Available online 16 October 2006

Abstract—A practical access to alkyl- and aryl-substituted (*E*)-2-(azidomethyl)alkenoates and related azido compounds from the corresponding allylic bromides in aqueous acetone is described. An alternative method to obtain the starting bromides based on heterogeneous catalysis under mild conditions was also investigated.

1. Introduction

While the enormous interest in the chemistry of azides and azido-related compounds[1] dates from the 19th century, only recently have the synthesis and reactivity of multifunctional allylic azides become an area of active research.[2] Allylic azides are versatile building blocks for the synthesis of natural products and nitrogen-containing heterocycles of pharmacological relevance.[3] However, the propensity of allylic azides to undergo dynamic [3,3]-sigmatropic rearrangement[4] at ambient temperature must be taken into account, because the thermodynamic ratio of the two equilibrating regioisomeric azides is normally substrate-dependent.[5] Therefore, the development of simple and efficient methods to selectively access allylic azides of structural complexity is highly desirable. 3-Aryl-2-(azidomethyl)alkenoates **1** are a class of stable allylic azides,[6] which are not prone to rearrangement, making them attractive intermediates for synthesis. Multifunctional allylic azides of structure **1** have been prepared by a two-step sequence involving acetylation of α-methylene-β-hydroxy esters **2** (Baylis–Hillman[7] adducts) followed by reaction of acetate **3** with NaN_3 in a S_N2'-type mechanism (Scheme 1).[8] However, nucleophilic displacements of this type involve long reaction times and the use of a toxic and high-boiling solvent such as DMSO. These shortcomings could be partially circumvented by the introduction of 1 equiv of 1,4-diazabicyclo[2.2.2]octane (DABCO) in aqueous THF to accelerate the substitution reaction,[9] although the required presence of an additive creates further environmental and economic concerns. Indeed, water or aqueous solutions[10] can be viewed as very attractive mediums for these transformations.[11]



Scheme 1.

In continuation of our studies on synthetic methodologies involving allylic azides and Baylis–Hillman adducts,[6,12,13] we envisaged that allylic bromides **4**, readily obtained[13,14] by direct bromination of Baylis–Hillman adducts **2**, would be the useful substrates[15] for an easy introduction of azide, as well as for other nucleophilic groups, onto the allylic framework. In this paper we describe a practical and efficient preparation of alkyl- and aryl-substituted (*E*)-2-(azidomethyl)alkenoates and related azido compounds from the corresponding allylic bromides in aqueous medium. We also investigate an alternative method to obtain the starting bromides based on heterogeneous catalysis under mild conditions.

2. Results and discussion

Allylic bromides such as **4** have been routinely prepared by treatment of Baylis–Hillman adducts **2** with a combination of HBr and H_2SO_4 in CH_2Cl_2 at low temperature.[13a,14a] In spite of the good yields commonly associated with this transformation, the utilization of large quantities of strong

Keywords: Baylis–Hillman reaction; Allylic azides; Allylic bromides; [3,3]-Sigmatropic rearrangement; Aqueous solvents; Heterogeneous catalysis.
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0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.09.059

mineral acids is a major drawback due to the safety procedures required for the manipulation of hazardous reagents and wastes. Also, substrates carrying acid-labile groups such as electron-rich olefins and aromatics are incompatible with the strongly acidic conditions, thus limiting the scope of the method. Heterogeneous catalysis is amongst the most efficient and environmentally friendly processes in chemical synthesis, allowing the performance of operationally-simple reactions without the use of toxic or corrosive reagents.[16] Alternative methods to access allylic bromides **4** employing inexpensive solid catalysts include the use of montmorillonite KSF clay and silica-supported $NaHSO_4$[17] in combination with a bromide source.[14b,d] In our hands, however, attempts to react substrates **2a** and **2b** under these conditions led to modest conversions to **4a** and **4b** (up to 40%). Montmorillonite K10, zeolite ZSM-5, and 5 Å molecular sieves were also ineffective catalysts under similar experimental procedure.

