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Synthesis of Isoquinolines by Cycloaddition of Arynes to 1,2,4-Triazines

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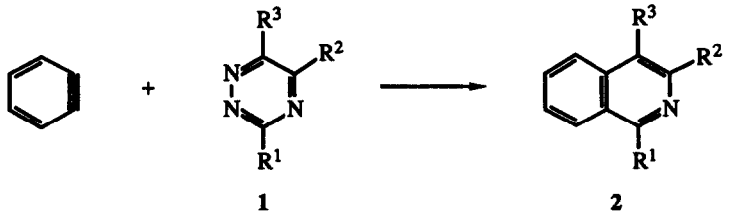
Abstract: Benzyne has been generated from benzenediazonium-2-carboxylate in the presence of several 1,2,4-triazines **1** and isoquinolines **2** have been isolated in moderate yield. 1-Aminobenzotriazole was also used as the source of benzyne and isoquinolines were again isolated in moderate yield from these reactions. 4-Methylbenzyne, which was generated from 5-methylanthranilic acid, reacted unselectively with the triazines to give mixtures of 6- and 7-methylisoquinolines **3** and **4** On the other hand reactions of 3-methylbenzyne with the triazines **1d** and **1e** proceeded with high regioselectivity, giving only the 5-methylisoquinoline **5a** and the 8-methylisoquinoline **6b**, respectively.

1,2,4-Triazines are well established as heterodienes in the Diels-Alder reaction; there are many examples of both intermolecular and intramolecular cycloadditions, in which the triazines normally act as the electron deficient reaction partners.[1] We have investigated the cycloaddition reactions of several 1,2,4-triazines with benzyne in order to evaluate the method as a route to isoquinolines. Benzyne is known to undergo cycloaddition to several types of cyclic heterodiene including 1,2,4,5-tetrazines [2] and oxazoles [3]. The reaction with oxazoles results in the formation of isoquinolines as byproducts. Benzyne has also been shown to react with *N*-benzylideneaniline to give a formal cycloadduct, 5,6-dihydro-5,6-diphenylphenanthridine, in low yield.[4] However, we wished to prepare isoquinolines with electron withdrawing substituents in the nitrogen containing ring, particularly isoquinoline-1-carboxylic esters bearing additional substituents, which are not readily available by existing routes.[5]

Reactions with Benzyne. A series of 1,2,4-triazines **1** was prepared by standard methods. Benzenediazonium-2-carboxylate was first used as the source of benzyne. Each of the triazines was dissolved in dioxan, the solution was heated under reflux, and dioxan solutions of anthranilic acid (in threefold excess) and isoamyl nitrite were added simultaneously to the solution over a period of about 20 min. The products were isolated by flash column chromatography.

From each of the triazines **1a** to **1f** a cycloadduct **2** was isolated (Scheme 1). The yields were moderate, ranging from 13% starting from the chlorotriazine **1a** to 56% starting from the triazinecarboxylic ester **1e**. The isoquinolines **2** (none of which has been prepared before) were fully characterised. A characteristic feature of the ^{1}H NMR spectra is a low field doublet for 8-H (Table) and this feature subsequently proved useful in assigning structures to adducts from methylbenzynes.



1 2

1, 2	a	$R^1 = Cl, R^2 = R^3 = Ph$
	b	$R^1 = Me, R^2 = R^3 = Ph$
	c	$R^1 = CO_2Et, R^2 = R^3 = Me$
	d	$R^1 = CO_2Et, R^2 = H, R^3 = Ph$
	e	$R^1 = CO_2Et, R^2 = R^3 = Ph$
	f	$R^1 = R^2 = R^3 = CO_2Et$

