Synthesis of chalcone ethynylogues with a pharmaceutical objective

PIERRE BABIN

Laboratoire de Pharmacie Chimique, Université de Bordeaux II, Place de la Victoire, 33000 Bordeaux, France

AND

PAULETTE LAPOUYADE AND JACQUES DUNOGUÈS[1]

Laboratoire de Chimie Organique et Laboratoire de Chimie des Composés Organiques du Silicium et de l'Etain associé au CNRS no 35, 351, Cours de la Libération, 33405 Talence Cédex, France

Received May 11, 1981

PIERRE BABIN, PAULETTE LAPOUYADE, and JACQUES DUNOGUÈS. Can. J. Chem. **60**, 379 (1982).

A simple route to chalcone ethynylogues, convenient even in the presence of alkoxy or acyloxy substituents, is proposed. This method is based on the use of ethynylsilanes, the involved trimethylsilyl group being recovered during the course of the reaction.

PIERRE BABIN, PAULETTE LAPOUYADE et JACQUES DUNOGUÈS. Can. J. Chem. **60**, 379 (1982).

Une méthode simple de synthèse d'éthynylogues de chalcones, utilisable même avec des substituants alcoxy ou acyloxy, est proposée. Cette méthode met en jeu la voie organosilicique, le groupe triméthylsilyle engagé étant récupérable en fin d'opération.

Several chalcone derivatives have found pharmaceutical uses. Thus, some flavonoids having a chalcone skeleton exhibit anti-aldose reductase properties (1) and a trimethoxy derivative of chalcone (2) is currently used as a qualitative and quantitative choleretic for biliary secretion (commercial name: Vesidryl (3)). Moreover a chalcone vinylogue, the divanillidene cyclohexanone, also is a commercially available choleretic (Vanilone[2]). In the context of our studies concerning the obtention of drug ethynylogues (4, 5) we have focused our interest on the synthesis of chalcone ethynylogues having potential pharmacological properties (products with aryl groups substituted by one or several alkoxy or acyloxy substituents).

In this series only Ph—C≡C—CO—CH=CH—Ph has been described to our knowledge (6–9). It has been made according to three synthetic methods which offer possibilities of comparison.

(*a*) Condensation of Ph—C≡C—Na with cinnamic anhydride, which does not afford chalcone in high yields (~33%) (6) and raises problems with acetoxy substituents (6*b*).

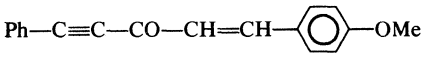
(*b*) Quantitative preparation of Ph—C≡C—Cu used as precursor of chalcone (7) presents danger (9).

(*c*) Chalcone is afforded by the direct condensation of Ph—C≡CH with a stoichiometric amount of cinnamoyl chloride in the presence of triethylamine and $(Ph_3P)_2PdCl_2$ and CuI as the catalyst (9):

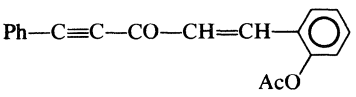
$$Ph—C{\equiv}C—H + Ph—CH{=}CH—COCl + Et_3N \xrightarrow[CuI]{(Ph_3P)_2PdCl_2} Ph—C{\equiv}C—CO—CH{=}CH—Ph$$
$$-Et_3N, HCl \qquad 80\%$$

Despite the formation of triethylamine hydrochloride and the use of an expensive catalyst we attempted this process for the synthesis of **13** and **7**, both previously undescribed: we obtained 55% yields in the first case but lower than 20% yield in the presence of the acyloxy substituent after 48 h, while most of the unreacted phenyl acetylene was recovered.

The proposed routes are not generally adaptable to the preparation of alkoxy or acyloxy substituted structures. For all these reasons we decided to investigate the synthesis of chalcone ethynylogues from alkynylsilanes and aryl substituted cinnamoyl chlorides since alkynylsilanes react with electrophiles (10, 11) such as acyl chlorides under Friedel–



13



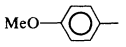
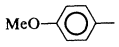
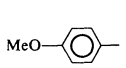
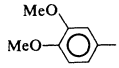
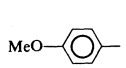
7

[1]Author to whom correspondence may be addressed.

[2]See ref. 3, p. 1290.

0008-4042/82/040379-04$01.00/0

TABLE 1. Synthesis of chalcone ethynylogues

Ar	Ar′	Yields % crude products	Yields % after recrystallization	Number
Ph-	Ph-	55	40	**6**
Ph-		60	40	**7**
	Ph—	50	30	**8**
		38	38[a]	**9**
		40	30	**10**
		60	40	**11**
		50	30	**12**

[a]Liquid product.

Crafts conditions, at least in the absence of alkoxy and acyloxy substituents.