A smooth conversion of Baylis–Hillman adducts **2** to the corresponding bromides **4** was achieved with Amberlist-15®/LiBr (or NaBr) in acetonitrile at ambient temperature (Table 1). High yields were obtained with alcohols bearing alkyl or electron-rich aryl groups (entries 1–6 and 9). Accordingly, piperonyl-substituted alcohol **2b** reacted almost instantaneously under the stated conditions to give bromide **4b** in excellent yield (entries 2 and 3). Even reused Amberlist-15® (which was readily recovered by filtration of the reaction mixture and successive washings with 1 M HCl and H_2O) was suitable for another cycle, in spite of the partially decreased catalytic activity (entry 4). Styryl-derived substrate **2d** is also very reactive toward Amberlist-15®/LiBr, but the formation of the expected (*E*,*E*)-diene **4d** was accompanied by small amounts of an unstable by-product, possibly a geometrical isomer, that could not be isolated. Gratifyingly, a fractional crystallization of the crude reaction mixture in ethanol gave bromide **4d** in higher purity and better yield than those obtained with the HBr–H_2SO_4 method (entry 6). However, the relative reactivity of alcohols **2** was remarkably dependent upon the substitution pattern. Very slow conversions were observed for electron-deficient substrates, even after a prolonged time under reflux (entries 7 and 8). The anticipated[13,14] *Z*-stereochemistry assigned to 2-(bromomethyl)-2-alkenoates **4** was based on the characteristic NMR shift of the β-olefinic hydrogen *cis* to the carboxyl group and also on the X-ray crystallography of **4b**.[18]

Next, the preparation of allylic azides **1** from bromides **4** was investigated. Bromide **4a** was selected as a model substrate for reactions with NaN_3 under different reaction parameters in order to achieve optimal conversions to azide **1a** (Table 2). Reaction rates were strongly influenced by the nature of the solvent (or solvent combination) used, slow conversions being a consequence of the low solubility of sodium azide (entries 1–3) or **4a** (entry 4) in the medium. DMSO (entry 5) and DMF (entry 6), typically employed for azide displacement of bromide,[2c,19] enabled quantitative conversion to allylic azide **1a** in 10 min. However, both solvents are toxic, expensive, and difficult to separate from the crude product by simple aqueous workup. In contrast, a combination of acetone/water proved to be the best solvent system for the reaction (entries 7–9). Allylic azide **1a** was quantitatively obtained with either 1.5 equiv of NaN_3 in 10 min (entry 8) or 2.0 equiv in 5 min (entry 9). It is also noteworthy that acceptable conversions to **1a** could be performed using a nearly equimolar amount of NaN_3 in 5 min (entry 10).

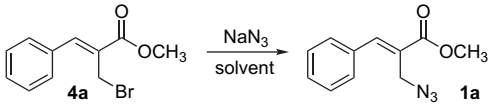
Encouraged by the excellent results achieved with the NaN_3/acetone/water system, we further extended this procedure to the azidation of representative allylic bromides **4** (Table 3). The corresponding aromatic-substituted (*E*)-allylic azides **1a–f** were cleanly obtained in nearly quantitative yields after purification in a short plug of silica gel. On the other hand, when aliphatic-substituted allylic bromides **4g–i** were subjected to the present protocol, NMR analysis of the crude reaction indicated the formation of the expected allylic azides **1g–i** accompanied by a minor product (5–30%), which was assigned as the rearranged regioisomers **5g–i** (Scheme 2).

Table 1. Synthesis of (*E*)-allylic bromides **4** from alcohols **2**[a]

Entry	Product	R	Yield (%) with HBr/H_2SO_4[b]	Yield (%)[c] with LiBr/Amberlist-15®	Time (h)
1	**4a**	C_6H_5	85	64	6
2	**4b**	3,4-$(OCH_2O)C_6H_3$	60	91	1
3	**4b**	3,4-$(OCH_2O)C_6H_3$		90[d]	1
4	**4b**	3,4-$(OCH_2O)C_6H_3$		77[e]	1
5	**4c**	2-$C_{10}H_7$	85	85	2
6	**4d**	(*E*)-C_6H_5CH═CH	64	75	0.5
7	**4e**	2-ClC_6H_4	80	45[f]	4
8	**4f**	4-$NO_2C_6H_4$	65	0	50
9	**4g**	CH_3	70	75	6

[a] Isolated yields.
[b] Data from Ref. 13a.
[c] Conditions: 1.0 mmol **2**, 1.0 g Amberlist-15®, 2.0 mmol LiBr, acetonitrile or acetone (3 mL) at 25 °C.
[d] Amberlist-15® (0.5 g/mmol **2b**) was used.
[e] The reaction was carried out with recycled Amberlist-15®.
[f] The reaction was carried out at reflux temperature for 4 h.