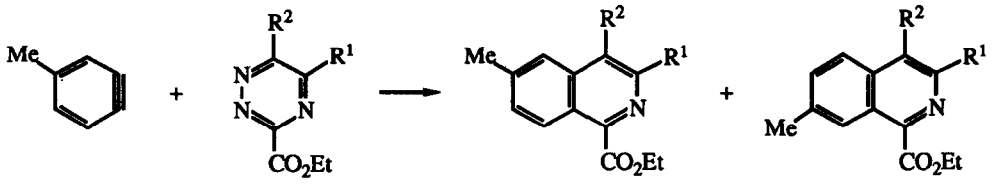
Scheme 1

Several attempts were made to improve the yields of isoquinolines. 1,2-Dimethoxyethane was used in place of dioxan for the generation and decomposition benzenediazonium carboxylate but the isoquinolines were formed in similar yield. The oxidation of 1-aminobenzotriazole by lead(IV) acetate is an excellent method for the generation of benzyne;[6] Whitney and Rickborn have recently described a variation of the technique in which benzyne was generated slowly, in order to avoid dimerisation to biphenylene.[3b] We have used this method for the oxidation of 1-aminobenzotriazole (in twofold excess) in the presence of several triazines. The method resulted in the formation of the isoquinoline **2e** in significantly better yield (77%) than from benzenediazonium carboxylate. With other triazines the yields of isoquinolines were not improved, although the chromatographic workup was generally easier because less byproducts were formed. We also investigated the oxidation of 1-aminobenzotriazole in the presence of triazines by the convential method of rapid addition of lead(IV) acetate: yields were only slightly lower than those obtained from the controlled oxidation. Biphenylene (25-35%) was also detected in all reactions where 1-aminobenzotriazole was a reagent (in twofold excess).

The results are in accord with the general trends of reactivity previously observed with these triazines; that is, that the reactions are most successful with triazines such as **1e** and **1f** which bear one or more conjugative electron withdrawing groups.

Reactions with Methylbenzynes. Cycloaddition reactions of 1,2,4-triazines with unsymmetrical dienophiles often show high regioselectivity when unsymmetrical dienophiles are used. We have investigated the reactions of three triazines, **1d, 1e** and **1f**, with 4-methylbenzyne (formed by diazotization of 5-methylanthranilic acid) and with 3-methylbenzyne (from 3-methylanthranilic acid) in order to discover whether the addition to these unsymmetrical arynes would show any regioselectivity.

With 4-methylbenzyne reactions were performed as before, the aryne being generated in threefold excess from 5-methylanthranilic acid in the presence of each of the triazines. In each case the isoquinolines were isolated as a mixture of isomers (Scheme 2). The presence of the isomers in a 1:1 ratio in each case was established from the ^1H NMR spectrum of the mixture, in particular from the signals for 8-H. The low field signal for the 6-methylisoquinolines **5** appeared as a doublet (showing additional *meta* coupling) whereas that for the 7-methylisoquinolines **6** appeared as a singlet (Table). The cycloaddion reactions of 4-methylbenzyne to these triazines thus show no regioselectivity. As the methyl substituent exerts a negligible steric effect and a relatively small electronic effect, this lack of selectivity is to be expected.

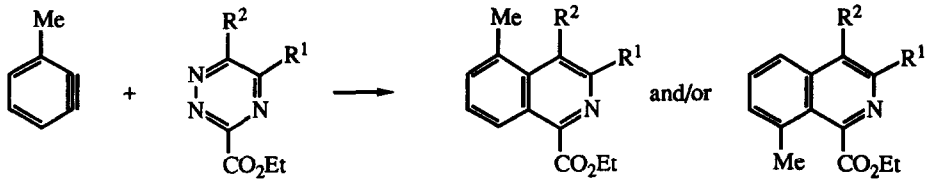


3 4

3, 4 a $R^1 = Ph, R^2 = H$
b $R^1 = R^2 = Ph$
c $R^1 = R^2 = CO_2Et$

Scheme 2

Reactions were carried out in the same way with 3-methylbenzyne (Scheme 3). With ethyl 5-phenyl-1,2,4-triazine-3-carboxylate **1d** a solid product was isolated (30%) which from its NMR spectrum was identified as a single isoquinoline, the 5-methyl isomer **5a**. The NMR spectrum showed a doublet, characteristic for 8-H, at δ 8.36. There was no evidence for the formation of the isomer **6a** in the reaction. With the diphenyltriazine **1e** an adduct was isolated (61%) which again proved to be a single isomer. In this case, however, the NMR spectrum indicated that the product was the 8-methylisoquinoline **6b**. (The NMR spectrum showed a trace impurity with a low field doublet at δ 8.4 which could indicate the presence of the 5-methyl isomer **5b**, but to an extent of less than 5%). A third reaction, performed with the triester **1f**, gave a product (69%) which from its NMR spectrum was identified as a 2:3 mixture of the 5-methylisoquinoline **5c** and the 8-methyl isomer **6c**.