Several routes were used for the preparation of ethynylsilanes. Ethynyltrimethylsilane was obtained by silylation of trichloroethylene (12); (*p*-methoxyphenylethynyl)trimethylsilane (15, 16) **5** was synthesized by condensation of ethynyltrimethylsilane on *p*-methoxy iodobenzene (13); (phenylethynyl)-trimethylsilane **1** was prepared from phenylacetylene (14), whereas the other substituted (phenylethynyl)trimethylsilanes (*o*-RO—C_6H_4—C≡C—$SiMe_3$, R = H, **2**, $SiMe_3$, **3**, COMe, **4**), also new compounds, were easily obtained from *o*-Me_3SiO—C_6H_4—C≡CH described in one of our previous publications (4).

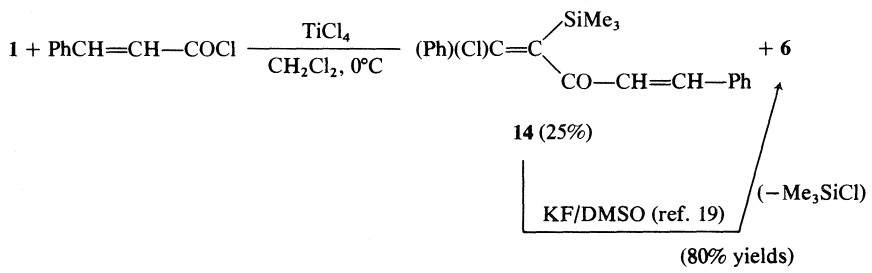
Chalcone ethynylogues were formed according to:

$$Ar—C{\equiv}C—SiMe_3 + Ar'—CH{=}CH—COCl \xrightarrow[CH_2Cl_2;\ 0°C]{AlCl_3} Ar—C{\equiv}C—CO—CH{=}CH—Ar' + Me_3SiCl$$

Results are summarized in Table 1. These results require the following comments.

(*i*) All the chalcone ethynylogues have a *trans* structure ($AlCl_3$ isomerizes *cis* to *trans* α,β-ethylenic ketones) (17).

(*ii*) In an attempt to improve the results we replaced $AlCl_3$ by $TiCl_4$, which often limits the formation of degradation products (18). The ethynylogue of the nonsubstituted chalcone was obtained in only 20% yields but the silylated intermediate **14** could be isolated. The stereochemistry of the reaction was not determined.



The route we propose for the synthesis of chalcone ethynylogues appears to be synthetically convenient even in the presence of acyloxy substituents since the involved trimethylchlorosilane was recovered during the acylation reaction.

Experimental

All the new compounds exhibit satisfactory C, H analyses. Microanalytical data are available on request.

Ethynylsilanes

H—C≡C—$SiMe_3$, **1**, and **5** were prepared according to refs. 12, 14, and 13 respectively. Compounds **2**, **3**, and **4** were synthesized from *o*-Me_3SiO—C_6H_4—C≡C—H (4) by classical replacement of the acetylenic proton by a Me_3Si group followed by hydrolysis or acetylation. Infrared cm^{-1}: 1250, 840, and 755 ($SiMe_3$); 2170 ($\nu_{C\equiv C}$) and 3500 (ν_{OH}) for **2**; 1760 ($\nu_{C=O}$) for **4**.

(2-Hydroxyphenylethynyl)trimethylsilane **2**

Boiling point: 80°C/1 Torr; nmr (CCl_4, TMS) δ ppm: 0.30 (s, 9H, $SiMe_3$), 6.1 (s, 1H, OH which disappears when added D_2O), 7.0–7.8 (m, 4 arom H).

(2-Trimethylsiloxyphenylethynyl)trimethylsilane **3**

Boiling point: 80–83°C/1 Torr; nmr δ ppm: 0.24 (s, 9H, $SiMe_3$), 0.30 (s, 9H, $SiMe_3$), 7.3–7.8 (m, 4 arom H).

(2-Acetoxyphenylethynyl)trimethylsilane **4**

Boiling point: 105°C/1 Torr; nmr δ ppm: 0.25 (s, 9H, $SiMe_3$), 2.23 (s, 3H, OCOMe), 6.9–7.5 (m, 4 arom H).

Chalcone etynylogues

The general procedure given by Birkofer *et al.* (10) was modified as follows: ethynylsilane (15 mmol in 20 mL Ch_2Cl_2) was added dropwise at −30°C to the complex formed from acyl chloride (15 mmol) and $AlCl_3$ (15 mmol) in 40 mL CH_2Cl_2 under N_2 atm. After 1 h at −30°C, the reaction mixture was left 2 h at 0°C, then poured into ice-cold water containing NH_4Cl and $NaHCO_3$. Products were extracted with CH_2Cl_2 and the organic layer washed, dried with Na_2SO_4, and the solvent and Me_6Si_2O evolved. Then the products were purified on a silica column (Kieselgel 60, 70–230 mesh ASTM) using benzene, benzene–ether, or methylene chloride as the eluent (as specified below).

