Tetrahedron Letters,Vol.25,No.52,pp 6027-6030,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

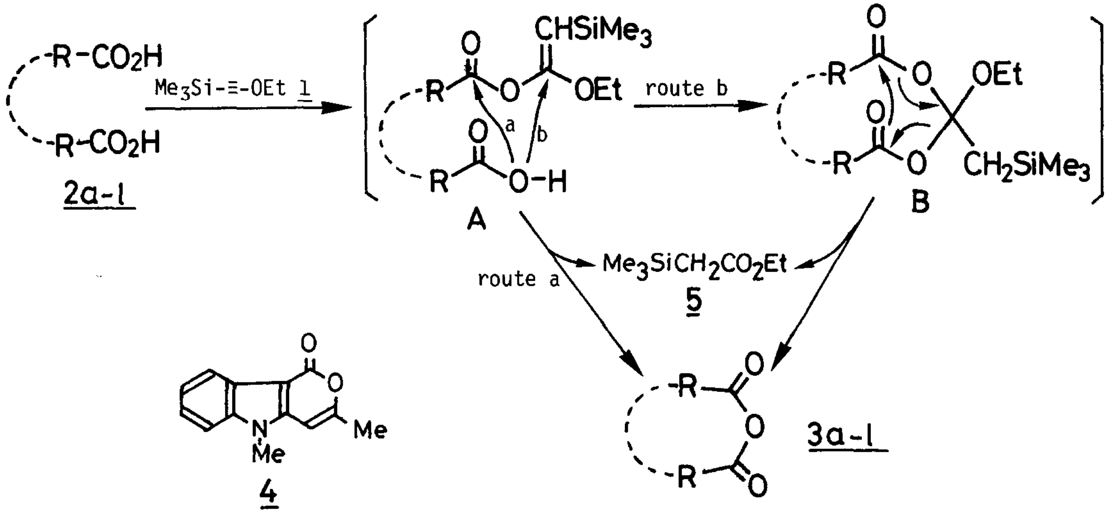
# A MILD AND FACILE SYNTHESIS OF CARBOXYLIC ANHYDRIDES

Y. Kita,* S. Akai, M. Yoshigi, Y. Nakajima, H. Yasuda, and Y. Tamura
Faculty of Pharmaceutical Sciences, Osaka University
1-6, Yamada-oka, Suita, Osaka, 565 Japan

Summary: Reaction of carboxylic acids with trimethylsilylethoxyacetylene in an inert solvent under mild conditions affords the corresponding carboxylic anhydrides in almost quantitative yields.

Carboxylic anhydrides are useful compounds as acylating agents or as important intermediates in organic synthesis, and usually prepared by dehydration of carboxylic acids with a powerful acylating or dehydrating agent such as acid chloride, acid anhydride, phosgene, thionyl chloride, benzenesulfonyl chloride, phosphorous oxychloride, ketene, phosphorous pentaoxide, dicyclohexylcarbodiimide, or N,N'-carbonyldiimidazole. For the preparation of the anhydrides from acid-sensitive or unreactive carboxylic acids, these methods are not always so effective. An active reagent which can react with substrate under neutral condition to give the product without aqueous work-up would be quite effective in these cases.1) In fact, ethoxyacetylene is known as a useful reagent for this purpose,2) but it has still some drawbacks in its handling probably because of its unstability, insolubility, and high-volatility.3) We now report here an analogous type of powerful dehydrating agent, trimethylsilylethoxyacetylene (1), which circumvents these disadvantages. The reagent, readily prepared by the trimethylsilylation of the commercially available ethoxyacetylene4) provides a quite effective method for dehydration of various types of carboxylic acids (2) including acid-sensitive carboxylic acids into the corresponding carboxylic anhydrides (3) under mild conditions, and allows easy isolation of pure products in almost quantitative yields.

