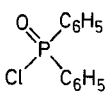
Activation of 2-Alkenoic Acids as Mixed Anhydrides with Diphenylphosphinic Acid for the Formation of Carboxamides

S. Bernasconi*, A. Comini, A. Corbella, P. Gariboldi, M. Sisti

Laboratorio di Chimica Organica, Facoltà di Scienze, Università degli Studi, Via Saldini 50, I-20133 Milano, Italia

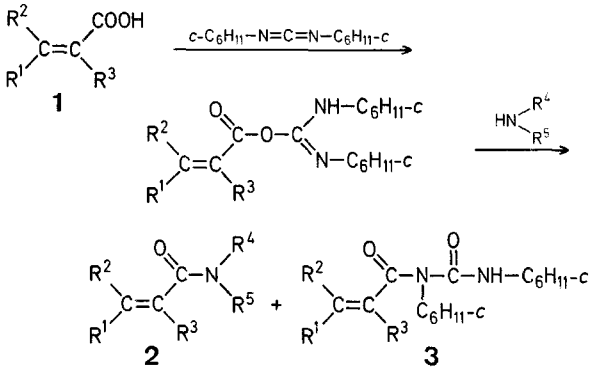
In the synthesis of a number of 2-alkenamides to be submitted to biological screenings, we faced some difficulties which led us to reconsider known methods commonly used for the activation of saturated acids and to compare their efficiency in our case. We summarize here the results of these studies which showed that diphenylphosphinic chloride,



a recently introduced reagent[1], is the reagent of choice for activating 2-alkenoic acids for amide formation.

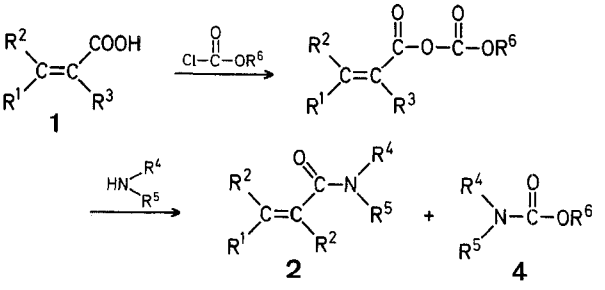
The formation of mixed anhydrides of 2-alkenoic acids and diphenylphosphinic acid has hitherto received no attention. The use of these anhydrides for carboxamide formation offers significant advantages over known procedures. The present method is convenient to perform and efficient, although in a few cases the yields are not distinctly higher than those obtained by other methods; however, the products are of satisfactory purity and are not contaminated with by-products of similar chemical or physical properties.

We compared the diphenylphosphinic mixed anhydride method with the dicyclohexylcarbodiimide method and with the mixed carbonate method (acyl carbonate method). The dicyclohexylcarbodiimide method usually leads to the formation of the acid ureide as a by-product in minor amounts; however, with 2-alkenoic acids (**1**) the ureide (**3**) is obtained as the main product so that the yield of the desired 2-alkenamide (**2**) is less than 20%. This result can be rationalized by the assumption that the intermediate *O*-acylisourea rearranges to the ureide **3** more rapidly than it reacts with the amine to give the carboxamide **2**.



Attempts to improve the yield of **2** by modifying the dicyclohexylcarbodiimide method by the addition of *N*-hydroxyphthalimide or *N*-hydroxysuccinimide were unsuccessful, the amount of ureide (**3**) being too large in all cases.

Similar problems were encountered with the acyl carbonate method. While in the case of saturated carboxylic acids the reaction of the acyl carbonate (obtained from the acid and methyl or ethyl carbonochloridate) with a primary or secondary amine leads mainly to the desired carboxamide, a considerable amount of alkyl carbamate (**4**) is formed in the analogous reaction of an acyl carbonate derived from a 2-alkenoic acid. This side reaction not only lowers the yield of the desired 2-alkenamide (**2**) but also leads to serious problems regarding separation of products. As expected, the ratio carboxamide/carbamate is better when isobutyl carbonochloridate in place of methyl carbonochloridate is used for acyl carbonate formation since the bulky isobutyl group ($R^6 = i\text{-}C_4H_9$) hinders the attack of the carbonate carbonyl group by the amine. The base used in the reaction also has an effect on the yield as can be seen from the results listed in Table 1; these results cannot be generalized, however.