Compound **6** also was synthesized from PhCH=CH—COCl/$TiCl_4$ according to a similar procedure ($TiCl_4$ replacing $AlCl_3$). Dechlorosilylation of **14** was carried out according to ref. 19 (3 h at 70°C); **7** and **13** also were prepared according to the method of Tohda *et al.* (9) starting from phenylacetylene (15 mmol).

Except for the nonsubstituted chalcone ethynylogue **6** previously described (9), all the other ethynylogues are new compounds.

5-(2'-Acetoxyphenyl) 1-phenyl pent-1-yn 4-enone **7**

Melting point (ether/pentane, 1:1 vol) 88°C; eluent: CH_2Cl_2; ir cm^{-1}: 2225 and 2195 (C≡C), 1775 (C=O ester), 1640 (C=O ketone), 1610 (C=C); nmr δ ppm: 2.23 (s, 3H, OCOMe), 6.56, 6.84, 7.72, 8.00 (AB spectr, $J \simeq 16.5$ Hz, 2H, CH=CH), 6.80–7.75 (m, 9 arom H).

1-(2'-Acetoxyphenyl) 5-phenyl pent-1-yn 4-enone **8**

Melting point (pentane) 72°C; **8** was purified by hplc (Jobin–Yvon Chromatospac Prep 100, silica column H 60 10–40 mesh, CH_2Cl_2 as the eluent); ir cm^{-1}: 2230 (C≡C), 1770 and 1750 (C=O ester), 1640 (C=O ketone), 1600 (C=C); nmr δ ppm: 2.31 (s, 3H, OCOMe), 6.66, 6.94, 7.80, 8.08 (AB spectr, $J \sim 16.5$ Hz, 2H, CH=CH), 7.05–7.80 (m, 9 arom H).

1,5-Bis(2'-acetoxyphenyl) pent-1-yn 4-enone **9**

Eluent: CHS_2Cl_2; ir cm^{-1}: 2220 (C≡C), 1765 (C=O ester), 1635 (C=O ketone), 1605 (C=C); nmr δ ppm: 2.23 (s, 6H, 2 OCOMe), 6.56, 6.83, 7.76, 8.03 (AB spectr, $J \sim 16$ Hz, 2H, CH=CH), 6.80–7.75 (m, 8 arom H).

Compounds **10**, **11**, **12**, and **13** were studied by 90 MHz nmr spectrometry with expansion of the aromatic region to specify some couplings.

1,5-Bis(4'-methoxyphenyl) pent-1-yn 4-enone **10**

Melting point (C_6H_{12}/Et_2O, 1:1 vol) 106°C; eluent: C_6H_6/Et_2O, 19:1 vol; ir cm^{-1}: 2220 and 2200 (C≡C), 1685 (C=O ketone), 1610 (C=C); nmr δ ppm: 3.70 (s, 6H, 2MeO), 6.36, 6.63, 7.45, 7.72 (AB spectr, 2H, $J \sim 16.5$ Hz), 6.69, 6.83, 7.36, 7.50 (AA'BB' spectr, $J \sim 9$ Hz, 4 arom H), 6.70, 6.84, 7.37, 7.51 (AA'BB' spectr, $J \sim 9$ Hz, 4 arom H).

5-(3',4'-Dimethoxyphenyl) 1-(4'-methoxyphenyl) pent-1-yn 4-enone **11**

Melting point (C_6H_{12}/Et_2O, 1:1 vol) 96°C; eluent: Et_2O/C_6H_6, 1:1 vol; ir cm^{-1}: 2220 and 2195 (C≡C), 1680 (C=O), 1605 (C=C); nmr δ ppm: 3.80 (s, 9H, 3MeO), 6.41, 6.68, 7.50 and 7.77 (AB spectr, $J \sim 16$ Hz, 2H, CH=CH), 6.71, 6.86, 7.40, 7.56 (AA'BB' spectr, $J \sim 9$ Hz, 4H of the disubstituted arom ring), 6.55–7.70 (m, 3 other arom H).

5-(2'-Acetoxyphenyl) 1-(4'-methoxyphenyl) pent-1-yn 4-enone **12**

Melting point (C_6H_{12}/Et_2O, 1:1 vol) 109°C; eluent: C_6H_6/Et_2O, 9:1 vol; ir cm^{-1}: 2230 and 2200 (C≡C), 1770 (C=O ester), 1645 (C=O ketone), 1616 (C=C); nmr δ ppm: 2.25 (s, 3H, OCOMe), 3.75 (s, 3H, MeO), 6.46, 6.73, 7.63, 7.90 (AB spectr, $J \sim 16$ Hz, 2H, CH=CH), 6.68, 6.83, 7.36, 7.51 (AA'BB' spectr, $J \sim 9$ Hz, 4H of the disubstituted arom ring), 6.65–7.65 (m, 3 other arom H).

