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THE CHEMISTRY OF VICINAL TRICARBONYLS
USE OF VINYL TRICARBONYL ESTERS IN THE FORMATION OF 3-HYDROXYPYRROLE-2-CARBOXYLATES

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Abstract: The reaction of primary amines with the vinyl tricarbonyl reagent **1** forms the basis of a general synthesis of N-substituted 3-hydroxypyrrole-2-carboxylates.

3-Hydroxypyrrole-2-carboxylates are related to the heterocyclic units found in natural products such as the prodigiosins.[1] These pyrrole derivatives are also of special interest in connection with the synthesis of porphyrins containing electron-releasing substituents,[2] and may well serve as possible precursors of plant products represented by the 2-oxo-3-pyrroline dimer isolated from *mercurialis leiocarpa*.[3] Additionally, the 3-hydroxypyrrole-2-carboxylates may react as β-keto esters, allowing alkylation at the 2-position.[4a,b] Application of this alkylation in an intramolecular sense affords potential access to a variety of naturally-occuring azacyclic systems, such as the pyrrolizidines and indolizidines.

We now report that the reaction of primary amines with the readily available vinyl tricarbonyl ester reagent **1**,[5] provides a novel and efficient synthesis of an extensive array of N-substituted 3-hydroxypyrrole-2-carboxylates **3**. This transformation, pictured in Scheme 1, takes place through the intermediate pyrrolidinone **2**, which can be isolated in neutral media. Conversion of **2** to the pyrrole occurs readily with dehydrating reagents such as silica gel, presumably through the iminium ion **2a**. This mild and efficient two-step procedure provides direct access to the 3-hydroxy-pyrrole-2-carboxylate system, avoiding the multi-step features and more vigorous condition of previous methods.[1b,c,6]

Scheme 1

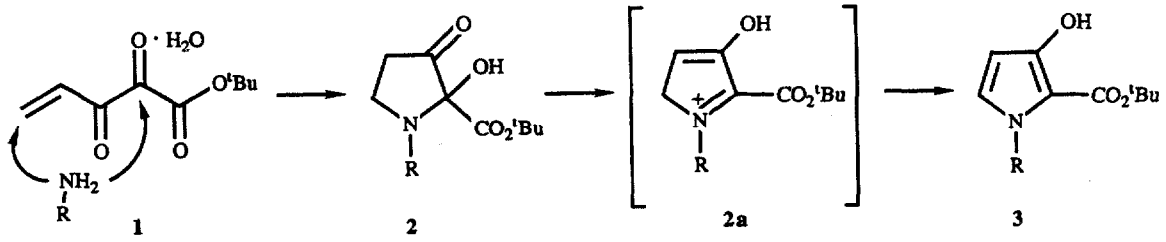
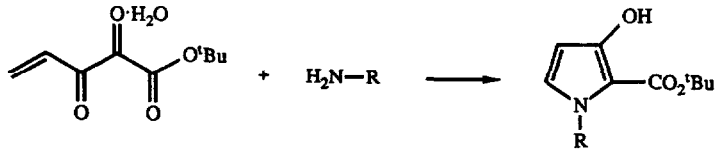
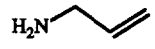
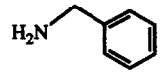
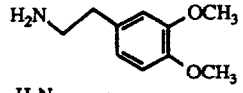
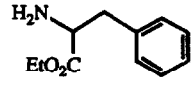


Table 1. Conversion of vinyl tricarbonyl reagent **1** to N-substituted 3-hydroxypyrrole-2-carboxylates **3**



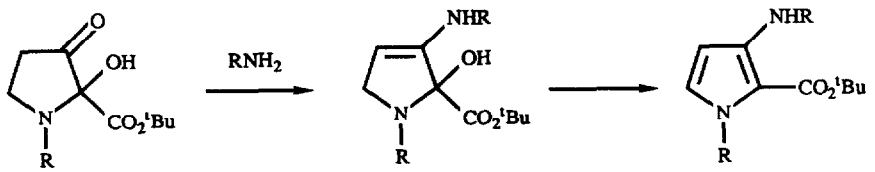
1 **3**

ENTRY	AMINE	YIELD(%)[a]
1	$H_2N—CH_3$	70
2	$H_2N—CH_2CH_3$	55
3		72
4		70[b,6]
5		76
6		67
7		75
8		50
9		51
10		65

a) Yields are for isolated products. b) For detailed procedure, see reference 7.

As outlined in Table 1, the isolated yields for a wide variety of pyrroles ranged from 50 to 75% overall for the two-step sequence. In our general procedure, the amine (1 mmol) was added to the vinyl tricarbonyl reagent **1** (1 mmol) dissolved in dichloromethane (30 mL). The reaction mixture was kept at room temperature for 30 min, after which silica gel (1.5 g) was added and the solution stirred overnight. Filtration, evaporation, and chromatography provided the pyrrole **3**.[7] In the case of highly polar amines such as amino acids (entry 8) an alternative procedure was used in which the amine (2 mmol) and the vinyl tricarbonyl ester reagent (1 mmol) were refluxed in acetonitrile/methanol (4:1, 2.5 mL) for 50 min. Workup as outlined above yielded the pyrrole **3** directly.