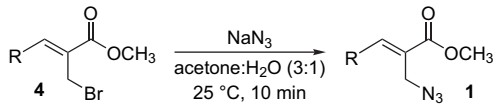
Table 2. Conversion of bromide **4a** to azide **1a** under different reaction conditions[a]



	Solvent system	NaN_3 (equiv)	Conversion to **1a** (%)[b]
1	THF	2.0	5
2	CH_3CN	2.0	18
3	Me_2CO	2.0	31
4	H_2O	2.0	0
5	DMSO[c]	2.0	100
6	DMF[c]	2.0	100
7	Me_2CO/H_2O 3:1	2.0	100
8	Me_2CO/H_2O 3:1	1.5	100
9	Me_2CO/H_2O 3:1[d]	2.0	100
10	Me_2CO/H_2O 3:1[d]	1.2	78

[a] Allylic bromide **4a** (1 mmol) and NaN_3 (1.2–2.0 mmol) in 4 mL of a given solvent were stirred at 25 °C for 10 min (unless otherwise stated), followed by quenching the reaction mixture with CH_2Cl_2 and H_2O.
[b] Determined by ^1H NMR spectrum (400 MHz, $CDCl_3$).
[c] Solvent residue (10–20%) present in the crude reaction product after aqueous workup.
[d] Reaction was quenched (CH_2Cl_2/H_2O) after 5 min.

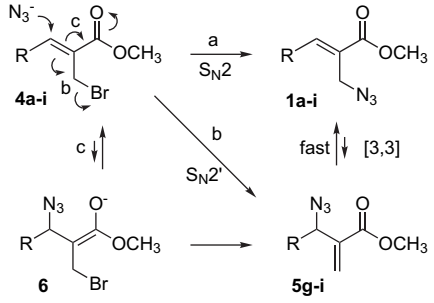
Table 3. Synthesis of (*E*)-allylic azides **1** from bromides **4** in acetone/water (3:1)



Product	R	Yield (%)[a]
1a	C_6H_5	97
1b	3,4-$(OCH_2O)C_6H_3$	93
1c	2-$C_{10}H_7$	95
1d	(*E*)-$C_6H_5CH{=}CH$	96
1e	2-ClC_6H_4	96
1f	4-$NO_2C_6H_4$[b]	97
1g	CH_3[c]	92
1h	$CH_3CH_2CH_2$[c]	95
1i	$CH_3CH_2(CH_3)CH$[c]	93

[a] Isolated yields.
[b] A higher acetone/water ratio (6:1) was used due to the low solubility of nitro-derivative **4f** in aqueous acetone.
[c] Obtained as inseparable mixture of regioisomers **1** and **5**.

Unfortunately, all attempts to isolate any compound by chromatography led to extensive decomposition to an intractable mixture of products.



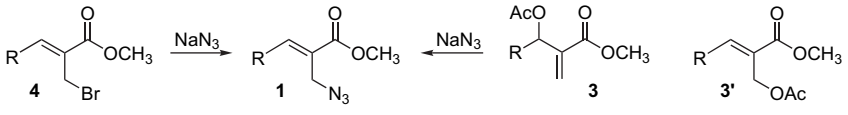
Scheme 2.

In order to monitor these transformations by ^1H NMR (400 MHz), reactions of phenyl- (**4a**) and methyl- (**4g**) substituted bromides were also performed in standard NMR tubes, using $(CD_3)_2CO/D_2O$ as the solvent system under the present conditions. For phenyl-substituted allylic bromide **4a**, products arising from rearrangement were not detected and a quantitative conversion to allylic azide **1a** reached completion after 2 min. In the case of methyl-substituted allylic bromide **4g**, however, conversion to both the allylic azide **1g** and the corresponding rearranged isomer **5g** (ratio **1g**:**5g** ~3:1) was observed in the early stages, with the isomeric ratio being unaltered throughout the entire course of the reaction (conversion higher than 95% was accomplished after 2 min).

