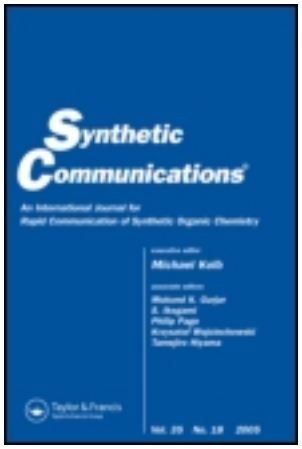

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Accepted author version posted online: 20 Jan 2012.Version of record first published: 05 Sep 2012.

To cite this article: Lai Chun Wong, Alexander Gehre, Stephen P. Stanforth & Brian Tarbit (2013): Convenient Synthesis of Highly Substituted Imidazole Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:1, 80-84

To link to this article: http://dx.doi.org/10.1080/00397911.2011.591957

Synthetic Communications®, 43: 80–84, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.591957

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CONVENIENT SYNTHESIS OF HIGHLY SUBSTITUTED IMIDAZOLE DERIVATIVES

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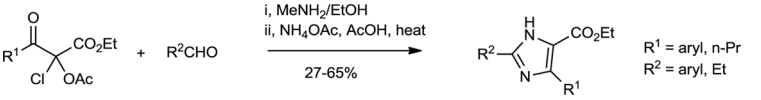
GRAPHICAL ABSTRACT



Abstract *A one-pot synthesis of the trisubstituted imidazole derivatives from α-acetoxy-α-chloro-β-keto-esters, aldehydes, and ammonium acetate has been developed.*

Keywords Imidazoles; tricarbonyl equivalents

INTRODUCTION

We recently described a short and convenient synthetic sequence for the preparation of α-acetoxy-α-chloro-β-keto-esters **2** from readily available and inexpensive β-ketoesters.[1–3] A practical advantage of this methodology is that purification of compounds **2** or their precursors, by either chromatography or distillation, is not required and multigram quantities of material can be prepared. We subsequently demonstrated that compounds **2** could be used as tricarbonyl equivalents **3** to effect a versatile one-pot synthesis of pyridine, 2,2′-bipyridyl and 2,2′:6′,2″-terpyridine derivatives.[1–3] In this article, we describe a synthesis of highly substituted imidazole derivatives **4** from compounds **2/3**. There are relatively few examples of tricarbonyls **3** being used as building blocks for the synthesis of imidazole derivatives. Brackeen and coworkers described the preparation of a range of imidazoles **4** in good yields from tricarbonyls **3**, aldehydes (R^2CHO) and ammonium acetate in boiling acetic acid solution[4] and a patent describes a similar procedure.[5] The tricarbonyls **3** required in these transformations were obtained from oxidation of the phosphorane derivatives **1**, which produces triphenylphosphine oxide as an

Received May 12, 2011.

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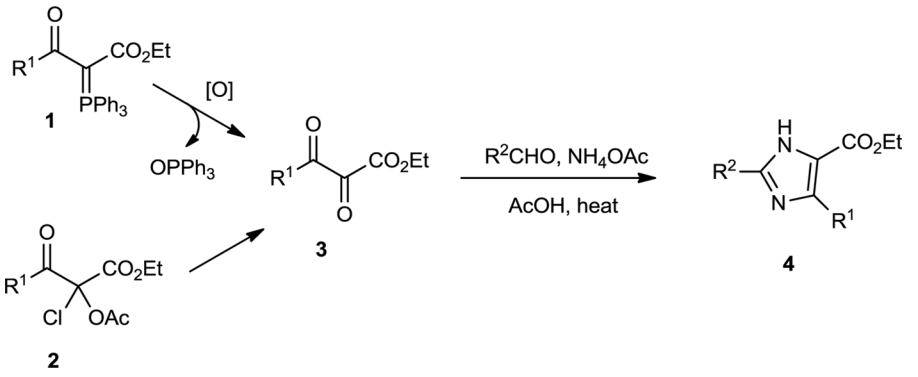

Scheme 1. Synthesis of imidazoles **4**.

unwanted by-product. Thus, we were interested in examining whether the readily prepared α-acetoxy-α-chloro-β-keto-esters **2**, which as noted can behave as tricarbonyl **3** equivalents, might also provide suitable building blocks for highly substituted imidazole derivatives **4** (Scheme 1).

