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# PHASE MANAGED ORGANIC SYNTHESIS 2. A NEW POLYMER ASSISTED SYNTHESIS OF ACID ANHYDRIDES.

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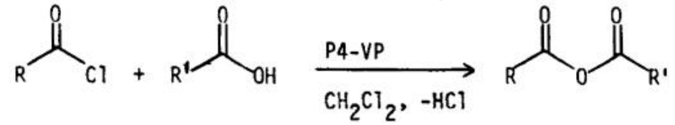
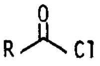
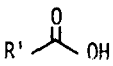
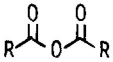
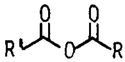
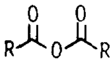
**Abstract**: A solid-phase copolymer of 4-vinylpyridine is shown to be a highly effective reagent/catalyst for the synthesis of acid anhydrides from mixtures containing equimolar quantities of carboxylic acids and acid chlorides. The process may be carried out in batch or column mode.

Acid anhydrides are among the most important classes of reagents used in organic synthesis. They are frequently the preferred reactive acid derivative for preparation of amides, esters, and peptides.[1] Therefore, a large number of synthetic procedures have been developed that furnish a wide variety of these substances. Despite general acknowledgement of the experimental simplicity and convenience of processes that use solid-phase polymeric reagents/catalysts, the literature contains a relatively small number of applications of this potentially important methodology to transacylation reactions.[2-8] Only a few investigations of polymer-bound anhydrides have been reported.[2-4] Prior to our recent work,[9] the polymeric reagents/catalysts used in anhydride synthesis,[5,6] for example polymer-bound DCC,[5] have not been readily available or have exhibited other serious limitations.

During our investigation of multiple phase techniques in organic synthesis, we discovered that a solid-phase co-polymer of 4-vinylpyridine[10](P4-VP) is an extremely effective reagent/catalyst for the formation of acid anhydrides in solutions that contain approximately equimolar quantities of an acid chloride and a carboxylic acid, Eq. 1., Table 1. The reaction may be carried out conventionally in a round-bottom flask with stirring or the P4-VP can be loosely packed in a column and reaction effected by passing a solution of the reactants in dichloromethane over the solid reactant/catalyst.[11]

1) 

## Table 1. Synthesis of Anhydrides[a]

| Reactants | | Reaction | Anhydrides[b] | | | |
|---|---|---|---|---|---|---|
| | | | | Composition,[c] Mole % | | |
|  |  | Temp. °C<br>Time, Min. | Yield<br>% |  |  |  |
| **Mixed Anhydrides** | | | | | | |
| R = Ph | R = $CH_3$ | rt/5 | 64.8[d] | 0.82[e] | 0.09 | 0.09 |
| Ph | $CH_3$ | rt/5 | 80.0 | 0.73[e] | 0.12 | 0.15 |
| Ph | $CH_3$ | 0/60 | 86.4 | 0.74[e] | 0.12 | 0.14 |
| $CH_3$ | Ph | 0/15 | 84.9 | 0.75[e] | 0.09 | 0.16 |
| Ph | $(CH_3)_2CH$ | 0/10 | 97.8 | 0.80 | 0.04 | 0.16 |
| Ph | $(CH_3)_3C$ | 0/10 | 82.6 | 0.69 | 0.12 | 0.19 |
| Ph | $CH_3(CH_2)_4$ | 0/10 | 91.5 | 0.76[e] | 0.16 | 0.08 |
| $CH_3(CH_2)_4$ | Ph | 0/10 | 94.6 | 1.00[e] | 0 | 0 |
| Ph | $CH_3(CH_2)_{10}$ | 0/210 | 91.6 | 0.41[e,f] | 0.39 | 0.20 |
| $CH_3(CH_2)_{10}$ | Ph | 0/60 | 90.6 | 1.00[e,f] | 0 | 0 |
| Ph | $CH_2{=}CH$ | 0/90 | 84.5 | 0.96[e,f] | 0 | 0.04 |
| Ph | $CH_2{=}C(CH_3)$ | 0/60 | 97.7 | 0.90[e,f] | 0.02 | 0.08 |
| $CH_3CH_2O$ | Ph | 0/30 | 80.3 | 1.00 | 0 | 0 |
| $(CH_3)_2CHCH_2O$ | Ph | rt/30 | 90.4 | 0.97 | 0.03 | 0 |
| $PhCH_2O$ | Ph | 0/30 | 75.5 | 1.00 | 0 | 0 |
| Ph | 2-$CH_3$Ph | rt/240 | 90.5 | 1.00[e] | 0 | 0 |
| Ph | 4-$CH_3$Ph | rt/180 | 91.3 | 1.00[e] | 0 | 0 |
| 2-$CH_3$Ph | 4-$CH_3$Ph | rt/240 | 89.8 | 1.00[e] | 0 | 0 |
| 4-$CH_3O$Ph | Ph | rt/60 | 95.2 | 1.00[e] | 0 | 0 |
| Ph | 4-$NO_2$Ph | rt/120 | 97.6 | 0.95[e] | 0 | 0.05 |
| Ph | 3,5-$(NO_2)_2$Ph | rt/60 | 95.6 | 0.92 | 0 | 0.08 |
| **Symmetric Anhydrides** | | | | | | |
| $CH_3(CH_2)_{10}$ | $CH_3(CH_2)_{10}$ | rt/60 | 87.2 | 1.00 | - | - |
| 2-$CH_3$Ph | 2-$CH_3$Ph | rt/360 | 90.8[e] | 1.00 | - | - |
| 4-$CH_3$Ph | 4-$CH_3$Ph | rt/180 | 93.2[e] | 1.00 | - | - |