These results indicate that alkyl-substituted azides **1g–i** might co-exist with their rearranged isomers **5g–i** in a fast equilibrium shifted to the thermodynamically more stable olefins[20] **1g–i**. The absence of rearranged products for the aryl series **1a–f** might have been due to a stronger stabilization of the double bond by an extensive conjugation through the carboxyl and the aromatic ring, precluding isomerization to the less stable **5a–f**. From a mechanistic view, nucleophilic attack of azide anion on an allylic bromide system would lead to the formation[21] of either S_N2- or S_N2'-type products **1** or **5**, respectively (Scheme 2). While the direct S_N2 attack leading to the more stable **1** (path a) seems to be the exclusive (or at least preferential) pathway for aryl-substituted bromides **4a–f**, the S_N2' mechanism (path b) or even an addition-elimination process via intermediate **6** (path c) could not be excluded at this moment to account for the formation of alkyl-substituted azides **1g–i**. The DABCO salt concept has been successfully applied for the introduction of nucleophiles at the secondary position of Baylis–Hillman adducts by S_N2'-type process.[22] In order to tentatively obtain the elusive azide **5a**, we treated bromide **4a** with DABCO followed by the addition of NaN_3, but the only product formed in the reaction was, again, the S_N2-type **1a**. Whether the mechanism is a direct S_N2 (path a) or S_N2' (path b) still remains to be determined, because in both the cases the product distribution (**1**:**5**) must be regarded as a thermodynamic rather than a kinetic control due to the fast equilibration between the regioisomeric allylic azides.

The superior reactivity of allylic bromides **4** over the acetates **3** was demonstrated by control experiments performed in acetone/water and in DMSO under equivalent conditions. The results summarized in Table 4 clearly show that allylic bromides **4** are much more reactive than acetates **3** (and

Table 4. Conversion (%)[a] of allylic acetates **3** and bromides **4** to allylic azides **1**



Entry	Compound	R	Solvent system	Conversion (%)	
				10 min	2 h
1	**4a**	C_6H_5	DMSO	100	
	3a	C_6H_5	DMSO	65	100
2	**4a**	C_6H_5	Acetone/H_2O (3:1)	100	
	3a	C_6H_5	Acetone/H_2O (3:1)	18	59
3	**4g**	CH_3	DMSO	100	
	3g[b]	CH_3	DMSO	47	78
4	**4g**	CH_3	Acetone/H_2O (3:1)	100	
	3g[b]	CH_3	Acetone/H_2O (3:1)	5	58

[a] Conversions to azide **1** were performed by adding NaN_3 (2 mmol) to a stirring solution of acetate **3** or bromide **4** (1 mmol) in 4 mL of acetone/H_2O (3:1) or DMSO, then quenching the reaction with CH_2Cl_2/H_2O after 10 min or 2 h. After aqueous workup the conversion (%) was determined by ^1H NMR integration (400 MHz, $CDCl_3$) of the crude mixture (~95% purity).
[b] Pure **3** or a mixture of **3**:**3**′ (3:1) was employed, leading to similar results.

3′) toward azide anion under any given conditions and this difference in reactivity is remarkably enhanced in acetone/water medium (entries 2 and 4).

Finally, simple azido compounds **7**–**10** (Fig. 1) were also prepared in high yields and short reaction times (10–30 min) from the corresponding bromides and NaN_3 under aqueous acetone as outlined here.

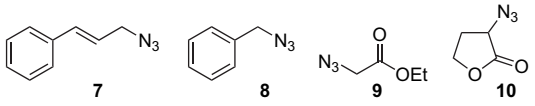


Figure 1.

3. Conclusion

The alternative access to 2-(bromomethyl)-2-alkenoates **4** by Amberlist-15®-mediated bromination of Baylis–Hillman adducts **2** is a synthetically useful transformation, particularly for substrates bearing electron-rich groups. The simple protocol for conversion of allylic bromides **4** to the corresponding azides **1** in acetone/H_2O is straightforward and superior to conventional methods, leading to fast reactions, reproducible conditions, easy workup, and excellent yields, avoiding the use of potential contaminants such as high-boiling solvents or organic additives. The mechanistic aspects involved in these nucleophilic displacements and the application of this simple methodology to more complex systems are currently being investigated.

4. Experimental

4.1. General

All chemicals were of reagent grade and were used as received. Melting points were determined using a Microquímica MQPF301 apparatus and are uncorrected. Infrared spectra were acquired with a Perkin–Elmer FTIR 1600 spectrometer using KBr for solids and film for liquid samples (range 4000–400 cm^{-1}). ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz, fully decoupled) spectra were recorded with a Varian AS-400 spectrometer. Samples were prepared in $CDCl_3$ solution containing 1–2% tetramethylsilane (TMS) as internal standard. Chemical shifts are reported in parts per million (δ) relative to TMS. Coupling constants (J) are measured in hertz (Hz). Elemental analyses were conducted in a Carlo Erba CHN equipment by UFSC-Central Analítica, Departamento de Química, Florianópolis, SC, Brazil. Purifications by column chromatography were performed with silica gel (Aldrich, 100–200 mesh particle size). Compounds **1a**,**b**[6,8a] and **4a–c**,**e–i**[13,14] were fully characterized spectroscopically (IR, ^1H NMR, CHN) and showed physical and spectral data in accordance with their expected structure and by comparison with spectral data in literature.

