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PHASE MANAGED ORGANIC SYNTHESIS 3. SYMMETRICAL ANHYDRIDES FROM CARBOXYLIC ACIDS VIA POLYMER ASSISTED REACTION.

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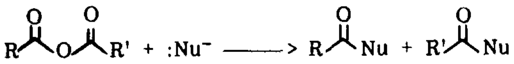
Abstract: Symmetrical anhydrides are produced quickly and in high yield by treating mixtures of a carboxylic acid and one-half equivalent thionyl chloride in dichloromethane with a solid-state copolymer of 4-vinylpyridine. This conversion is accomplished equally well in batch or column mode.

The availability of symmetrical anhydrides is important for many transacylation applications. Acylation with symmetrical anhydrides precludes formation of side-products due to attack at the second acyl carbonyl of mixed anhydrides, Eq. 1. This concern is particularly important in derivatization reactions of anhydrides of relatively weak acids, because their carbonyl groups are relatively unreactive to nucleophiles.[1] It is also relevant in solid-phase peptide synthesis where acylation product of high purity is essential.[2]

1)



Synthesis of symmetrical anhydrides is usually accomplished by dehydration of the corresponding acids. We have found that carboxylic acids can be converted directly to the related anhydride by treatment with 0.55 equiv thionyl chloride in the presence of 3.5-4.0 equiv solid-phase copolymer of 4-vinylpyridine (P4-VP).[3] The reaction as illustrated by Eq. 2 is carried out in dichloromethane

2)

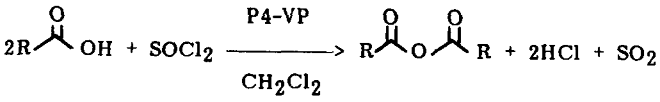


Table 1. Conversion of Carboxylic Acids to Acid Anhydrides

Batch Mode[a]

Reactant, RCOOH	Thionyl Chloride Addition	Conditions Time (Min)	Anhydride[b] Yield (%)
CH_3COOH	One portion	5	88.8
CH_3CH_2COOH	One portion	5	96.0
$(CH_3)_2CHCOOH$	One portion	5	94.6
$CH_2{=}CHCOOH$	Dropwise, 20 min	120	55.6[c,d]
$CH_2{=}CHCOOH$	Dropwise, 20 min	60	52.5[d]
$CH_2{=}C(CH_3)COOH$	Dropwise, 20 min	60	86.5
PhCH=CHCOOH	Dropwise, 20 min	60	89.7
PhCOOH	Dropwise, 20 min	60	Trace[e]
PhCOOH	Dropwise, 20 min	60	98.6
4-CH_3PhCOOH	Dropwise, 20 min	60	~100
4-CH_3OPhCOOH	Dropwise, 20 min	60	~100
4-ClPhCOOH	Dropwise, 20 min	60	96.9
CBZ-Alanine[3]	Dropwise, 20 min	60	81.6
BOC-Phenylalanine[3]	Dropwise, 20 min	60	f

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[a] Mixtures containing 0.005 mole carboxylic acid, 3.5-4.0 equiv (based on pyridine) P4-VP and 20 mL dichloromethane were treated with 0.55 equiv thionyl chloride either in one portion or dropwise in 10 mL dichloromethane with stirring at 22-25°C (Ambient) unless otherwise noted. Filtration to remove P4-VP and rotary evaporation furnished pure samples of anhydrides.

[b] Product identity was established by comparison of melting point, ^{1}H-NMR and/or IR data with published values.

[c] Reaction temperature - 0°C.

[d] An excellent material balance for the reaction is obtained with the mass discrepancy for product just equal to mass gain by P4-VP.

[e] Control experiment in which no P4-VP was used.

[f] Product mixture contained acids and anhydrides with and without the BOC group.