5 6

5, 6 a $R^1 = Ph, R^2 = H$
b $R^1 = R^2 = Ph$
c $R^1 = R^2 = CO_2Et$

Scheme 3

The high regioselectivity which we observe in the cycloaddition of 3-methylbenzyne to the triazines **1d** and **1e** contrasts with the results of an earlier study of the cycloaddition of this aryne to 2-substituted furans, in which very little selectivity was found.[7] The selectivity may be partly steric in origin, but there are other examples of high and opposite regioselectivity in cycloadditions of such mono- and diphenyltriazine esters which is not due to steric effects.[8]

TABLE ^1H Chemical Shifts (δ) for 8-H of Isoquinolines

2a	2b	2c	2d	2e	2f	3a	3b	3c	4a	4b	4c	5a	5c
8.42	8.22	8.60	8.61	8.63	8.72	8.42	8.53	8.54	8.31	8.39	8.40	8.36	8.38

EXPERIMENTAL

General. ^{1}H N.m.r. spectra were recorded on a Bruker AC200 spectrometer operating at 200 MHz. Signals are singlets where no multiplicity is shown. Deuteriochloroform was used as the solvent except where indicated otherwise. M.p.'s were recorded on a Reichert hot stage apparatus and are uncorrected. Flash column chromatography was performed using Merck 9385 silica as the stationary phase.

1,2,4-Triazines. The following triazines were prepared by literature procedures: 3-methyl-5,6-diphenyl-1,2,4-triazine **1b**, [9] ethyl 5,6-dimethyl-1,2,4-triazine-3-carboxylate **1c**,[10] ethyl 5-phenyl-1,2,4-triazine-3-carboxylate **1d**,[11] ethyl 5,6-diphenyl-1,2,4-triazine-3-carboxylate **1e**[10] and triethyl 1,2,4-triazine-3,5,6-tricarboxylate **1f**.[12]

3-Chloro-5,6-diphenyl-1,2,4-triazine **1a**. 3-Amino-5,6-diphenyl-1,2,4-triazine[13] (0.2 g, 0.8 mmol) was dissolved in a mixture of chloroform (10 ml), water (5 ml) and HCl (2.3 ml, 37%). To this solution, cooled to 0 °C, a saturated aqueous solution of sodium nitrite (0.2 g) was added dropwise. The solution was stirred at 0 °C for 1.5 h and at room temperature for 1 h. The solution was diluted with water, extracted with chloroform and the organic solvent was evaporated off. Workup by flash chromatography (hexane-ethyl acetate 3:1) gave the triazine **1a** (72 mg, 34%) as a pale yellow solid. m.p, 155-157 °C (from ethyl acetate) (lit.[14], m.p. 156-157 °C);. δ 7.30-7.59 (10 H, m); δ (^{13}C) 128.67, 128.77, 129.41, 129.92, 130.06, 131.57, 134.02, 134.25; m/z 269 (M^+, 6.75%), 267 (M^+, 20.2), 178 (100), 152 (6), 89 (11) and 76 (13). Further elution gave 5,6-diphenyl-1,2,4-triazine **1b** (4.5%) as a yellow solid. m.p,113-115 °C (lit.,[15] m.p 116-117 °C); δ 7.10-7.46 (10 H, m) and 9.40 (1 H, 3-H). m/z 233 (M^+, 35%), 178 (100), 89 (11) and 76 (13).

Reactions with Benzyne: General Procedures

(a) From anthranilic acid. The 1,2,4-triazine (10 mmol) was dissolved in 1,4-dioxan (10ml) and the solution was heated under reflux while separate solutions of anthranilic acid (30mmol) and isoamyl nitrite (30 mmol) each in 1,4-dioxan (10ml) were added simultaneously by means of two dropping funnels over 20 min. The reaction mixture was heated under reflux for 0.5 hr and then cooled.The solution was diluted with ether (60 ml) and stirred with aqueous potassium hydroxide (3M). The aqueous phase was extracted with ether and the combined ether extracts were washed with water, dried (Na_2SO_4) and evaporated to leave the crude isoquinoline which was purified by flash column chromatography.

