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An Efficient and Mild Synthesis of Highly Substituted Imidazoles

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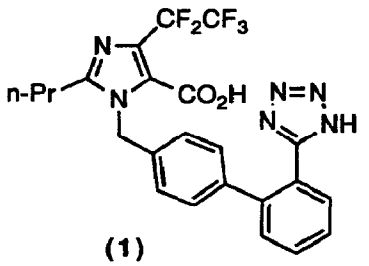
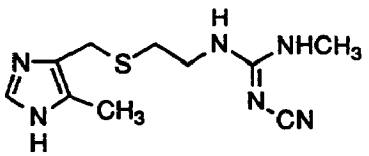
Abstract: A versatile, one-step imidazole synthesis employing vicinal tricarbonyl compounds is described.

The vicinal tricarbonyl moiety has received much attention due to its existence as an important component of the macrocyclic immunosuppressants FK-506 and rapamycin.[1] This versatile functional group has also been recently used for synthesis of a wide variety of heterocycles[2] and alkaloids.[3] The imidazole nucleus, however, has not yet been fashioned using the vicinal tricarbonyl group. Owing to the proven importance of substituted imidazoles as pharmaceutical agents (e.g., DuP-532 (1), a potent angiotensin II receptor antagonist for the treatment of hypertension,[4] and cimetidine (2), an H2-antagonist for the treatment of gastrointestinal ulcers[5]), we were intrigued at the possibility of extending the utility of tricarbonyl compounds to include a one step synthesis of highly functionalized imidazoles. Imidazoles have long been prepared by the cyclocondensation reaction of simple α-dicarbonyl compounds with ammonia and an aldehyde.[6] By incorporation of an ester group into the α-dicarbonyl the present synthesis not only extends the scope of the classical procedure, but also adds a versatile functional group that can be manipulated in a number of different ways. In this Letter we describe our successful efforts which have led to the discovery of a convergent and extremely versatile imidazole synthesis.



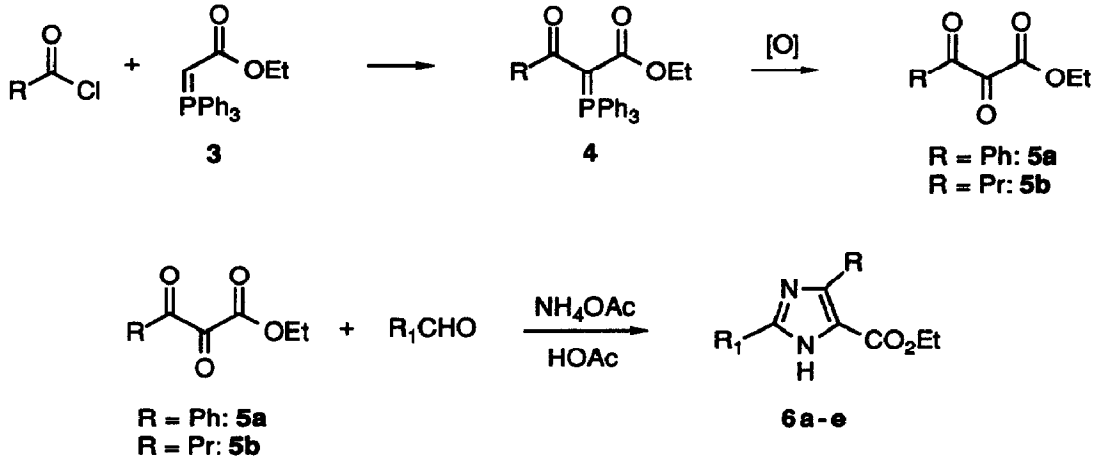
(1)



(2)

As shown below, treatment of tricarbonyl **5** with an aldehyde in the presence of ammonium acetate in acetic acid delivers imidazole **6**.[7] The generality and simplicity of this imidazole synthesis is manifested by the ready availability of both tricarbonyl **5**, which can be prepared in two steps from an acid chloride,[8] and the

alkyl/aryl aldehyde. Thus, the cyclocondensation reaction allows the combination of alkyl and/or aryl groups on C-2 and C-4 of the imidazole with concomitant installation of an ester group on C-5.



The results are summarized in the Table. The isolated yields of imidazole **6** are quite respectable in all cases. Importantly, either enolizable or nonenolizable vicinal tricarbonyls and aldehydes participate effectively in this reaction (entries 2-4). Furthermore, 4,5-disubstituted imidazoles can be obtained by simply using formaldehyde as the aldehyde component (entry 5).[9] It should be noted that the presence of the ester group in the starting tricarbonyl moiety considerably enhances the electrophilicity of the central (and reacting) carbonyl. This subtle electronic effect allows the reaction to proceed under much more mild conditions than the cyclocondensation procedure of a simple α-dicarbonyl compound.[6] The versatility of this process is further extended by virtue of the C-5 ester from which a wide variety of functional groups can be obtained.

Table. Synthesis of Imidazoles **6** from Vicinal Tricarbonyls **5**

entry	R	R_1	product	conditions[a]	yield[a] (%)
1	Ph	Ph	6a	65 °C, 30 min	88
2	Ph	Pr	6b	65 °C, 15 min	76
3	Pr	Ph	6c	65 °C, 15 min	81
4	Pr	Pr	6d	65 °C, 15 min	66
5	Ph	H	6e	65 °C, 15 min	90

[a] Yields & conditions are unoptimized.