4.2. Typical procedure for the synthesis of 2-(bromomethyl)-2-alkenoates (4)

To a stirred solution of a Baylis–Hillman adduct **2** (1.0 mmol) in 3.0 mL of acetonitrile at 25 °C were added 2.0 mmol of LiBr and 1.0 g of Amberlist-15® (Merck) and stirring was continued for the time presented in Table 1. The final mixture was filtered, the catalyst was rinsed with CH_2Cl_2, and the filtrate was washed with H_2O, satd $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by chromatography on a short plug of silica gel (hexane/ethyl acetate 9:1) to give the corresponding methyl 2-(bromomethyl)-2-alkenoates **4** in the yields presented in Table 1 (not optimized). Solid products were purified by recrystallization with ethanol.

4.2.1. Methyl (2*E*,4*E*)-2-(bromomethyl)-5-phenyl-2,4-pentadienoate (4d). Yellow solid; mp 86.1–86.6 °C; IR (KBr): ν_{max} 3017, 2942, 1711, 1604, 1236, 742 cm^{-1}; ^1H NMR: δ 3.85 (s, 3H), 4.47 (s, 2H), 7.03 (d, J=15.5 Hz, 1H), 7.13 (dd, J=15.5, 11.0 Hz, 1H), 7.36–7.41 (m, 3H), 7.51 (d, J=11.0 Hz, 1H), 7.53–7.56 (m, 2H); ^{13}C NMR: δ 24.7, 52.2, 122.4, 126.8, 127.5 (2×C_{Ar}), 128.9 (2×C_{Ar}), 129.6, 135.8, 142.7, 142.8, 166.3. Anal. Calcd for $C_{13}H_{13}BrO_2$ (%): C, 55.54; H, 4.66. Found: C, 55.93; H, 5.01.

4.3. Typical procedure for the synthesis of 2-(azidomethyl)-2-alkenoates (1)

To a stirred solution of the allylic bromides **4** (1.0 mmol) in 4.0 mL of acetone/H_2O (3:1) at 25 °C was added 2.0 mmol of NaN_3 and stirring was continued for a further 10 min. The final mixture was diluted with CH_2Cl_2, washed with H_2O, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by chromatography on a short plug of silica gel (hexane/ethyl acetate 9:1) to give the corresponding methyl 2-(azidomethyl)-2-alkenoates **1** quantitatively.

4.3.1. Methyl (*E*)-2-(azidomethyl)-3-(2-naphthyl)-2-propenoate (1c). Clear yellow oil; IR (neat): ν_{max} 3065, 2998, 2951, 2926, 2850, 2109, 1709, 1626 cm^{-1}; ^1H NMR: δ 3.90 (s, 3H), 4.24 (s, 2H), 7.46–7.50 (m, 3H), 7.80–7.91 (m, 4H), 8.09 (s, 1H); ^{13}C NMR: δ 47.1, 52.4, 126.3, 126.6, 127.3, 127.6, 127.8, 128.4, 128.6, 129.8, 131.5, 133.0, 133.5, 144.5, 167.4. Anal. Calcd for $C_{15}H_{13}N_3O_2$ (%): C, 67.40; H, 4.90; N, 15.72. Found: C, 67.11; H, 4.88; N, 15.80.

4.3.2. Methyl (2*E*,4*E*)-2-(azidomethyl)-5-phenyl-2,4-pentadienoate (1d). White solid; mp 59.2–59.6 °C; IR (KBr): ν_{max} 2946, 2105, 1705, 1615, 1283 cm^{-1}; ^1H NMR: δ 3.84 (s, 3H), 4.24 (s, 2H), 7.00 (d, J=15.0 Hz, 1H), 7.07 (dd, J=15.0, 10.5 Hz, 1H), 7.33–7.39 (m, 3H), 7.49–7.51 (m, 2H), 7.61 (d, J=10.5 Hz, 1H); ^{13}C NMR: δ 46.2, 52.5, 122.4, 124.7, 127.8 (2×C_{Ar}), 129.1 (2×C_{Ar}), 129.8, 135.9, 143.2, 143.8, 167.5. Anal. Calcd for $C_{13}H_{13}N_3O_2$ (%): C, 64.19; H, 5.39; N, 17.27. Found: C, 64.53; H, 5.74; N, 16.91.