(b) From 1-aminobenzotriazole. To a solution of the 1,2,4-triazine (1 mmol) in dichloromethane (15 ml) at room temperature and under argon, solutions of 1-aminobenzotriazole (2 mmol) and lead(IV) acetate (2.2 mmol) each in dichloromethane (15 ml) were added simultaneously by means of two syringe pumps over a period of 1.5 hr. After the addition was complete the reaction mixture was washed with saturated aqueous sodium hydrogencarbonate and the dichloromethane layer was separated off, dried (Na_2SO_4) and evaporated The residue was purified by flash column chromatography to give the isoquinoline; biphenylene was isolated as a byproduct .

Isoquinolines from Benzyne

1-Chloro-3,4-diphenylisoquinoline **2a.** 3-Chloro-5,6-diphenyl-1,2,4-triazine **1a** gave, by procedure (a) followed by flash chromatography [hexane, then hexane-ethyl acetate (3:1)] the *isoquinoline* **2a** (13%) as a yellow solid, m.p. 194-195 °C (from ethyl acetate-hexane) (Found: C, 80.0; H, 4.4; N, 4.4. $C_{21}H_{14}ClN$ requires C, 79.9; H, 4.4; N, 4.4%); δ 7.16-7.25 (5 H, m), 7.33-7.39 (5 H, m), 7.65-7.68 (3 H, m) and 8.42 (1 H, dd); m/z 317 (M^+, 26%), 316 (46), 315 (M^+, 78) and 314 (100).

1-Methyl-3,4-diphenyl-isoquinoline **2b.** 3-Methyl-5,6-diphenyl-1,2,4-triazine **1b** gave, by procedure (a) followed by flash chromatography [hexane, then hexane-ethyl acetate (3:1)] the *isoquinoline* **2b** (18%) as a yellow solid, m.p. 154-156 °C (from hexane) (Found: C, 89.5: H, 5.8; N, 4.7. $C_{22}H_{17}N$ requires C, 89.4; H, 5.8; N, 4.7%); δ 3.1 (3 H), 7.18-7.28 (5 H, m), 7.31-7.40 (3 H, m) and 8.22 (1 H, dd); m/z 295 (M^+, 47%), 294 (100) and 252 (13).

Ethyl 3,4-dimethylisoquinoline-1-carboxylate **2c.** Ethyl 5,6-dimethyl-1,2,4-triazine-3-carboxylate **1c** gave, by procedure (a) followed by flash chromatography [hexane-ethyl acetate (3:1)] the *isoquinoline* **2c** (27%) as an oil . δ 1.48 (3 H, t), 2.63 (3 H), 2.76 (3 H), 4.56 (2 H, q), 7.57 (1 H, m), 7.71 (1 H, m), 8.02 (1 H, d, 5-H), and 8.60 (1 H, d); m/z 229 (M^+, 10%), 157 (100), 116 (9) and 87 (13). *Ethyl 3,4-diphenylisoquinoline-1-carboxylate picrate* was prepared, m.p. 144-146° C (from ethanol) (Found: C, 52.5; H, 3.9; N, 12.1. $C_{20}H_{18}N_4O_9$ requires C, 52.4; H, 3.9; N, 12.2%).

The isoquinoline **2c** was also prepared (12%) by procedure (b).

Ethyl 3-phenylisoquinoline-1-carboxylate **2d** Ethyl 5-phenyl-1,2,4-triazine-3-carboxylate**1d** gave, by procedure (b) followed by flash chromatography [hexane, then hexane-ethyl acetate (3:1)] the *isoquinoline* **2d** (26.5%) as an oil (Found: C, 77.5; H, 5.4; N, 5.0. $C_{18}H_{15}NO_2$ requires C, 77.9; H, 5.4; N, 5.0%);. δ 1.52 (3 H, t), 4.60 (2 H, q) 7.38-7.59 (3 H, m), 7.59-7.76 (2 H, m, 6-H and 7-H), 7.90 (1 H, dd, 5-H), 8.15-8.20 (3 H, m), and 8.61 (1 H, dd).

Ethyl 3,4-diphenylisoquinoline-1-carboxylate **2e.** Ethyl 5,6-diphenyl-1,2,4-triazine-3-carboxylate **1e** gave, by procedure (b) followed by flash chromatography [hexane, then hexane-ethyl acetate (3:1)] the *isoquinoline* **2e** (77%) as a yellow solid, m.p. 110-112 °C (from hexane-ether) (Found: C, 81.6; H, 5.4; N, 3.9. $C_{24}H_{19}NO_2$ requires C, 81.6; H, 5.4; N, 3.9%); δ 1.49 (3 H, t), 4.59 (2 H, q), 7.16-7.23 (5 H, m), 7.33-7.36 (5 H, m), 7.58-7.67 (3 H, m) and 8.63 (1 H, dd); m/z (CI, ammonia) 354 (M+ H^+, 100%).