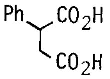
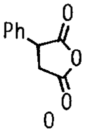
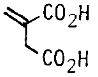
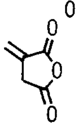
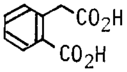
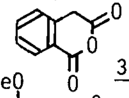
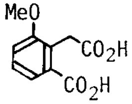
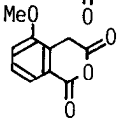
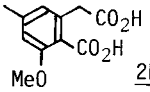
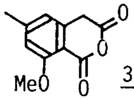
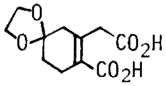
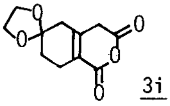
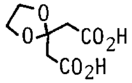
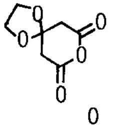
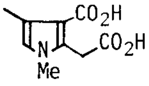
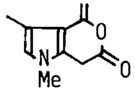
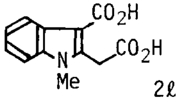
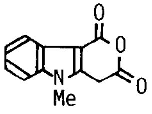
The typical reaction is as follows: To a suspension of carboxylic acid (2 mmol) or dicarboxylic acid (1 mmol) in dichloromethane or 1,2-dichloroethane (5 ml) was added 1 (1.5 mmol) and the mixture was stirred at room temperature until the acid dissolved in the solution. After an additional stirring for 1 h under the same conditions, the solution was concentrated under reduced pressure to give the carboxylic anhydride (3) in a quantitative yield. The reaction usually proceeds completely at room temperature within several hours to give the desired 3 accompanied by the volatile ethyl trimethylsilylacetate (5) as the only side product, but some acids were recovered unchanged under the conditions possibly because of their insolubility. The problem was easily resolved by heating of the mixture and/or addition of a small amount of tetrahydrofuran into the mixture (Runs 2-5, 7, 11, and 12). Both cinnamic and palmitic acids can be readily converted to the corresponding carboxylic anhydrides (Runs 2 and 3), whereas they were inert with ethoxyacetylene.[3] The present method is able to convert 3-carboxy-1-methylindol-2-ylacetic acid (2ℓ) into the desired anhydride (3ℓ) quantitatively (Run 12), although dehydration of 2ℓ in refluxing acetic anhydride according to the reported method[5] gave 3ℓ accompanied by a plenty amount of 3,5-dimethylpyrano-[4,3-b]indol-1(5H)-one (4) after many runs, which is thought to be produced by further acetylation of 3ℓ followed by rearrangement and decarboxylation. All known products were identified by comparison with authentic samples. New compound was characterized by $^1$H-NMR, IR, exact mass, and analytical data. The reaction conditions, yields, and melting points are summarized in the Table.



The plausible mechanism for the formation of 3 from 2 is as follows: The reaction occurs by initial addition of carboxylic acid (2) to the α-position of acetylenic bond of 1 to give the ketene acetal intermediate A, which turns to 3 directly with the elimination of ethyl trimethylsilylacetate (5) (route a) or turns to the orthoester intermediate B followed by rapid decomposition to give 3 with the elimination of 5 (route b).[6]

The present method is superior to those reported previously for the dehydration of acid-sensitive and unreactive carboxylic acids (2) because of the ready availability and stability of the reagent, the mild reaction conditions, the ease of performance and work-up, and the high yields of the products (3).

Table Preparation of Carboxylic Anhydrides (3)

| Run | Starting Acids (2) | Reaction Conditions | Carboxylic Anhydrides (3) | Yield[a)] of 3 (%) | M.p.[b)] (°C) Found[c)] (Recryst. Solv.) | Reported |
|---|---|---|---|---|---|---|
| 1 | *o*-BrPhCO$_2$H 2a | CH$_2$Cl$_2$, r.t., 3h | (*o*-BrPhCO)$_2$O 3a | quant. | 77-78 (ether) | 76-77.5[7)] |
| 2 | *E*-PhCH=CHCO$_2$H 2b | CH$_2$Cl$_2$, reflux, 15h | (*E*-PhCH=CHCO)$_2$O 3b | quant. | 137-138 (benzene-n·hex) | 135-136[8)] |
| 3 | CH$_3$(CH$_2$)$_{14}$CO$_2$H 2c | ClCH$_2$CH$_2$Cl, 50-60°, 2d | [CH$_3$(CH$_2$)$_{14}$CO]$_2$O 3c | 97 | 62.5-63.5 (n·hex) | 63.8-64[9)] |
| 4 |  2d | CH$_2$Cl$_2$, reflux, 5h |  3d | quant. | 47-49 (ether-n·hex) | 49-52[10)] |
| 5 |  2e | CH$_2$Cl$_2$, reflux, 5h |  3e | quant. | 68-68.5 (ether) | 64-65[11)] |
| 6 |  2f | CH$_2$Cl$_2$, r.t., 7h |  3f | quant. | 144-145 (benzene) | 140-141[12)] |
| 7 |  2g | CH$_2$Cl$_2$, reflux, 5h |  3g | quant. | 157.5-158.5 (benzene-n·hex) | 156.5-157.5[13)] |
| 8 |  2h | CH$_2$Cl$_2$, r.t., 5h |  3h | quant. | 172-172.5 (acetone-n·hex) | 171-173[14)] |
| 9 |  2i | CH$_2$Cl$_2$, r.t., 3h |  3i | quant. | 181-184 (THF) | 174-177[15)] |
| 10 |  2j | CH$_2$Cl$_2$, r.t., 3h |  3j | 91 | 113-114 (chloroform-pet·ether) | 112-113[16)] |
| 11 |  2k | ClCH$_2$CH$_2$Cl:THF(10:1), 50-60°, 2.5d |  3k | 90 | 162-165 (THF) | — |
| 12 |  2ℓ | ClCH$_2$CH$_2$Cl:THF(10:1), 50-60°, 3d |  3ℓ | quant. | 233-235 (DMSO) | 252-253[5)]<br>253-254[17)] |

a) Isolated yields were based on 2 and the purity of the products (ca. ≥95%) was determined by IR and NMR.

b) The melting points are not corrected.

c) The melting points before recrystallization: 3a, 70-74.5°C; 3b, 107-110°C; 3c, 60-62.5°C; 3d, 45-46°C; 3e, 64-66°C; 3f, 144-145°C; 3g, 156-158°C; 3h, 168.5-169°C; 3i, 174-180.5°C; 3j, 111-113°C; 3k, 154-158°C; 3ℓ, 222-224°C.