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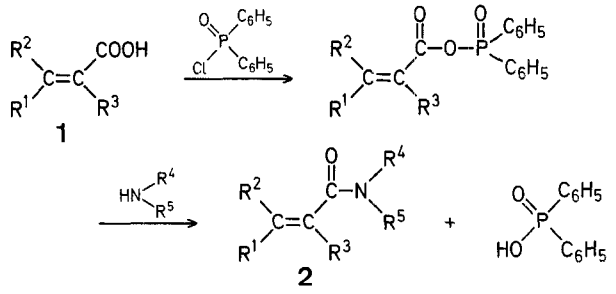
On the other hand, the diphenylphosphinic anhydride method which has not previously been applied to 2-alkenoic acids works quite well with the compounds tested. The only by-product formed is diphenylphosphinic acid which can be easily removed by washing the reaction mixture with aqueous base. No attack at the β-carbon of the conjugate system is observed; this fact is in accord with the strong electrophilic character of the carbonyl group activated by the phosphinic anhydride formation.



It should be noted that the diphenylphosphinic anhydride method works better with primary amines than with secondary amines such as piperidine.

2-Alkenamides (2) from 2-Alkenoic Acids (1) and Primary or Secondary Amines via Reactive Acid Derivatives; General Procedures:

Dicyclohexylcarbodiimide Method: Dicyclohexylcarbodiimide (2.064 g, 0.01 mol) is added to a vigorously stirred solution of the 2-alkenoic acid (**1**; 0.01 mol) and the amine (0.01 mol) in dry ethyl acetate (50 ml) under an inert atmosphere at −10 °C. Stirring is continued for 12 h at room temperature, and the mixture filtered. The precipitate on the filter which consists mainly of dicyclohexyl-

Table 1. 2-Alkenamides (**2**) from 2-Alkenoic Acids (**1**) and Primary or Secondary Amines via Reactive Acid Derivatives

	R¹	R²	R³	R⁴	R⁵	Yield [%] using						
						Dicyclohexyl-carbodiimide		Methyl carbono-chloridate		Isobutyl carbono-chloridate		Diphenylphos-phinic chloride
						2	**3**	**2**	**4**	**2**	**4**	**2**
a	CH_3	CH_3	H	$-CH_2-CH_2-C_6H_5$	H	15	42	52[a]	34[a]	57[a]	31[a]	94[a]
								60[b]	31[b]	67[b]	29[b]	85[b]
b	H	CH_3	CH_3	$-CH_2-CH_2-C_6H_5$	H	19	72	40[a]	36[a]	44[a]	40[a]	83[a]
								44[b]	31[b]	49[b]	42[b]	71[b]
c	H	H	CH_3	$-CH_2-CH_2-C_6H_5$	H	27	40	52[a]	19[a]	60[a]	16[a]	81[a]
								36[b]	14[b]	64[b]	14[b]	74[b]
d	C_6H_{11}[c]	CH_3	H	$-CH_2-CH_2-C_6H_5$	H	21	65	73[a]	21[a]	76[a]	31[a]	92[a]
								76[b]	26[b]	79[b]	23[b]	79[b]
e	CH_3	CH_3	H	i-C_3H_7	i-C_3H_7	—	88					
f	CH_3	CH_3	H	$-(CH_2)_5-$		35	35	24[a]	15[a]	21[a]	20[a]	61[a]
g	CH_3	CH_3	H	$-(CH_2)_2-O-(CH_2)_2-$		11	71	8.5[a]	12[a]	3.2[a]	24[a]	35[a]

[a] Using triethylamine as tertiary base.
[b] Using *N*-methylmorpholine as tertiary base.
[c] A ~6+4 mixture of (2*E*)- and (2*Z*)-geranic acids was used as starting material.