Ethyl 3,4-diphenylisoquinoline-1-carboxylate **2e** was also prepared (56%) by procedure (a).

Triethyl isoquinoline-1,3,4-tricarboxylate **2f.** Triethyl 1,2,4-triazine-3,5,6-tricarboxylate **1f** gave, by procedure (a) followed by flash chromatography (dichloromethane) the *isoquinoline* **2f** (48%) as a colourless solid, m.p. 90-92 °C (from hexane-ether) (Found: C, 62.6; H, 5.5; N, 4.0. $C_{18}H_{19}NO_6$ requires C, 62.6; H, 5.5; N, 4.0%); δ 1.45 (3 H, t), 1.46 (3 H, t), 1.50 (3 H, t), 4.48-4.68 (6 H, 3 x q), 7.81-7.89 (2 H, m, 6-H and 7-H), 8.02 (1 H, dd, 5-H) and 8.72 (1 H, dd); m/z 345 (M^+, 14%), 300 (11), 272 (35), 227 (69) and 199 (100).

Reactions with Methyl-substituted Benzynes. General Procedure. To the 1,2,4-triazine (10 mmol) in dioxan (10 ml) at 100 °C solutions of either 5-methylanthranilic acid or 3-methylanthranilic acid (30 mmol) in dioxan (10 ml) and ioamyl nitrite (30 mmmol) in dioxan (10 ml) were added simultaneously dropwise during 20 min. The solution was heated under reflux for a further 30 min then cooled. It was diluted with ether (60 ml) and stirred with aqueous potassium hydroxide (3M). The aqueous phase was extracted with ether and the combined ether extracts were washed with water, dried (Na_2SO_4) and evaporated to leave the crude isoquinoline which was purified by flash column chromatography.

6- And 7-Methylisoquinolines from 5-Methylanthranilic acid

Ethyl 6-methyl-3-phenylisoquinoline-1-carboxylate **3a** *and ethyl 7-methyl-3-phenylisoquinoline-1-carboxylate* **4a.** Ethyl 5-phenyl-1,2,4-triazine-3-carboxylate**1d** gave, by flash chromatography [hexane, then hexane-ethyl acetate (3:1)], the *isoquinolines* **3a** and **4a** (1:1 mixture) (20%) as an oil, δ 1.33-1.44 (3 H, 2 x t), 2.46 (1.5 H), 2.48 (1.5 H), 4.45-4.57 (2 H, 2 x q), 7.34-7.51 (4 H, m), 7.60 (0.5 H, 5-H of **3a**), 7.74 (0.5 H, d, H-5 of **4a**), 8.00-8.08 (3 H, m), 8.31 (0.5 H, d, H-8 of **4a**) and 8.42 (0.5 H, 8-H of **3a**); m/z 291 (M^+, 4%), 223 (100), 219 (14), 204 (4),and 194 (11). The mixture of **3a** and **4a** was hydrolysed with aqueous potassium hydroxide to give 6-methyl-3-phenylisoquinoline-1-carboxylic acid and 7-methyl-3-phenylisoquinoline-1-carboxylic acid (1:1 mixture), m.p 150-152°C (from ether).(Found: C, 77.4; H, 4.9; N, 5.3. $C_{17}H_{13}NO_2$ requires C, 77.6; H, 4.9; N, 5.3%).

Ethyl 3,4-diphenyl-6-methylisoquinoline-1-carboxylate **3b** *and ethyl 3,4-diphenyl-7-methylisoquinoline-1-carboxylate* **4b.** Ethyl 5,6-diphenyl-1,2,4-triazine-3-carboxylate **1e** gave, by flash chromatography [hexane, then hexane-ethyl acetate (3:1)], the *isoquinolines* **3b** and**4b** (1:1 mixture) (44%) as a colourless solid, m.p. 106-108 °C and 126-128 °C (from ether-hexane) (Found: C, 81.8; H, 5.8; N, 3.7. $C_{25}H_{21}NO_2$ requires C, 81.7; H, 5.7; N, 3.8%); δ 1.50 (1.5 H, t), 1.51 (1.5 H, t), 2.44 (1.5 H), 2.57 (1.5 H), 4.56 (1 H, q), 4.69 (1 H, q), 7.18-7.27 (5 H, m), 7.36-7.39 (5 H, m), 7.44-7.46 (1.5 H, m), 7.61 (0.5 H, d, 5-H of **4b**), 8.39 (0.5 H, 8-H of **4b**) and 8.53 (0.5 H, d, 8-H of **3b**); m/z 367 (M^+, 36%), 295 (100) and 280 (18).

