One-Pot Synthesis of Functionalized 2*H*-Chromene (= 2*H*-1-Benzopyran) Derivatives *via* a Three-Component Reaction between a CH-Acid, a Dialkyl Acetylenedicarboxylate, and Methyl Chloroglyoxylate or Benzyl Carbonochloridate Mediated by Triphenylphosphine

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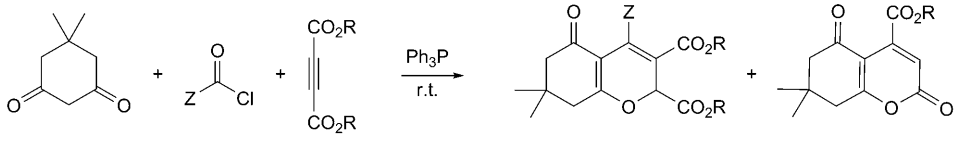
An effective route to functionalized 2*H*-chromene (= 2*H*-1-benzopyran) derivatives **4** is described (*Scheme 1*). This involves the reaction of a 1,1-diactivated alkene, resulting from the reaction of dimedone (= 5,5-dimethylcyclohexane-1,3-dione; **1a**) with methyl chloroglyoxylate (ClC(=O)COOMe), benzyl carbonochloridate (ClC(=O)OCH$_2$Ph) or 3,5-dinitrobenzoyl chloride (3,5-(NO$_2$)$_2$C$_6$H$_3$C(=O)Cl), and a dialkyl acetylenedicarboxylate (= dialkyl but-2-ynedioate) in the presence of Ph$_3$P which undergo intramolecular *Wittig* reaction to produce 2*H*-chromene derivatives (*Scheme 1*).

Introduction. – The developments of multicomponent reactions have attracted much attention from the vantage point of combinatorial and medicinal chemistry [1]. The 2*H*-chromene (= 2*H*-1-benzopyran) moiety is a common structural feature of numerous biologically active molecules [2][3] and is widely occurring in many natural flavonoids and anthocyanins [4] as well as in members of the vitamin E family (tocopherols and tocotrienes) [5]. Substituted chromenes are a new class of anticancer compounds [6]. A variety of methods are known for the synthesis of this class of compounds [3][5][7], typically starting with 2-hydroxyacetophenone derivatives or directly from phenols *via* cyclization methods, electrophilic aromatic substitution, or by relying on Pd-catalyzed processes.

Herein, we report a simple one-pot reaction between a reactive 1,1-diactivated alkene, derived from the reaction of dimedone (= 5,5-dimethylcyclohexane-1,3-dione; **1a**) or *N*,*N*′-dimethylbarbituric acid (= 1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione; **1b**) as CH-acids with active carbonyl compounds **2**, such as methyl chloroglyoxylate (= methyl 2-chloro-2-oxoacetate), benzyl carbonochloridate or 3,5-dinitrobenzoyl chloride, and a dialkyl acetylenedicarboxylate (= dialkyl but-2-ynedioate) **3** in the presence of Ph$_3$P leading to 2*H*-chromene derivatives **4** (*Scheme 1*). The reaction proceeded *via* a smooth 1:1:1 addition in CH$_2$Cl$_2$ at room temperature, to produce 2*H*-chromene derivatives **4a**–**4f** in 65–90% yields.

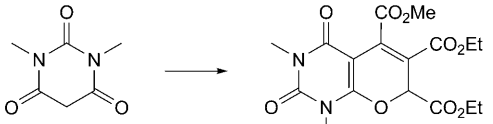
Results and Discussion. – The one-pot three-component condensation, mediated by Ph$_3$P, of CH-acid **1** with active carbonyl compounds **2** and electron-deficient acetylenic esters **3** proceeded in anhydrous CH$_2$Cl$_2$ or toluene and was completed after 24 h to