Table 2. Conversion of Carboxylic Acids to Acid Anhydrides Column Mode[a]

Reactant, RCOOH	Contact Time (Min.)	Anhydride[b] Yield (%)
CH_3COOH	10	88.6
CH_3CH_2COOH	10	95.0
$(CH_3)_2CHCOOH$	10	94.5
$(CH_3)_3CCOOH$	10	96.6
PhCOOH	20	98.3
$4\text{-}CH_3PhCOOH$	20	98.8

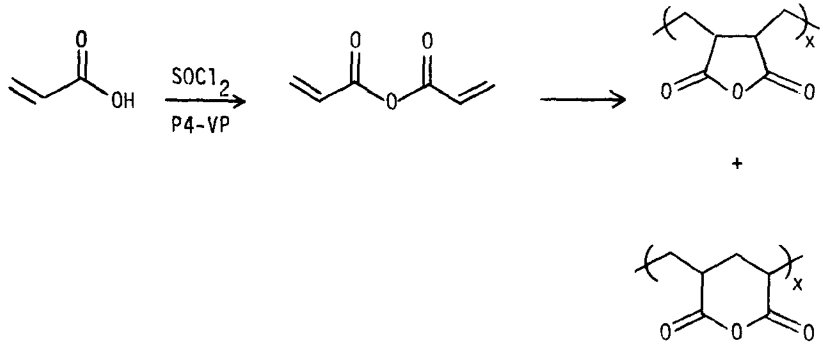
[a] Solutions of 0.005 mole carboxylic acid, 0.55 equiv thionyl chloride, and 20 mL dichloromethane were passed through a column of P4-VP (9-10 equiv based on pyridine). The flow rate was adjusted to provide contact/reaction times of 10 or 20 minutes. The column was washed with dichloromethane to complete transfer of product, which was obtained in a high state of purity after evaporation.

[b] Product identity was established by comparison of melting point, 'H-NMR and/or IR data with published values.

solution. The P4-VP is used to bind gaseous, acidic side-products as well as promote reaction. There is no evidence for release of hydrogen chloride and sulfur dioxide to the atmosphere during reaction. The P4-VP can be regenerated by treatment with excess triethylamine in dichloromethane or aqueous sodium hydroxide.

The results of syntheses performed by the batch mode (stirred reaction, round bottom flask) are summarized in Table 1, and the results obtained using the column mode are given in Table 2. Yields of anhydride are uniformly high (≥90%) for all but three acids, CBZ-alanine[4] (81%), BOC-phenylalanine,[4] and acrylic acid (55%). The conversion of CBZ-alanine to its anhydride derivative appears to be a useful procedure, however more easily deblocked amino acids, eg.; BOC-phenylalanine, are decomposed during anhydride formation. Acrylic acid gives poor yields due to polymerization, presumably of the anhydride during reaction,[5,6] Eq. 3. The more stable unsaturated acids, methacrylic acid and cinnamic acid, give high yields of the related anhydrides.

3)



The experimental convenience of the methodology described in this letter, its applicability to a wide variety of carboxylic acids including appropriately blocked-amino acids, the internal trapping of toxic by-products and the ready availability of the P4-VP catalyst/reagents combine to make this method the one of choice for laboratory synthesis of most symmetrical anhydrides, and the companion method described in the preceding letter[3] the best current laboratory method for most mixed anhydrides.

Acknowledgement:

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References and Footnotes

1. For an introduction to applications of polymeric reagents/catalysts in the synthesis of anhydrides, see: a) N. K. Mathur, C. K. Narang, and R. E. Williams, "Polymers as Acids in Organic Chemistry", Academic Press, New York, 1980, p. 187 ff; b) L. J. Mathias and C. E. Carraher, Jr., "Crown Ethers and Phase Transfer Catalysts in Polymer Science", Plenum Press, New York, 1984, p. 83.
2. J. Rebek and D. Feitler, J. Am. Chem. Soc., **1974**, 96, 1606.
3. See the preceding letter for a description of P4-VP and the details of a related study.
4. CBZ-alanine ≡ N-Benzyloxycarbonyl-L-alanine;
   BOC-Phenylalanine ≡ N-t-Butoxycarbonyl-L-phenylalanine.
5. a) A. Crawshaw and G. B. Butler, J. Am. Chem. Soc., **1958**, 80, 5464.
   b) G. B. Butler and A. Matsumoto, J. Polym. Sci. Polym. Lett. Ed., **1981**, 19, 167.
6. T. Ohya and T. Otsu, J. Polym. Sci. Polym. Chem. Ed., **1983**, 21, 3503.

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