Tetrahedron Letters, Vol 32, No 42 pp 6039-6042, 1991
Printed in Great Britain

0040-4039/91 \$3 00 + 00
Pergamon Press plc

BENZILIC ACID REARRANGEMENTS IN THE REACTIONS OF ARYL VICINAL TRICARBONYL DERIVATIVES WITH ALDEHYDE SCHIFF BASES

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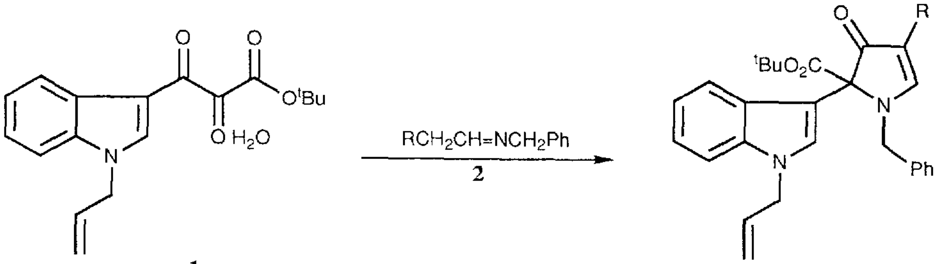
Abstract Reactions of aryl and hetero vicinal tricarbonyl derivatives with aldehyde Schiff bases of the general structure RCH_2CHO lead to pyrrolinone derivatives by benzilic acid-related rearrangements, driven, most probably, by iminium ion intermediates

During studies related to the synthesis of the tremorgic mycotoxin, fumitremorgin B,[1] we explored the reactions of the tricarbonyl derivative **1** with aldehyde Schiff bases of structure $RCH_2CH{=}NCH_2Ph$ **2** Based on analogies with other indole-tricarbonyl interactions,[2] we originally reported the products from these reactions to be carbazole derivatives [3] Subsequent reexamination of these substances by X-ray crystallography showed that they are instead, indolylpyrrolinone carboxylates **3** formed by a benzilic acid type of rearrangement [4,9]



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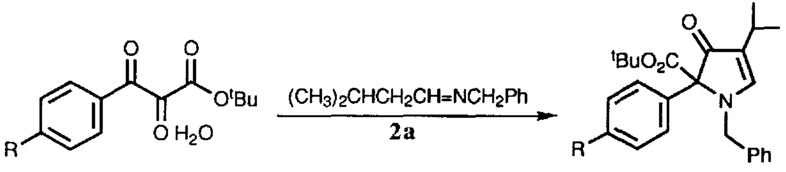
3

$R = (CH_3)_2CH, CH_3(CH_2)_2, CH_3(CH_2)_3$

We now report that this rearrangement takes place generally with aryl tricarbonyl derivatives as outlined in the Table Of the series of Schiff bases **2** employed in our earlier work, the product **2a** derived from isovaleraldehyde and benzylamine was used as the nucleophile of choice for the present investigation This selection was based on the favorable reactivity of **2a** with the indole derivative **1**

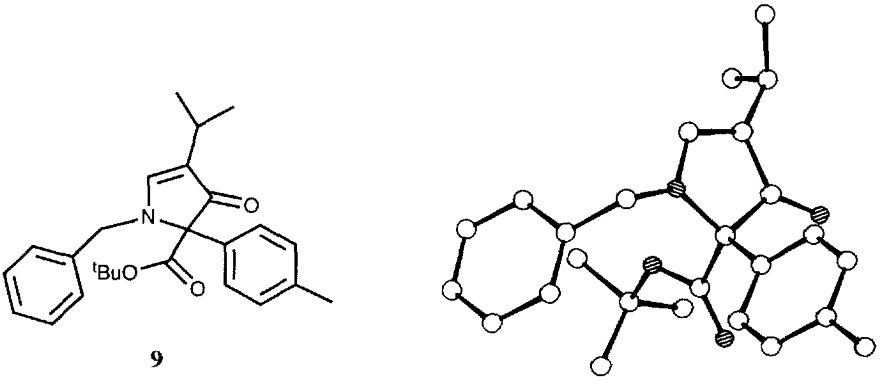
Table Pyrrolinone Carboxylates from Vicinal Tricarbonyl Esters



Vicinal Tricarbonyl	Arylpyrrolinone, Yield(%)	
4, R = H	**8**, R = H	(59)
5, R = Me	**9**, R = Me	(54)
6, R = OMe	**10**, R = OMe	(63)
7, R = NMe$_2$	**11**, R = NMe$_2$	(61)

In each of the cases studied (Table), the vicinal tricarbonyl esters **4-7** were treated with an excess of **2a** in benzene and stirred at room temperature for 48 h No significant improvement in the yields was observed at higher temperatures The products, isolated after chromatography on silica gel, all showed nearly identical NMR and IR spectra [5] An X-Ray analysis of a representative product **9** [5] (Figure) confirmed the assigned structures

Figure: UPLOT of Arylpyrrolinone **9**



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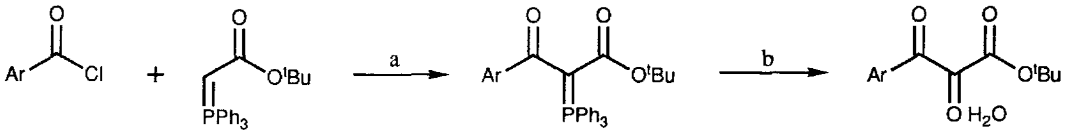
The tricarbonyl derivatives **4**, **5**, and **6** were prepared from the corresponding carboxylic acids using the acyl phosphorane route which we have previously described (Scheme 1) [6]