Scheme 1



1a **2** **3** **4a – 4e** **5a**, **5b**

CH-Acid	Z	R	Product **4** ([%])	Product **5** ([%])
1a	$PhCH_2O$	Me	**4a** (90)	**5a** (8)
1a	$PhCH_2O$	Et	**4b** (85)	**5b** (10)
1a	CO_2Me	Me	**4c** (75)	
1a	CO_2Me	Et	**4d** (80)	
1a	3,5-Dinitrophenyl	Me	**4e** (70)	
1b[a])	CO_2Me	Et	**4f** (65)[a])	

[a]) 

1b **4f**

afford corresponding 2*H*-chromene systems **4a** – **4f** in moderate to good yields. ^{1}H- and ^{13}C-NMR spectra of the crude products clearly indicated the formation of **4a** – **4f**. The structures of **4a** – **4f** were deduced from their elemental analyses, and IR and ^{1}H- and ^{13}C-NMR spectra. The mass spectra of **4a** – **4f** displayed the molecular-ion peak at the expected *m*/*z* values. Initial fragmentations involved loss of the side chains and scission of the heterocyclic system.

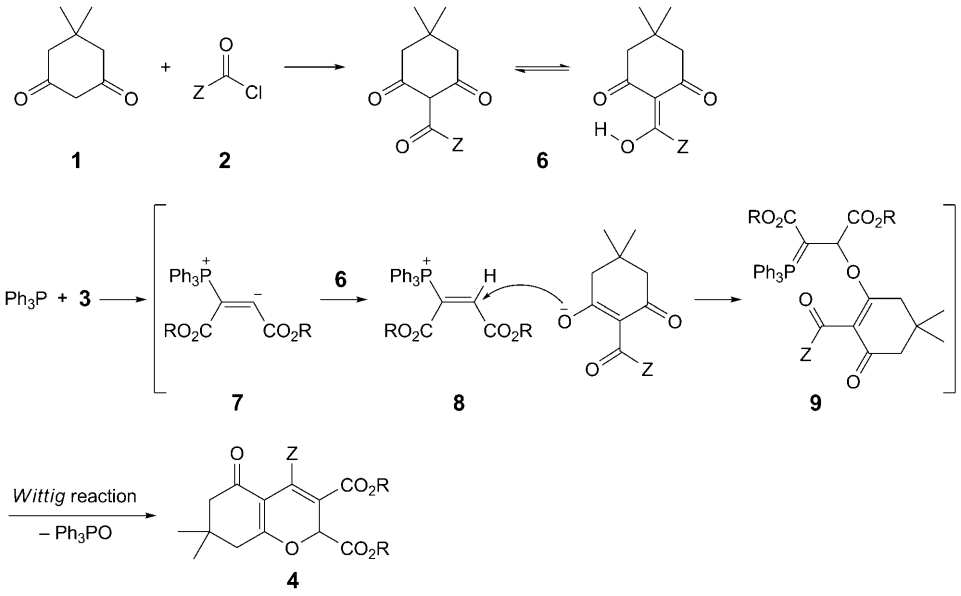
The ^{1}H-NMR spectrum of **4a** consisted of four *s* for Me and MeO groups (δ 1.05, 1.10, 3.63, and 3.73) and a further *s* for the CH H-atom (δ 4.57). The CH_2 H-atoms of the benzyl group are diastereotopic and exhibited an *AB* system ($J_{AB} = 12.0$ Hz, δ_A 5.23, and δ_B 5.28). The ^{1}H-decoupled ^{13}C-NMR spectrum of **4a** showed 20 sharp signals in agreement with the proposed structure. The signal of the CH group of **4a** appeared at δ *ca.* 50. The ^{1}H- and ^{13}C-NMR spectra of **4b** – **4e** are similar to those of **4a**, except for the activated carbonyl and ester moieties (see *Exper. Part*). The structural assignments, made on the basis of the ^{1}H- and ^{13}C-NMR spectra of **4a**, are supported by the IR spectra. The spectrum of **4a** showed strong absorption at 1735 and 1681 cm^{-1} attributable to the C=O groups.