The following procedure is representative: To a slurry of NH_4OAc (860 mg, 11.2 mmol) in acetic acid (3 mL) was added tricarbonyl monohydrate **5a** (230 mg, 1.1 mmol) followed by benzaldehyde (236 mg, 2.2 mmol). The mixture was heated to 65 °C and stirred for 30 min at which time TLC analysis indicated complete consumption of starting tricarbonyl **5a**. The solution was cooled to rt and the acetic acid was evaporated to give an oily residue. This residue was dissolved in ethyl acetate and washed with sat. $NaHCO_3$, water, and brine. The organic phase was then dried over $MgSO_4$, filtered, concentrated under reduced pressure. Silica gel chromatography (9:1, hexanes:ethyl acetate) provided **6a** as a white solid (287 mgs, 88%). m.p. 165-67 °C. ^1H NMR (300 MHz, DMSO-d_6, mixture of two tautomers) δ 1.24 (t, 3, J = 6.3), 1.26 (t, 3, J = 5.57), 4.34 (m, 4), 7.55-7.88 (m, 16), 8.22 (bs, 4). MS (FAB) *m/z* (%): 293 [$(M+H)^+$, 100), 247 (33). Anal calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 73.97; H, 5.57; N, 9.61.

We have described a simple and convergent imidazole synthesis, which utilizes vicinal tricarbonyls. The present procedure should assume an important role in imidazole synthesis.

Acknowledgement

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References and Notes

1. (a) FK-506: Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031. (b) Rapamycin: Findlay, J.A.; Radics, L. *Can. J. Chem.* **1980**, *58*, 597. Swindells, D.C.N.; White, P.S.; Findlay, J.A. *Can. J. Chem.* **1978**, *56*, 2491.
2. Synthesis of: (a) pyrroles: Wasserman, H.H.; Fukuyama, J.; Murugesan, N.; van Duzer, J.; Lombardo, L.; Rotello, V.; McCarthy, K. *J. Am. Chem. Soc.* **1989**, *111*, 371. (b) substituted β-lactams: Wasserman, H.H.; Han, W.T. *Tetrahedron Lett.* **1984**, *25*, 3743. Wasserman, H.H.; Henke, S.L.; Luce, P.; Nakanishi, E. *J. Org. Chem.* **1990**, *55*, 5821. (c) carbazoles: Wasserman, H.H.; van Duzer, J.H.; Vu, C.B. *Tetrahedron Lett.* **1990**, *31*, 1609.
3. (a) Isoquinoline alkaloids: Wasserman, H.H.; Amici, R.; Frechette, R.; van Duzer, J.H. *Tetrahedron Lett.* **1989**, *30*, 869. (b) Vincamine-related alkaloids: Wasserman, H.H.; Kuo, G.H. *Tetrahedron Lett.* **1989**, *30*, 873. (c) Substituted indolizidines: Wasserman, H.H.; Cook, J.D.; Vu, C.B. *J. Org. Chem.* **1990**, *55*, 1701.
4. Carini, D.J.; Chiu, A.T.; Wong, P.C.; Johnson, A.L.; Wexler, R.R.; Timmermans, P.B.M.W.M. *Biorg. Med. Chem. Lett.* **1993**, *3*, 895.
5. Brogden, R.N. *et al. Drugs* **1978**, *15*, 93.
6. Wynberg, H.; DeGroot, A. *Chem. Commun.* **1965**, 171.
7. Other syntheses of trisubstituted imidazoles patterned after **6** have been reported: (a) By reacting aromatic amideoximes with propiolate esters: Heindel, N.D.; Chun, M.C. *Tetrahedron Lett.* **1971**, *12*, 1439. (b) By condensing α-oximino-β-diketo esters with allyl and benzylic amines: Veronese, A.C.; Cavicchioni, G.; Servadio, G.; Vecchiati, G. *J. Heterocyclic Chem.* **1980**, *17*, 1723. Veronese, A.C.;

Vecchiati, S.S.; Orlandini, P. *Synthesis* **1985**, 300. (c) 4,5-Disubstituted imidazoles can be obtained by condensing α-chloro-β-keto esters with formamide: Durant, G.J.; Emmett, J.C.; Ganellin, C.R.; Roe, A.R. G.B. Patent 1,341,375 (1973).

8. Keto phosphoranes **4** and tricarbonyl monohydrates **5** were prepared according to the Wasserman procedure: Wasserman, H.H.; Ennis, D.S.;Blum, C.A.; Rotello, V.M. *Tetrahedron Lett.* **1992**, *33*, 6003. Vicinal tricarbonyl synthesis via Dess-Martin oxidation of β-hydroxy and β-ketoamides, esters and ketones has recently been reported: Batchelor, M.J.; Gillespie, R.J.; Golec, J.C.; Hedgecock, C.R. *Tetrahedron Lett.* **1993**, *34*, 167.
9. For entry **5**, paraformaldehyde (500 mol %) was used as the formaldehyde source.

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