4.3.3. Methyl (*E*)-2-(azidomethyl)-3-(2-chlorophenyl)-2-propenoate (1e). Clear yellow oil; IR (neat): ν_{max} 3063, 2999, 2952, 2847, 2099, 1716, 1638 cm^{-1}; ^1H NMR: δ 3.90 (s, 3H), 4.09 (s, 2H), 7.32–7.45 (m, 4H), 8.04 (s, 1H); ^{13}C NMR: δ 46.9, 52.3, 126.7, 128.4, 129.5, 130.2, 130.4, 132.5, 134.1, 140.9, 166.7. Anal. Calcd for $C_{11}H_{10}ClN_3O_2$ (%): C, 52.50; H, 4.01; N, 16.70. Found: C, 52.34; H, 3.81; N, 16.58.

4.3.4. Methyl (*E*)-2-(azidomethyl)-3-(4-nitrophenyl)-2-propenoate (1f). Yellow solid; mp 102.5–103.5 °C; IR (KBr): ν_{max} 3107, 3082, 3006, 2955, 2110, 1722, 1633, 1514, 1263 cm^{-1}; ^1H NMR: δ 3.92 (s, 3H), 4.14 (s, 2H), 7.59 (d, J=8.0 Hz, 2H), 7.96 (s, 1H), 8.29 (d, J=8.0 Hz, 2H); ^{13}C NMR: δ 46.5, 52.6, 123.7 (2×C_{Ar}), 129.8, 130.1 (2×C_{Ar}), 140.2, 141.3, 147.8, 166.5. Anal. Calcd for $C_{11}H_{10}N_4O_4$ (%): C, 50.38; H, 3.84; N, 21.36. Found: C, 50.43; H, 4.04; N, 21.31.

4.3.5. Methyl (*E*)-2-(azidomethyl)-2-butenoate (1g) and methyl 3-azido-2-methylenebutanoate (5g). Unstable oil, obtained as a mixture with the corresponding isomer **5g** in 90–95% purity (ratio **1g/5g** ~4:1); IR (neat): ν_{max} 2993, 2954, 2853, 2107, 1717, 1652 cm^{-1}; major isomer (**1g**) exhibited the following spectral properties: ^1H NMR: δ 1.93 (d, J=7.0 Hz, 3H), 3.79 (s, 3H), 4.08 (s, 2H), 7.19 (q, J=7.0 Hz, 1H); ^{13}C NMR: δ 14.9, 45.6, 52.0, 127.4, 143.9, 166.6. Data for minor isomer (**5g**): ^1H NMR: δ 1.36 (d, J=6.5 Hz, 3H), 3.74 (s, 3H), 4.44 (q, J=6.5 Hz, 1H), 5.81 (s, 1H), 6.30 (s, 1H); ^{13}C NMR: δ 19.3, 51.7, 56.6, 125.5, 139.8, 165.7.

4.3.6. Methyl (*E*)-2-(azidomethyl)-4-methyl-2-hexenoate (1i). Unstable oil, obtained as a mixture with the corresponding isomer **5i** in 90–95% purity (ratio **1g/5g** ~9:1); IR (neat): ν_{max} 2962, 2930, 2875, 2105, 1719, 1646 cm^{-1}; ^1H NMR: δ 0.96 (t, J=7.5 Hz, 3H), 1.06 (d, J=3.5 Hz, 3H); 1.35–1.52 (m, 2H), 2.41–2.51 (m, 1H), 3.83 (s, 3H), 4.05 (s, 2H), 6.85 (d, J=10.5 Hz, 1H); ^{13}C NMR: δ 11.7, 20.0, 29.4, 35.2, 45.9, 52.4, 125.3, 154.0, 167.5.

Acknowledgements

The authors wish to thank Mr. Angelo Ruzza, Mr. Fabio Roehrs, and Central de Análises (Departamento de Química, UFSC, Florianópolis) for spectroscopic analysis. L.F. and M.D.R. are grateful to CAPES and CNPq (Brazil) for fellowships. Financial support by MCT/CNPq (Brazilian Research Council) and FAPESC (Santa Catarina State Research Council, Brazil) is also gratefully acknowledged.

References and notes

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