We also used other CH-acidic compounds such as *Meldrum*'s acid (= 2,2-dimethyl-1,3-dioxane-4,6-dione), barbituric acid (= pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione), or indan-1,3-dione for the same reaction sequence, but the yields of the corresponding 2*H*-chromenes were very low, and in three cases several by-products were observed (based on TLC).

Although the mechanism of the reaction between Ph_3P and dialkyl acetylenedicarboxylates **3** in the presence of 1,1-diactivated alkene **6** (derived from C-acylation of

dimedone (**1a**) by **2**) has not yet been established unambiguously by experiment, a possible mechanistic sequence is proposed in *Scheme 2*. Based on the well-established chemistry of trivalent phosphorus nucleophiles [8], it is reasonable to assume that product **4** results from initial addition of Ph_3P to the dialkyl acetylenedicarboxylate **3**, leading to **7**, which on protonation by the acidic alkene **6** yields the 1:1 adduct **8**. Then, conjugate addition of the resulting O-enolate results in the formation of phosphorane **9**, which is converted to **4** *via* an intramolecular *Wittig*-type ring closure.

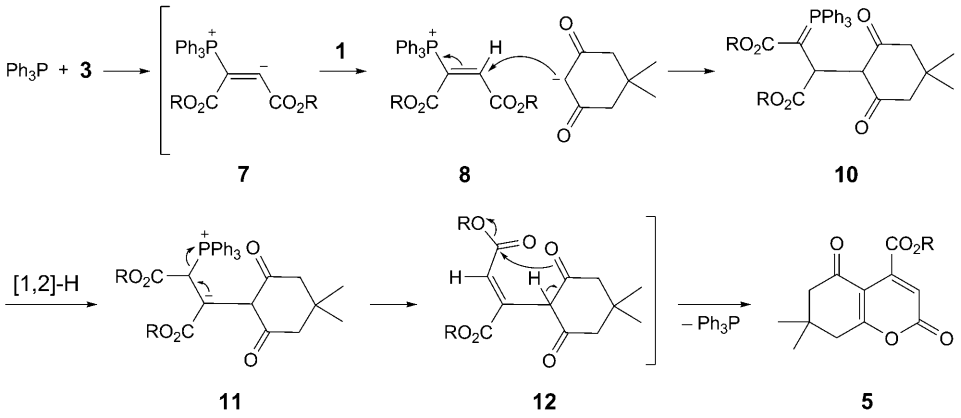
Scheme 2



From the reaction of dialkyl acetylenedicarboxylate with dimedone and benzyl carbonochloridate in the presence of Ph_3P, in addition to the 2*H*-chromene derivative **4**, fused 2*H*-pyran-2-ones **5** were isolated. In fact, the fused 2*H*-pyran-2-ones **5** are the major product in the absence of **2**. The mechanism for the formation of **5a** and **5b** is proposed in *Scheme 3*. In this case, intermediate **8** is directly attacked by the dimedone anion to form phosphorane **10**. This intermediate undergoes a H-atom transfer to yield **11**, which furnishes **12** by loss of Ph_3P. Finally, cyclization of **12** leads to compound **5** [8][9].

In conclusion, we developed a convenient one-pot procedure for preparing 2*H*-chromenes **4** of potential synthetic interest. The present method offers the advantage that the reaction proceeds under neutral conditions and, moreover, the substances can be mixed without any prior activation or modification. The simplicity of the present procedure makes it an interesting alternative to complex multi-step syntheses. Although the reaction sequence involves several steps, the preparation can be carried out in only one practical step (one-pot preparation).