Scheme 1



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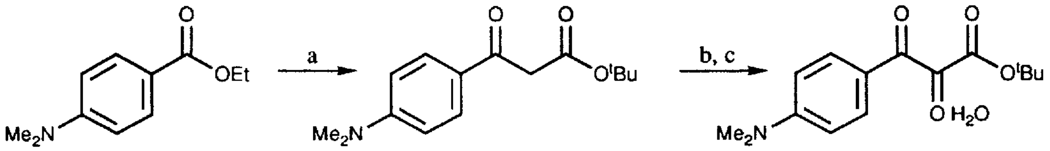
Reagents (a) BSA, PhH, 10°C, 5 min , then add acid chloride at 25°C, (b) Oxone®, aq THF, r t , 2 h

In the formation of **7** by the above sequence, oxidative cleavage of the intermediate keto ylide **12** with either singlet oxygen, ozone, or Oxone® was unsuccessful due to the sensitivity of the activated aromatic system We therefore prepared the tricarbonyl starting material by a Claisen condensation followed by oxidation with N,N-dimethyl-4-nitrosoaniline followed by hydrolysis according to the Sachs procedure, providing **7** (48%) (Scheme 2)[7]

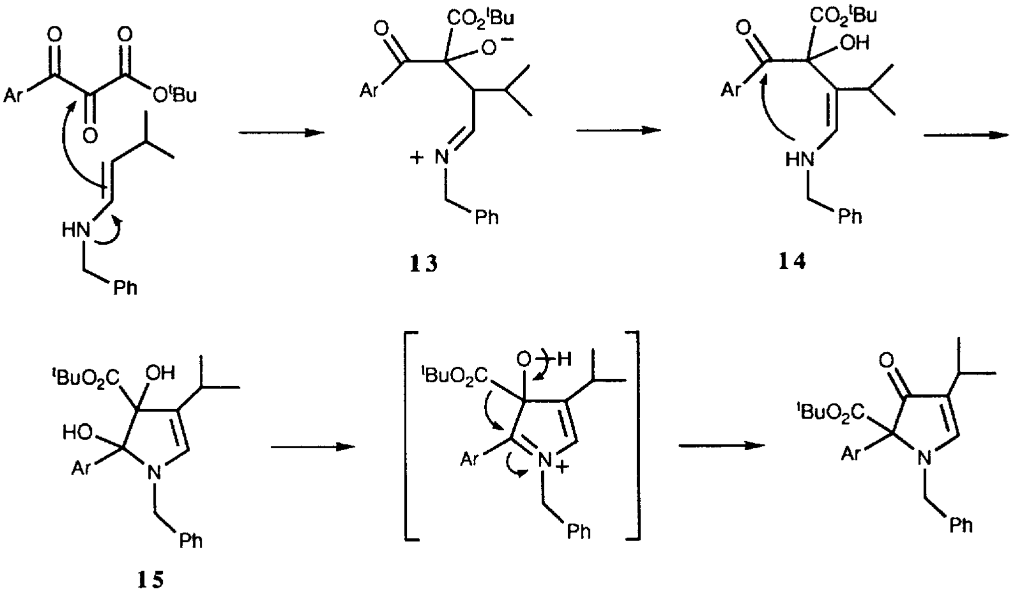
Scheme 2



Reagents (a) $MeCO_2{}^tBu$, LDA, THF, -78°C, 0 5 h, (b) N,N-dimethyl-4-nitrosoaniline, KOH, EtOH, r t, 48 h, (c) 6 N HCl, CH_2Cl_2, 0°C

Formation of pyrrolinone carboxylate derivatives in this process appears to take place through the intermediate **13**, formed by attack of the enamine tautomer of the Schiff base at the central carbonyl group (Scheme 3)[8] Proton transfer, forming **14**, followed by cyclization to **15**, then sets the stage for an iminium ion-driven benzilic acid type of rearrangement yielding the observed products[9] We are investigating related rearrangements in systems modeled after the latent tricarbonyl functions of the immunosuppressant FK-506

Scheme 3



Acknowledgements Support for this work was provided by Grants GM-07874 and GM-31350 from the NIH We thank J E Baldwin for helpful discussions

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5 Spectroscopic and X-ray Date for 9 ^{1}**H NMR** d(CDCl$_3$) 7 47 (1H, s), 7 33 (2H, m), 7 20 (7H, m), 4 43 (1H, d, *J*, 15 Hz), 4 27 (1H, d, *J* 15 Hz), 2 65 (1H, septet), 2 34 (3H, s), 1 48 (9H, s), 1 07 (3H, d, *J* 3 Hz), 1 05 (3H, d, *J* 3 Hz) ppm **IR** υ_{max} (film), 3040, 2970, 1736, 1672, 1580, 1252, and 1035 **X-ray Analysis** Arylpyrrolinone **9** was recrystallized from ethyl acetate/hexane (1 1) at 25°C and the crystals were isolated as colorless plates, $C_{26}H_{31}NO_3$ (FW 405 54) monoclinic, P21/n, a=9 025 (2)Å, b=21 744 (4)Å, c=12 816 (2)Å, ß=108 89 (2)°, V=2379 7 (9)Å^3, Z=4, CuKα radiation (λ=1 54178 Å), 298K, Rigaku AFC5S diffractometer with graphite monochromater, 3925 reflections were collected, of which 3669 were unique reflections (R_{int} =0 019) with $2\theta \leq 114$°C, of those reflections 2099 (52%) with $I \geq 3\sigma(I)$ were adjudged observed The structure was solved using MITHRIL and refined by full-matrix least square to R=0 063 and R_w=0 077

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8 We found that treating tricarbonyls **4-7** with enamines derived from secondary amines gave no reaction

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(Received in UK 9 August 1991)