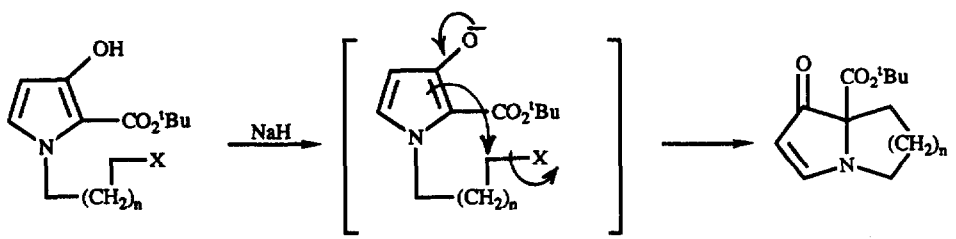
A minor by-product observed in a number of the cases was the 3-amino derivative **4**, formed most probably by the addition of the amine to the carbonyl group at the 3-position of the pyrrolidinone to give the enamine, followed by dehydration to the 3-aminopyrrole-2-carboxylate. In reactions where this impurity was found, separation from the hydroxypyrrole was accomplished by washing an ethereal solution of the crude product with dilute aqueous HCl.

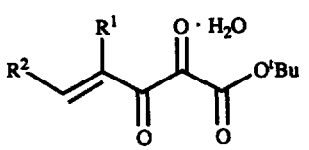


2 **4**

We are currently investigating the use of selected pyrrole derivatives (Table 1, entry 10) as precursors to pyrrolizidine and indolizidine skeletons through processes involving intramolecular alkylation according to Scheme 2. Studies are also in progress using alkenyl tricarbonyl esters **5** to generate pyrroles for use in systems substituted at the 4 and/or 5-positions. An example of 5-substituted pyrrole formation by this route is found in a synthesis of prodigiosin described in the following communication.

Scheme 2





5

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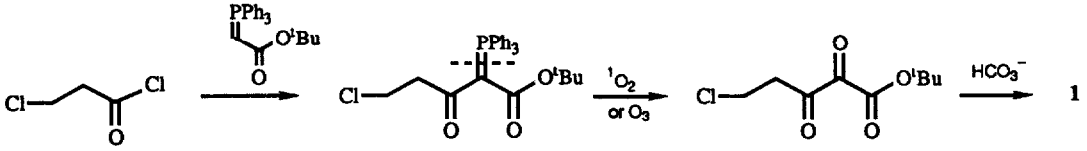
   b. Rapoport, H.; Holden, K.G. ibid., **1962**, *84*, 635.
   c. Boger,D.; Patel, M. *J. Org. Chem.* **1988**, *53*, 1405.

2. The Porphyrins, D. Dolphin, ed. Academic Press, Inc., N.Y. **1978** vol. 2, Part B.

3. Masui, Y.; Kawabe, C.; Mastumoto, K.; Abe, K.; Miwa, T. *Phytochem.* **1986**, *25*, 1470.

4. a. Momose, T.; Tanaka, T.; Yokota, T.; Nagamoto, N.; Yamada, K. *Chem. Pharm. Bull.* **1978**,*26*, 3521.
   b. Chong, R.; Clezy, P.S. Aust. J. Chem. **1967**, *20*, 935.

5. The vinyltricarbonyl ester can be conveniently prepared from β-chloropropionyl chloride[8] as shown in the following scheme:
   Wasserman, H.H.; Fukuyama, J.; Murugesan, N.; VanDuzer, J.; Lombardo, L.; Rotello, V; McCarthy, K., *J. Am. Chem. Soc.* **1989**, *111*, 371.



6. Momose, T.; Tanaka, T.; Yokota, T.; Nagamoto, N.; Yamada, K. *Chem.Pharm. Bull.* **1978**, *26*, 2224.

7. In a typical run (entry 4), benzylamine (367 mg, 3.5 mmol) was added to a solution of 1 (700 mg, 3.5 mmol) in 100 mL dichloromethane. The solution was maintained at room temperature for 30 min, and then 5 g silica gel was added. The solution was stirred overnight, filtered, and the solvent removed to give an oil. Chromatography (3:1 hexanes/ethyl acetate) gave 676 mg (70%) of pyrrole as a colorless solid, mp 62-64° (lit mp 63-64°).[6]

8. For a recent report on the synthesis of tricarbonyl esters by the reaction of acid chlorides with 1,2-diethoxy-1,2-bis(trimethylsiloxy)ethylene in the presence of zinc chloride, see Reetz, M.T.; Kyung, S.-H. *Tetrahedron Lett.* **1985**, *26*, 6333.

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