5-(4'-Methoxyphenyl) 1-phenyl pent-1-yn 4-enone **13**

Melting point (Et_2O/n-C_6H_{14}, 1:1 vol) 105°C; no elution; ir cm^{-1}: 2220 (C≡C), 1640 (C=O), 1610 (C=C); nmr δ ppm: 3.76 (s, 3H, MeO), 6.38, 6.66, 7.48, 7.76 (AB spectr, $J \sim 16.5$ Hz, 2H, CH=CH), 6.70, 6.84, 7.36, 7.50 (AA'BB' spectr, $J \sim 8.5$ Hz, 4H of the disubstituted arom ring), 6.70–7.70 (m, 5 other arom H).

1,5-Diphenyl 1-chloro 2-trimethylsilyl penta-1,4-dienone **14**

Melting point (C_6H_6/C_6H_{12}, 1:1 vol) 133°C; eluent: C_6H_6; ir cm^{-1}: 1645 (C=O); nmr δ ppm: 0.15 (s, 9H, $SiMe_3$), 6.72, 6.98 (part A of AB spectr, $J \sim 16$ Hz, 1H of CH=CH), 7.28–7.85 (m, 11 other H); ms: signals at 342 and 340 (mol. peaks), 305 (M − Cl), 131 (PhCH=CH—CO), 103 (PhCH=CH), 73 ($SiMe_3$).

1. Actualités de chimie thérapeutique. 7ème série. 1290 (1980).
2. A. Lespagnol. Chimie des Médicaments. Vol. 2. Entreprise Moderne d'Edition, Paris. 1974. p. 390.
3. Dictionnaire Vidal, O.V.P. (Paris). 56th ed. 1980. p. 1308.
4. P. Babin, P. Bourgeois, and J. Dunoguès. C.R. Acad. Sci. Ser. C, **283**, 149 (1976).
5. P. Babin, J. Dunoguès, and F. Duboudin. J. Heterocycl. Chem. **18**, 519 (1981).
6. (*a*) D. Nightingale and F. T. Wadsworth. J. Am. Chem. Soc. **67**, 416 (1945); (*b*) **69**, 1181 (1947).
7. A. M. Sladkov and I. R. Golding. Khim. Atsetilena, Tr. Vses. Konf., 3rd. *Edited by* A. A. Petrov. Nauka, Moscow, USSR. 1968.
8. L. Rampazzo, A. Inesi, and A. Zeppa. J. Electroanal. Chem. **76**, 175 (1977).
9. Y. Tohda, K. Sonogashira, and N. Hagihara. Synthesis, 777 (1977).
10. L. Birkofer, A. Ritter, and H. Uhlenbrauck. Chem. Ber. **96**, 3280 (1963).
11. (*a*) R. Calas and P. Bourgeois. C.R. Acad. Sci. Ser. C,

268, 1525 (1969); (*b*) P. BOURGEOIS and R. CALAS. J. Organometal. Chem. **22**, 89 (1970); (*c*) P. BOURGEOIS, G. MÉRAULT, and R. CALAS. J. Organometal. Chem. **59**, C 4 (1973); (*d*) P. BOURGEOIS, G. MÉRAULT, N. DUFFAUT, and R. CALAS. J. Organometal. Chem. **59**, 145 (1973); (*e*) G. DÉLÉRIS, J. DUNOGUÈS, and R. CALAS. Tetrahedron Lett. 2449 (1976); (*f*) G. DÉLÉRIS, J. DUNOGUÈS, and R. CALAS. J. Organometal. Chem. **116**, C 45 (1976); (*g*) J.-P. PILLOT, J. DUNOGUÈS, and R. CALAS. Synthesis, 469 (1977).

12. Société Rhône–Poulenc. French Patent no. 2079814 (1970).
13. K. SONOGASHIRA, Y. TOHDA, and N. HAGIHARA. Tetrahedron Lett. 4467 (1975).
14. V. CHVALOVSKÝ and J. RATHOUSKÝ. Organosilicon compounds. Academic Press, New York and London. 1965.
15. C. EABORN and D. WALTON. J. Organometal. Chem. **2**, 95 (1964).
16. R. OLIVER and D. R. M. WALTON. Tetrahedron Lett. 5209 (1972).
17. G. COMBAUD and L. GIRAL. Bull. Soc. Chim. Fr. 3258 (1969).
18. T. MUKAIYAMA. Angew. Chem. Int. Ed. Engl. **16**, 817 (1977).
19. R. F. CUNICO and E. M. DEXHEIMER. J. Am. Chem. Soc. **94**, 2868 (1972).