Scheme 3



Experimental Part

General. Methyl chloroglyoxylate (= methyl 2-chloro-2-oxoacetate), benzyl carbonochloridate, *N*,*N*′-dimethylbarbituric acid, and other reagents and solvents used in this work were obtained from *Fluka* (Buchs, Switzerland) and used without further purification. Column chromatography = CC. M.p.: *Gallenkamp-9100* electrothermal apparatus; uncorrected. IR Spectra: *Bruker-Tensor-27* spectrometer; KBr pellets; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker-DRX-300-Avance* instrument; $CDCl_3$ as solvent; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Shimadzu-QP-GC Mass-1100-EX* spectrometer operating at an ionization potential of 70 eV; in *m*/*z* (rel. %). Elemental analyses: *Heraeus-CHN-O-Rapid* analyzer; exper. values in agreement with calc. values.

*General Procedure, Exemplified for Dimethyl 4-(Benzyloxy)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-2*H*-1-benzopyran-2,3-dicarboxylate* (**4a**). To a soln. of dimedone (**1a**; 0.140 g, 1 mmol) and benzyl carbonochloridate (0.170 g, 1 mmol) in dry CH_2Cl_2 (5 ml), magnetically stirred for 8 h, PPh_3 (0.262 g, 1 mmol) was added, followed by dropwise addition of a soln. of dimethyl but-2-ynedioate (0.142 g, 1 mmol) in dry CH_2Cl_2 (3 ml) at r.t. over 10 min. The mixture was stirred for 24 h. The solvent was evaporated and the residue separated by CC (silica gel (*Merck* 230–240 mesh), hexane/AcOEt 8 :2): **4a** (0.360 g, 90%). Orange oil. IR: 2929 (C–H), 1735 and 1681 (C=O), 1199 (C–O). ^{1}H-NMR: 1.05, 1.10 (2*s*, Me_2C); 2.26 (*AB q*, ^2J = 16.2, CH_2); 2.30 (*AB q*, ^2J = 17.7, CH_2); 3.63, 3.73 (2*s*, 2 MeO); 4.57 (*s*, CH); 5.25 (*AB q*, ^2J = 12.0, PhCH_2O); 7.29–7.40 (*m*, 5 arom. H). ^{13}C-NMR: 27.33, 28.98 (Me_2C); 32.50, 36.45 (2 CH_2); 40.28 (Me_2C); 50.46 (CH); 51.63, 52.53 (2 MeO); 71.74 (CH_2O); 84.05 (CH*C*=C); 117.73 (OC=*C*); 127.67, 128.58, 128.66, 135.12 (arom. C); 159.25 (O*C*=C); 163.47 (CHC=*C*); 165.52, 172.68 (2 C=O ester); 195.84 (C=O). EI-MS: 400 (1, M^+), 277 (100), 262 (48), 199 (16), 183 (37), 152 (17), 119 (34), 91 (41), 77 (24), 51 (20). Anal. calc. for $C_{22}H_{24}O_7$ (400.43): C 65.99, H 6.04; found: C 65.9, H 6.1.

*Diethyl 4-(Benzyloxy)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-2*H*-1-benzopyran-2,3-dicarboxylate* (**4b**): Yield 0.364 g (85%). Yellow oil. IR: 2925 (CH), 1735, 1671 (C=O), 1197 (C–O). ^{1}H-NMR: 1.10, 1.15 (2*s*, Me_2C); 1.20, 1.31 (2*t*, ^3J = 7.0, 2 MeCH_2O); 2.25 (*AB q*, ^2J = 15.0, CH_2); 2.45 (*AB q*, ^2J = 15.5, CH_2); 4.11 (*q*, ^3J = 7.0, 1 MeCH_2O); 4.15–4.30 (*m*, 1 MeCH_2O); 4.56 (*s*, CH); 5.28 (*AB q*, ^2J = 12.0, PhCH_2O); 7.25–7.45 (*m*, 5 arom. H). ^{13}C-NMR: 14.10, 14.29 (2 *Me*CH_2O); 27.24, 29.07 (Me_2C); 32.67, 36.67 (2 CH_2); 40.32 (Me_2C); 60.34, 61.24 (2 MeCH_2O); 71.71 (PhCH_2O); 84.99 (CH*C*=C); 111.73 (OC=*C*); 127.73, 128.53, 128.61, 135.18 (arom. C); 158.91 (O*C*=C); 163.40 (CHC=*C*); 165.02, 172.68 (2 ester C=O); 195.90 (C=O). EI-MS: 400 (1.5, M^+), 355 (13), 307 (6), 277 (27), 219 (6), 91 (100), 83 (7). Anal. calc. for $C_{24}H_{28}O_7$ (428.48): C 67.28, H 6.59; found: C 67.1, H 6.7.