Table 2. Data of 2-Alkenamides (**2**)

2	b.p./torr [°C]	Molecular formula[a]	I.R. (film)[b] ν [cm⁻¹]	¹H-N.M.R. ($CDCl_3$/TMS)[c] δ [ppm]
a	202–205°/1.5	$C_{13}H_{17}NO$ (203.3)	3300; 1670; 1630; 1540	7.30 (s, 5H$_{arom}$); 5.75 (m, 1H, NH); 5.55 (m, 1H, C=CH); 3.55 (bt, 2H, CH_2–N); 2.85 (t, 2H, J=7 Hz, N–CH_2–CH_2); 2.15 (bs, 3H, CH_3); 1.82 (bs, 3H, CH_3)
b	153–157°/1.3	$C_{13}H_{17}NO$ (203.3)	3310; 1660; 1620; 1530	7.30 (s, 5H$_{arom}$); 6.40 (m, 1H, NH); 5.85 (m, 1H, C=CH); 3.57 (bq, 2H, N–CH_2); 2.85 (t, 2H, J=7 Hz, N–CH_2–CH_2); 1.75 (s, 3H, CH_3); 1.70 (bd, 3H, CH_3)
c	150–154°/0.7	$C_{12}H_{15}NO$ (189.3)	3310; 1655; 1615; 1535	7.30 (s, 5H$_{arom}$); 6.10 (m, 1H, NH); 5.65 (bs, 1H, C–CH); 5.30 (bs, 1H, C=CH); 3.58 (bq, 2H, N–CH_2); 2.87 (t, 2H, N–CH_2–CH_2); 1.92 (bs, 3H, CH_3)
d	210–215°/2.8	$C_{18}H_{25}NO$ (271.4)	3300; 1655; 1630; 1540	7.30 (s, 5H$_{arom}$); 5.72 (m, 1H, NH); 5.53 (bs, 1H, C–CH–CO); 5.11 (m, 1H, C=CH); 3.55 (bq, 2H, N–CH_2); 2.82 (t, 2H, J=7 Hz, N–CH_2–CH_2); 2.15 (bs, 3H, CH_3); 1.70 (bs, 3H, CH_3); 1.61 (bs, 3H, CH_3); 1.80–2.80 (m, 4H, all other protons)
f	215–217°/1.8	$C_{10}H_{17}NO$ (167.3)	1650; 1620	5.82 (bs, 1H, C=CH); 3.54 (m, 4H, CH_2–N–CH_2); 1.85 [bs, 6H, $(CH_3)_2C$=]; 1.65 (m, 6H, all other protons)
g	112–115°/0.15	$C_9H_{15}NO_2$ (169.2)	(nujol): 1650; 1620	5.80 (bs, 1H, C–CH); 3.65 [bs, 8H, $N(CH_2CH_2)_2O$]; 1.90 (bs, 3H, =C–CH_3); 1.85 (bs, 3H, –C–CH_3)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.28; H, ±0.15; N, ±0.23.
[b] Measured on a Perkin Elmer 257 Infracord Spectrophotometer.
[c] Measured on a Perkin Elmer R 24 instrument.

Table 3. Data of Ureides (**3**) and Carbamates (**4**)