## References and Notes

1) We have developed extremely useful silylating and acylating agents, which provide ready silylation and acylation under neutral condition, and allow easy isolation of pure products without aqueous work-up in almost quantitative yields: Y. Kita, H. Yasuda, Y. Sugiyama, F. Fukata, J. Haruta, and Y. Tamura, Tetrahedron Lett., 24, 1273 (1983); Y. Kita, J. Haruta, H. Yasuda, K. Fukunaga, Y. Shirouchi, and Y. Tamura, J. Org. Chem., 47, 2697 (1982); Y. Kita, J. Haruta, T. Fujii, J. Segawa, and Y. Tamura, Synthesis, 1981, 451; Y. Kita, J. Haruta, J. Segawa, and Y. Tamura, Tetrahedron Lett., 1979, 4311; Y. Tamura, J. Haruta, S. Okuyama, and Y. Kita, ibid., 1978, 3737.

2) Edman and Simmons found that the use of ethoxyacetylene for the dehydration of norbornadiene-2,3-dicarboxylic acid is the most satisfactory way, and all other anhydride syntheses tried, including the carbodiimide method, gave poor yields: J. R. Edman and H. E. Simmons, J. Org. Chem., 33, 3808 (1968).

3) Ethoxyacetylene has low boiling point (50-52 °C) and turns straw colored even in a refrigerator and polymerizes gradually if allowed to stand at room temperature. This compound is thermally unstable and explodes at about 100 °C in a sealed tube to give ketene and ethylene. Eglinton has stated that cinnamic and palmitic acids were inert with ethoxyacetylene, possibly because of their insolubility: G. Eglinton, E. R. H. Jones, B. L. Shaw, and M. C. Whiting, J. Chem. Soc., 1954, 1860.

4) The reagent (1) was prepared from commercially available ethoxyacetylene by the method of Shchukovskaya, b.p. 57 °C/34 mmHg: L. L. Shchukovskaya and R. I. Pal'chik, Izv. Akad. Nauk SSSR, Ser. Khim., 1964, 2228 [Chem. Abstr., 62, 9167b (1965)]; R. A. Ruden, J. Org. Chem., 39, 3607 (1974).

5) G. A. Bahadur, A. S. Bailey, N. W. Middleton, and J. M. Peach, J. Chem. Soc. Perkin I, 1980, 1688.

6) Anhydride formation in the reaction of alkoxyacetylene with carboxylic acid has been shown to occur via an orthoester intermediate by Wasserman: H. H. Wasserman and P. S. Wharton, J. Am. Chem. Soc., 82, 1411 (1960).

7) M. S. Newman and J. A. Cella, J. Org. Chem., 39, 2084 (1974).

8) J. D. M. Simpson and S. S. Israelstam, J. S. African Chem. Inst., 2, 165 (1949) [Chem. Abstr., 45, 6196f (1951)].

9) N. O. V. Sonntag, J. R. Trowbridge, and I. J. Krems, J. Am. Oil Chemists' Soc., 31, 151 (1954) [Chem. Abstr., 48, 6715d (1954)].

10) C. A. Miller, U. S. 2,995,580 (1961) [Chem. Abstr., 57, 11112f (1962)].

11) Z. Horii, Japan. 2922 (1960) [Chem. Abstr., 54, 24557h (1960)].

12) O. Grummitt, R. Egan, and A. Buck, Org. Synth., Coll. Vol. 3, 449 (1955).

13) Y. Tamura, M. Sasho, S. Akai, A. Wada, and Y. Kita, Tetrahedron, in press.

14) Y. Tamura, F. Fukata, T. Tsugoshi, M. Sasho, Y. Nakajima, and Y. Kita, Chem. Pharm. Bull., 32, 3259 (1984).

15) Y. Tamura, S. Akai, M. Sasho, and Y. Kita, Tetrahedron Lett., 25, 1167 (1984).

16) F. V. Brutcher, Jr., W. D. Vanderwerff, and B. Dreikorn, J. Org. Chem., 37, 297 (1972).

17) F. A. Trofimov, V. I. Ryabchenko, and A. N. Grinev, Khim. Geterotsikl. Soedin., 1975, 1343 [Chem. Abstr., 84, 43754a (1976)].

(Received in Japan 27 September 1984)