*Trimethyl 5,6,7,8-Tetrahydro-7,7-dimethyl-5-oxo-2*H*-1-benzopyran-2,3,4-tricarboxylate* (**4c**): Yield 0.264 g (75%). Orange oil. IR: 2957 (C–H), 1736, 1671 (C=O), 1204 (C–O). ^{1}H-NMR: 1.11, 1.13

(2*s*, Me_2C); 2.34 (*AB q*, ^2J = 16.2, CH_2); 2.47 (br. *s*, CH_2); 3.68, 3.80, 3.86 (3*s*, 3 MeO); 4.47 (*s*, CH). ^{13}C-NMR: 27.13, 29.07 (Me_2C); 32.39, 36.76 (2 CH_2); 40.56 (Me_2C); 50.25 (CH); 52.78, 53.18, 53.52 (3 MeO); 108.76 (CH*C*=C); 112.11 (OC=*C*); 144.70 (O*C*=C); 161.20 (CHC=*C*); 164.69, 165.33, 170.34 (3 ester C=O); 195.82 (C=O). Anal. calc. for $C_{17}H_{20}O_8$ (352.34): C 57.95, H 5.72; found: C 57.8, H 5.6.

*2,3-Diethyl 4-Methyl 5,6,7,8-Tetrahydro-7,7-dimethyl-5-oxo-2*H*-1-benzopyran-2,3,4-tricarboxylate* (**4d**): Yield 0.304 g (80%). Yellow oil. IR: 2960 (C–H), 1736, 1672 (C=O), 1198 (C–O). ^{1}H-NMR: 1.10, 1.14 (2*s*, Me_2C); 1.19, 1.32 (2*t*, ^3J = 6.9, 2 *Me*CH_2O); 2.25 (*AB q*, ^2J = 16.0, CH_2); 2.45 (*AB q*, ^2J = 15.5, CH_2); 3.81 (*s*, MeO); 4.10–4.25 (*m*, 2 MeCH_2O); 4.46 (*s*, CH). ^{13}C-NMR: 13.90, 13.97 (2 *Me*CH_2O); 26.90, 29.62 (Me_2C); 32.46, 36.93 (2 CH_2); 40.52 (Me_2C); 50.34 (CH); 52.98 (MeO); 61.72, 61.80 (2 MeCH_2O); 108.81 (CH*C*=C); 112.55 (OC=*C*); 144.29 (O*C*=C); 161.20 (CHC=*C*); 164.18, 164.80, 169.65 (3 ester C=O); 196.19 (C=O). Anal. calc. for $C_{19}H_{24}O_8$ (380.39): C 59.99, H 6.36; found: C 60.1, H 6.4.

*Dimethyl 4-(3,5-Dinitrophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-2*H*-1-benzopyran-2,3-dicarboxylate* (**4e**): Yield 0.322 g (70%). Yellow paste. IR: 2960 (CH), 1738, 1680 (C=O), 1212 (C–O). ^{1}H-NMR: 1.15, 1.16 (2*s*, Me_2C); 2.39 (*AB q*, ^2J = 16.5, CH_2); 2.50 (*AB q*, ^2J = 16.5, CH_2); 3.67, 3.74 (2*s*, 2 MeO); 4.75 (*s*, CH); 8.62 (*d*, ^3J = 1.2, 2 H_o); 9.08 (*t*, ^3J = 1.2, H_p). Anal. calc. for $C_{21}H_{20}N_2O_{10}$ (460.4): C 54.78, H 4.38, N 6.08; found: C 54.8, H 4.3, N 6.2.