Compound	m.p. or b.p. [°C]	Molecular formula[a]	I.R.[b] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ [ppm]
3a	m.p. 158–160° (ethyl acetate)	$C_{18}H_{30}N_2O_2$ (306.5)	(KBr): 3230; 1700; 1640; 1600; 1530	7.55 (m, 1H, NH); 5.90 (m, 1H, C=CH); 3.83 (m, 2H, CH—N—CO); 2.07 (bs, 3H, CH_3); 1.92 (bs, 3H, CH_3); 0.90–2.20 (20H, all other protons)
3b	m.p. 177–179° (ethyl acetate)	$C_{18}H_{30}N_2O_2$ (306.5)	(nujol): 3415; 3290; 1685; 1650; 1625; 1500	6.80 (m, 1H, NH); 5.90 (m, 1H, C=CH); 3.70 (m, 2H, CH—N—CO); 0.90–2.20 (26H, all other protons)
3c	m.p. 163–164° (ethyl acetate)	$C_{17}H_{28}N_2O_2$ (292.2)	(nujol): 3440; 3290; 1690; 1650; 1625; 1500	7.35 (m, 1H, NH); 5.25 (m, 2H, C=CH_2); 3.80 (m, 2H, CH—N—CO); 1.97 (bs, 3H, CH_3); 0.95–2.30 (20H, all other protons)
3d	b.p. 180°/ 2.8 torr	$C_{23}H_{38}N_2O_2$ (374.6)	(film): 3310; 1710; 1680; 1640; 1520	7.20 (m, 1H, NH); 5.90 (bs, 1H, C=CH—CO); 5.15 (m, 1H, C=CH); 3.80 (m, 2H, CH—N—CO); 0.90–2.30 (33H, all other protons)
4a (R^6=CH_3)	b.p. 120–123°/ 0.8 torr	$C_{10}H_{13}NO_2$ (179.2)	(film): 3330; 1710; 1600; 1540; 1500	7.23 (s, 5H_{arom}); 4.90 (m, 1H, NH); 3.60 (s, 3H, CH_3); 3.34 (bq, 2H, CH_2—NH); 2.75 (t, 2H, J=7 Hz, CH_2—C_6H_5)
4a (R^6=*i*-C_4H_9)	b.p. 119–120°/ 0.8 torr	$C_{13}H_{19}NO_2$ (221.3)	(film): 3320; 1700; 1600; 1530; 1500	7.30 (s, 5H_{arom}); 4.65 (m, 1H, NH); 3.85 (d, 2H, J=7 Hz, O—CH_2); 3.45 (m, 2H, CH_2—N); 2.82 (t, 2H, J=7 Hz, CH_2—C_6H_5); 1.90 (m, 1H, CH); 0.90 [d, 6H, J=7 Hz, $(CH_3)_2$C]

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.28; H, ±0.15; N, ±0.23.
[b] Measured on a Perkin Elmer 257 Infracord Spectrophotometer.
[c] Measured on a Perkin Elmer R 24 instrument.

urea and the *N,N'*-dicyclohexyl-2-alkenureide **3** is washed throughly with ethyl acetate and then separated by preparative chromatography on silica gel H (type 60) Merck using benzene/ethyl acetate (4/1) as eluent. The filtrate is evaporated in vacuo and the residual product **2** is chromatographed in order to remove the still present by-products urea and ureide.

Mixed Carbonic Anhydride Method: A solution of the alkyl carbonochloridate (0.01 mol) in dry ethyl acetate (5 ml) is added dropwise to a stirred solution of the 2-alkenoic acid (**1**; 0.01 mol) and a tertiary amine (0.01 mol) in dry ethyl acetate (50 ml) under an inert atmosphere at −10 °C. Stirring is continued for 1 h at −10 °C and the primary or secondary amine (0.01 mol) then added over a 15 min period. The mixture is allowed to warm to room temperature, held at that temperature for 12 h, and then heated at 40 °C for 5 min. After cooling, the mixture is filtered through celite and the filtrate washed with 1 normal hydrochloric acid, then with 5% sodium hydrogen carbonate solution and water. The organic layer is dried with sodium sulfate and evaporated. The products are chromatographed through a silica gel column using benzene/ethyl acetate (3/1) as eluent.

Mixed Diphenylphosphinic Anhydride Method: A tertiary amine (0.01 mol) is added dropwise to a stirred solution of the 2-alkenoic acid (**1**; 0.01 mol) and diphenylphosphinic chloride (2.61 g, 0.011 mol) in dry ethyl acetate under an inert atmosphere at −10 °C. Stirring is continued for 1 h at −10 °C and the primary or secondary amine (0.01 mol) and again the tertiary amine (0.01 mol) are added dropwise. The mixture is stirred at room temperature for 12 h and then filtered. The filtrate is washed with 1 normal hydrochloric acid (10 ml), 10% sodium carbonate solution (20 ml), and water (15 ml). The organic layer is dried with sodium sulfate and the solvent evaporated. The residual, practically pure carboxamide **2** is distilled in vacuo.

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* Address for correspondence.

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