Triethyl 6-methylisoquinoline1,3,4-tricarboxylate **3c** *and triethyl 7-methylisoquinoline-1,3,4-tricarboxylate* **4c.** Triethyl 1,2,4-triazine-3,5,6-tricarboxylate **1f** gave, by flash chromatography [hexane, then hexane-ethyl acetate (5:1) and hexane-ethyl acetate (3:1)] the *isoquinolines* **3c** and **4c** (1:1 mixture) (69%) as a colourless solid, m.p. 92-93 °C (from ether-hexane) (Found: C, 63.5; H, 5.8; N, 3.8. $C_{19}H_{21}NO_6$ requires C, 63.5; H, 5.8; N, 3.9%); δ 1.39-1.5 (9 H, m), 2.51 (1.5 H), 2.53 (1.5 H), 4.37-4.57 (6 H, m), 7.59-7.70 (1 H, m), 7.60 (0.5 H, 5-H of **3c**) 7.89 (0.5 H, d, 5-H of **4c**), 8.40 (0.5 H, 8-H of **4c**) and 8.54 (0.5 H, d, 8-H of **3c**); m/z 359 (M^+, 2%), 319 (12), 287 (75), 241 (70) and 213 (100).

5- And 8-Methylisoquinolines from 3-Methylanthranilic acid

Ethyl 5-methyl-3-phenylisoquinoline-1-carboxylate **5a.** Ethyl 5-phenyl-1,2,4-triazine-3-carboxylate **1d** gave, by flash chromatography (dichloromethane) the *isoquinoline* **5a** (30%) as a yellow solid m.p. 100-103 °C (from hexane) (Found: C, 78.4; H, 6.0; N, 4.5. $C_{19}H_{17}NO_2$ requires C, 78.3; H, 5.8; N, 4.8); δ 1.53 (3 H, t), 2.76 (3 H), 4..61 (2 H, q), 7.45-7.51 (6 H, m), 8.19 (1 H, d, 6-H), 8.31 (1 H, 4-H) and 8.36 (1 H, dd, 8-H); m/z 291(M^+, 32%), 219 (100), 204 (22) and 140 (12).

Ethyl 3,4-diphenyl-8-methylisoquinoline-1-carboxylate **6b.** Ethyl 5,6-diphenyl-1,2,4-triazine-3-carboxylate **1e** gave, by flash chromatography [hexane, hexane-ethyl acetate (3:1) and hexane-ethyl acetate (1:1)] the *isoquinoline* **6b** (61%) as a colourless solid m.p. 166-168 °C (from hexane) (Found: C, 81.8; H, 5.8; N, 3.7. $C_{25}H_{21}NO_2$ requires C, 81.7; H, 5.7; N, 3.8%); δ 1.50 (3 H, t), 2.80 (3 H),. 4.62 (2 H, q) and 7.20-7.60 (13 H, m); m/z 367 (M^+, 27%), 338 (100) and 295 (27).

Triethyl 5-methylisoquinoline-1,3,4-tricarboxylate **5c** *and triethyl 8-methylisoquinoline-1,3,4-tricarboxylate* **6c.** Ethyl 5-phenyl-1,2,4-triazine-3-carboxylate **1d** gave, by flash chromatography [hexane-ethyl acetate (3:1), then hexane-ethyl acetate (1:1)] the *isoquinolines* **5c** and **6c** (2:3 mixture) (69%) as an oil. (Found: N, 4.1. $C_{19}H_{21}NO_6$ requires N, 3.9%); δ 1.40-1.53 (9 H, 3 x t), 2.74 (3 H), 4.42-4.65 (6 H, 3 x q), 7.61-7..77 (2 H, m), 7.80 (0.6 H, d, 5-H of **6c**) and 8.38 (0.4 H, dd, 8-H of **5c**); m/z 359 (M^+, 25%), 330 (98), 314 (21), 284 (29) and 256 (100).

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