*6,7-Diethyl 5-Methyl 1,3,4,7-Tetrahydro-1,3-dimethyl-2,4-dioxo-2*H*-pyrano[2,3-*d*]pyrimidine-5,6,7-tricarboxylate* (**4f**): Yield 0.257 g (65%). Yellow oil. IR: 2924 (C–H), 1717, 1681 (C=O), 1200 (C–O). ^{1}H-NMR: 1.33, 1.41 (2*t*, 2 *Me*CH_2O); 3.45, 3.61 (2*s*, 2 MeN); 3.95 (*s*, MeO); 4.28–4.32 (*m*, 2 MeCH_2O); 4.47 (*s*, CH). ^{13}C-NMR: 14.33, 14.42 (2 *Me*CH_2O); 39.16, 39.59 (2 MeN); 53.04 (CH); 53.79 (MeO); 62.75, 63.79 (2 Me*C*H_2O); 85.59 (OC=*C*); 116.09 (CH*C*=C); 143.50 (CHC=*C*); 152.60, 157.71 (C=O); 160.17 (O*C*=C); 161.38, 164.55, 169.79 (3 ester C=O). Anal. calc. for $C_{17}H_{20}N_2O_9$ (396.35): C 51.52, H 5.09, N 7.07; found: C 51.6, H 5.2, N 7.1.

*Methyl 5,6,7,8-Tetrahydro-7,7-dimethyl-2,5-dioxo-2*H*-1-benzopyran-4-carboxylate* (**5a**): Yield 0.02 g (8%). White powder. M.p. 95–97°. IR: 2925 (C–H), 1760, 1725 (C=O). ^{1}H-NMR: 1.18 (2*s*, Me_2C); 2.42, 2.70 (2*s*, 2 CH_2); 3.92 (*s*, MeO); 6.21 (*s*, =CH). ^{13}C-NMR: 28.12, 28.14 (Me_2C); 32.48, 36.50 (2 CH_2); 42.15 (Me_2C); 53.24 (MeO); 111.32 (OC=*C*); 111.75 (=CH); 145.54 (*C*=CH); 159.10 (O*C*=C); 165.75, 174.19 (2 ester C=O); 192.35 (C=O). Anal. calc. for $C_{13}H_{14}O_5$ (250.25): C 62.39, H 5.64; found: C 62.4, H 5.6.

*Ethyl 5,6,7,8-Tetrahydro-7,7-dimethyl-2,5-dioxo-2*H*-1-benzopyran-4-carboxylate* (**5b**): Yield 0.026 g (10%). Pale yellow paste. IR: 2928 (C–H), 1758, 1720 (C=O). ^{1}H-NMR: 1.16 (2*s*, Me_2C); 1.38 (*t*, ^3J = 7.2, *Me*CH_2O); 2.45, 2.76 (2*s*, 2 CH_2); 4.41 (*q*, ^3J = 7.2, MeCH_2O); 6.19 (*s*, =CH). ^{13}C-NMR: 14.12 (*Me*CH_2O); 28.13, 28.115 (Me_2C); 32.47, 36.49 (2 CH_2); 42.17 (Me_2C); 61.45 (Me*C*H_2O); 111.30 (OC=*C*); 111.74 (=CH); 145.53 (*C*=CH); 159.14 (O*C*=C); 165.72, 174.16 (2 ester C=O); 192.30 (C=O). Anal. calc. for $C_{14}H_{16}O_5$ (264.27): C 63.63, H 6.10; found: C 63.7, H 6.1.

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