[a] Reaction mixtures containing 0.005 mole acid chloride, 0.006 mole carboxylic acid, 3.0 equiv P4-VP, and 25 mL dichloromethane were stirred to complete reaction (no acid chloride). The dichloromethane solution was separated by filtration, washed with 10% aqueous potassium carbonate, dried over anhydrous potassium carbonate and rotary evaporated to obtain the product.

[b] Product identity was established by comparison of melting point, $^1$H-NMR, and/or IR data with published values except where noted otherwise.

[c] Product composition was estimated by integration of NMR spectra.

[d] Reaction catalyzed by 1.6 equiv P4-VP was incomplete. Product mixture contained 23.3% unreacted benzoyl chloride.

[e] Mass spectral analysis showed the appropriate molecular ion.

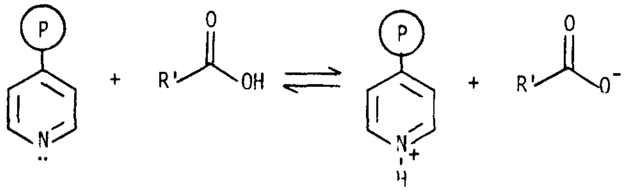
[f] No published data are available for this compound.

The hydrogen chloride produced during reaction remains bound to the P4-VP after work-up. Catalyst regeneration is easily accomplished by treatment with aqueous sodium hydroxide or triethylamine in dichloromethane.

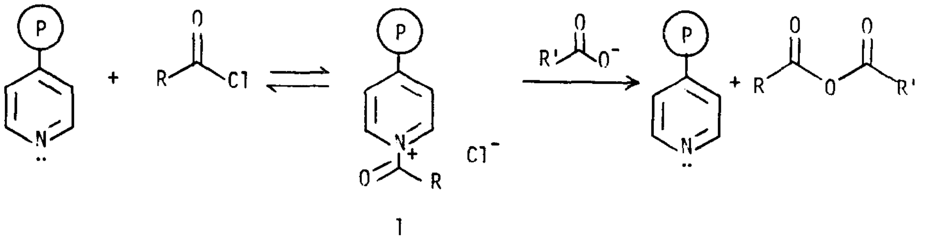
This two-phase method represents an extremely convenient procedure for obtaining a wide variety of acid anhydrides in high yield, generally >90%, and sufficiently pure for direct use in subsequent reactions. The successful synthesis of the mixed anhydrides, acetic benzoic anhydride, acrylic benzoic anhydride, and isobutylcarbonic benzoic anhydride, demonstrates the synthetic capability and scope of the method.

The reaction is believed to follow the typical transacylation pathway shown below, Eqs. 2 and 3. Acid chlorides are known to acylate pyridine and form 1-acylpyridinium ions, 1, which are readily converted to anhydrides by carboxylate ions.[12,13]

2)



3)



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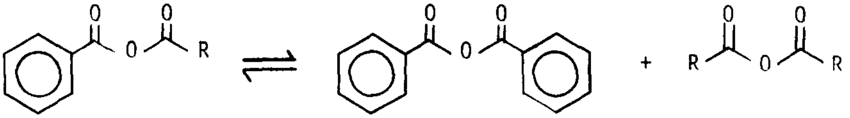
Mixed anhydrides of aliphatic and aromatic carboxylic acids are known to undergo disproportionation,[14] Eq. 4. Furthermore, mixtures of carboxylic acids and acid chlorides readily equili-

4) 2



brate to mixtures of the two acids and two acid chlorides,[15] Eq. 5. Our results indicate that the

5)

best yields of alkylcarboxylic arylcarboxylic anhydrides are usually obtained by using the alkoyl chloride and the arylcarboxylic acid, Table 1.

Development and application of multiple phase techniques in synthesis and reactions of acid anhydrides is an area of continuing interest in our laboratory.

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