RESULTS AND DISCUSSION

Pretreatment of compounds **2** with methylamine (33% in EtOH) has been described previously as a method for generating the tricarbonyls **3**.[1–3] Subsequent addition of an aromatic aldehyde (R^2CHO), and an excess of ammonium acetate to the mixture afforded the known imidazole derivatives **4a**[4,5] (mp 167 °C, lit.[4] 165–167 °C) and **4b**[4] (mp decomp. > 140 °C, lit.[4] not reported) and the additional examples **4c–4f** (Table 1, entries 1–6) after heating in acetic acid at 70–80 °C for 2–3 h. The yields of the imidazole products **4** were generally moderate at best, but in view of the simplicity of the procedure and the availability of compounds **2**, the overall synthesis does provide a convenient method for the preparation of this important class of heterocyclic compound. Without pretreatment of compound **2** ($R^2 = Ph$) with methylamine, a comparable yield (41%) of the imidazole product **4a** was obtained. Imidazole **4g** (entry 7) bearing an aliphatic 2-substituent could not be prepared satisfactorily using this protocol. However, by performing the

Table 1. Structures and yields of imidazole derivatives **4**

Entry	R^1	R^2	Product	Yield (%)
1	Ph	Ph	**4a**	38
2	n-Pr	Ph	**4b**	65
3	n-Pr	4-$MeOC_6H_4$	**4c**	43
4	n-Pr	4-ClC_6H_4	**4d**	27
5	n-Pr	4-$(O_2N)C_6H_4$	**4e**	37
6	n-Pr	2-$(O_2N)C_6H_4$	**4f**	63
7	Ph	Et	**4g**	46

reaction in ethanol at room temperature for 3 days, a reasonable yield of the required imidazole derivative **4g** was obtained.

CONCLUSION

We have demonstrated that the tricarbonyl equivalents **2** can be successfully used in the synthesis of highly substituted imidazole derivatives **4**. This methodology avoids the production of triphenylphospine oxide as a by-product, which as noted is formed in current routes to these imidazole derivatives **4**.

EXPERIMENTAL

^{1}H NMR spectra (270 MHz) and ^{13}C NMR spectra (68 MHz) were recorded on a Jeol EX270 instrument. High-resolution mass spectrometry (HRMS) (electrospray) was performed by the EPSRC mass spectrometry service. Infrared (IR) spectra were obtained via a diamond anvil sample cell using a Perkin-Elmer 1000 spectrometer. Melting points are reported uncorrected as determined on a Stuart SMP 1 melting-point apparatus. Thin-layer chromatography (TLC) was performed on Merck plastic foil plates precoated with silica gel 60 F_{254}. Merck silica gel 60 was used for column chromatography.

Typical Procedure Illustrating the Synthesis of Ethyl 2-(4-Methoxyphenyl)-4-propylimidazole-5-carboxylate 4c

Methylamine (0.49 mL, 33% w/w in ethanol, 3.98 mmol) was added to a stirred solution of compound **2** (R^1 = n-Pr) (500 mg, 1.99 mmol) in ethanol (5 mL) The mixture was stirred (1 h) at room temperature and evaporated. 4-Methoxybenzaldehyde (543 mg, 3.99 mmol) and a solution of ammonium acetate (1.53 g, 19.8 mmol) in acetic acid (6 mL) were added to the residue, and the mixture was heated (3 h) at 70 °C. The solvent was evaporated, and the residue was taken up in ethyl acetate (12 mL). The organic extract was washed sequentially with saturated aqueous $NaHCO_3$ solution (12 mL), water (12 mL), and brine (12 mL); dried over ($MgSO_4$); and evaporated, giving the crude product (612 mg) as a brown solid. Purification by column chromatography over silica gel (eluent; EtOAc–hexane, 1:1) gave imidazole **4c** (247 mg, 43%) as a yellow solid, mp 180–181 °C. ^{1}H NMR ($CDCl_3$): δ 7.82 (d, 2H, J = 8.9 Hz), 6.96 (d, 2H, J = 8.9 Hz), 4.37 (q, 2H, J = 7.2 Hz), 3.86 (s, 3H), 2.89 (t, 2H, J = 7.7 Hz), 1.80–1.64 (m, 2H), 1.39 (t, 3H, J = 7.2 Hz), 0.99 (t, 3H, J = 7.4 Hz)) ppm. The >N*H* signal was not located; IR (υ_{max} cm^{-1}): 2965, 1705, 1495, 1440, 1313, 1252, 1204, 1187, 1103, 1033, 970, 837, 739; HRMS (ESI) for $C_{16}H_{21}N_2O_3$ $[M + H]^+$: calculated 289.1547; measured 289.1545.

Ethyl 2-(4-Chlorophenyl)-4-propylimidazole-5-carboxylate 4d

Yellow solid, mp 193–196 °C; ^{1}H NMR ($CDCl_3$): δ 7.83 (d, 2H, J = 8.4 Hz), 7.43 (d, 2H, J = 8.4 Hz), 4.38 (q, 2H, J = 6.9 Hz), 2.90 (t, 2H, J = 7.7 Hz), 1.80–1.60 (m, 2H), 1.40 (t, 3H, J = 7.2 Hz), 0.99 (t, 3H, J = 7.4 Hz) ppm. The >N*H* signal was not located; IR (υ_{max} cm^{-1}): 2966, 1708, 1480, 1322, 1220, 1112,

1093, 972, 852, 736: HRMS (ESI) for $C_{15}H_{18}ClN_2O_2$ $[M+H]^+$: calculated 293.1051; measured 293.1045.

Ethyl 2-(4-Nitrophenyl)-4-propylimidazole-5-carboxylate 4e

Yellow-orange solid, mp 222–223 °C; ^{1}H NMR ($CDCl_3$): δ 8.33 (d, 2H, $J = 9.2$ Hz), 8.07 (d, 2H, $J = 9.2$ Hz), 4.40 (q, 2H, $J = 7.2$ Hz), 3.10–2.88 (m, 2H), 1.82–1.71 (m, 2H), 1.42 (t, 3H, $J = 7.2$ Hz), 1.01 (t, 3H, $J = 7.4$ Hz) ppm. The >N*H* signal was not located; IR (υ_{max} cm^{-1}): 2964, 1706, 1517, 1340, 1320, 1309, 1291, 1207, 1100, 857, 711; HRMS (ESI) for $C_{15}H_{18}N_3O_4$ $[M+H]^+$: calculated 304.1292; measured 304.1291.

Ethyl 2-(2-Nitrophenyl)-4-propylimidazole-5-carboxylate 4f

Tan-colored wax. ^{1}H NMR ($CDCl_3$): (60:40 mixture of tautomers), major tautomer δ 10.33–10.13 (br, 1H, N*H*), 8.02 (dd, 1H, $J = 7.9$ and 1.2 Hz), 7.94 (d, 1H, $J = 7.9$ Hz), 7.74–7.65 (m, 1H), 7.62–7.54 (m, 1H), 4.37 (q, 2H, $J = 7.2$ Hz), 2.90 (t, 2H, $J = 7.7$ Hz), 1.81–1.67 (m, 2H), 1.40 (t, 3H, $J = 7.2$ Hz), 0.99 (t, 3H, $J = 7.4$ Hz) ppm, minor tautomer δ 10.13–9.97 (br, 1H, N*H*), 8.19 (dd, 1H, $J = 7.9$ and 1.0 Hz), 7.94 (d, 1H, $J = 7.9$ Hz), 7.74–7.65 (m, 1H), 7.62–7.54 (m, 1H), 4.40 (q, 2H, $J = 7.2$ Hz), 3.03 (t, 2H, $J = 7.7$ Hz), 1.81–1.67 (m, 2H), 1.40 (t, 3H, $J = 7.2$ Hz), 1.02 (t, 3H, 6-H, $J = 7.4$ Hz) ppm; IR (υ_{max} cm^{-1}): 2964, 1702, 1323, 1215, 1113, 714, 694; HRMS (ESI) for $C_{15}H_{18}N_3O_4$ $[M+H]^+$: calculated 304.1292; measured 304.1291.

Synthesis of Ethyl 2-Ethyl-4-phenylimidazole-5-carboxylate 4g

Ammonium acetate (9.43 g, 122 mmol) was added to a mixture of compound **2** ($R^2 = Ph$) (3.87 g, 13.6 mmol) and freshly distilled propionaldehyde (0.789 g, 13.6 mmol) in EtOH (120 mL). The reaction mixture was stirred (3 days) at room temperature and evaporated. The residue was dissolved in CH_2Cl_2 (20 mL) and washed with H_2O (3 × 20 mL), and the organic fraction was dried ($MgSO_4$) and evaporated. The resulting crude product was purified by column chromatography over silica gel (eluent; EtOAc–CH_2Cl_2, 1:9, increasing polarity to EtOAc–CH_2Cl_2, 1:1), yielding the product ($R_f = 0.62$, EtOAc) as a tan-colored solid (1.54 g, 46%), mp 150–152 °C. ^{1}H NMR ($CDCl_3$): δ 7.75–7.67 (m, 2H), 7.38–7.24 (m, 3H), 4.22 (q, 2H, $J = 7.2$ Hz), 2.61 (q, 2H, $J = 7.5$ Hz), 1.24–1.12 (m, 6H) ppm. The>N*H* signal was not located; ^{13}C NMR ($CDCl_3$): δ 162.0, 151.5, 131.9, 129.3, 128.4, 127.8, 60.6, 21.7, 14.2, 12.6 ppm; IR (υ_{max} cm^{-1}): 1708, 1538, 1294, 1227, 1126, 1021, 762, 690: HRMS (ESI) for $C_{14}H_{17}N_2O_2$ $[M+H]^+$: calculated 245.1285; measured 245.1286.

ACKNOWLEDGMENTS

We thank Vertellus Specialty Materials for generous financial support and the EPSRC mass spectrometry service (Swansea) for high resolution mass spectra.

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