SHORT PAPER

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The 1,3-dipolar cycloaddition of ethyl *N*-(ethoxycarbonylmethyl)benzimidate with *N*-aryl maleimides†

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1,3-Dipolar cycloaddition of ethyl N-(ethoxycarbonylmethyl)benzimidate (**1**) with N-aryl maleimides (**2**) gave a pair of pyrrolo[3,4-*c*]pyrrole isomers (**3**, **4**) and a 7-azabicyclo[2.2.1]heptane derivative (**5**). The configuration of isomers **3** and **4** was confirmed by ^{1}H-NMR.

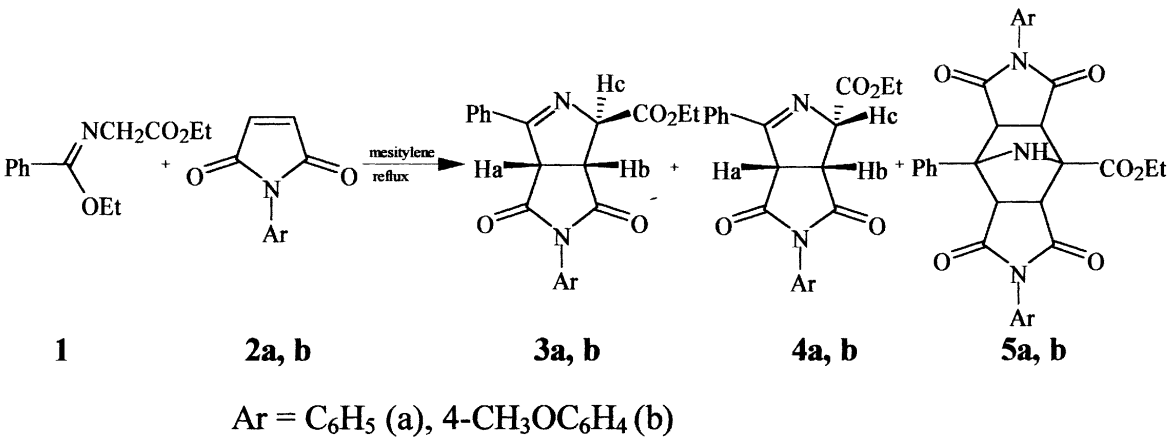
Keywords: 1,3-dipolar cycloaddition

1,3-Dipolar cycloaddition is an important reaction in heterocyclic chemistry.[1] The 1,3-dipolar cycloaddition of azomethine ylides to alkynes is, in principle, a useful procedure for obtaining pyrrole derivatives.[2] Because many pyrrolidines and pyrroles have important pharmacological activity (*e.g.* as antivirals, anthelmintics or α-glucosidase inhibitors), their synthesis has attracted much attention.[3–5] Here we report the 1,3-dipolar cycloaddition of ethyl N-ethoxycarbonylmethylbenzimidate (**1**) with N-arylmaleimides (**2**) to give pyrrole derivatives **3**, **4**, and **5** (Scheme 1).

Azomethine ylides, which were first reported in 1966, are classified as allyl-type 1,3-dipolar compounds[6] and can be obtained by ring opening of aziridines. There are other methods, such as desilylation of α-silyl onium salts,[7] 1,2-prototropic rearrangement of imines,[8] and addition of carbenes or carbenoids to imines.[9] An imino-thioether derived from an α-amino acid ester is a potential 1,3-dipole, which can undergo 1,2-prototropy to give azomethine ylides which may then react with *N*-phenylmaleimide.[10] The imidate **1** is a well-known synthetic intermediate[11] and similar to a thioimino ether of an α-amino acid ester in structure. We supposed that ethyl *N*-(ethoxycarbonylmethyl)benzimidate (**1**) could generate an azomethine ylide through 1,2-prototropy, and therefore studied the 1,3-dipolar cycloaddition reaction of the imidate **1** with the maleimide **2**.

Refluxing the imidate **1** with *N*-phenylmaleimide in toluene or xylene failed to give any cycloadduct, although 1,3-dipolar cycloaddition of imines has been reported in these solvents.[8,10] However, when a solution of **1** and *N*-aryl maleimide **2** was refluxed in mesitylene for 10 h, cycloaddition products were obtained, which included a pair of pyrrolo[3,4-*c*]pyrrole isomers (**3, 4**) and the unexpected 7-azabicyclo[2.2.1]heptane derivative (**5**). The formation of compound **5** can be rationalised via a 1,3-dipolar cycloaddition of the imidate **1** with two *N*-aryl maleimides **2**. We observed the epimerisation of the isomers **3** and **4** in hot mesitylene. Although the total yields (59% and 53%) of products for both reactions are moderate, the yield of each individual product is low because the reactivity of **3** (or **4**) with **2** is similar to that of **1** under the experimental conditions.

The configuration of the isomers **3** and **4** was confirmed by comparison of their ^{1}H-NMR coupling constants with those from compounds **6** and **7**,[10] as listed in Table 1.



Scheme 1

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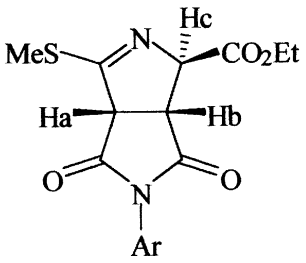
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



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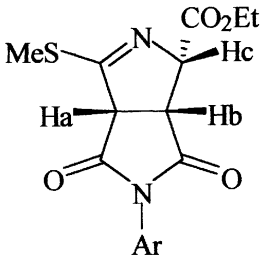

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Table 1 The comparison of $J_{b\text{-}c}$

Compound	6	3a	3b	7	4a	4b
$J_{b\text{-}c}$ (Hz)	2.57	2.4	2.4	9.9	9.0	10.2

Experimental

IR spectra were taken on a Shimadzu IR-408 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL FX-60Q spectrometer and chemical shifts (δ_H) were referred to TMS. MS spectra were taken on a VG-ZAB-HS spectrometer. Elemental analyses were recorded on a Perkin-Elmer-240C element analyzer. Ethyl *N*-ethoxycarbonyl-methylbenzimidate (**1**) was prepared by a literature method.[12]

General procedure

A solution of the imidate **1** (2.35 g, 10 mmol) and *N*-arylmaleimide **2** (20 mmol) in mesitylene (15 ml) was refluxed for 8–10 h. After the reaction mixture was cooled, the crude compound **5** was obtained by filtration, and purified by recrystallisation from ethyl acetate. The filtrate was evaporated and the residue was purified by column chromatography on silica gel (300–400 mesh, eluent: ethyl acetate/petroleum ether (60–90°C) = 1:5 v/v) to give **3** and **4**, which were recrystallised from dichloromethane/petroleum ether (60–90°C) for further purification.

Ethyl 1,3a,4,5,6,6a-hexahydro-4,6-dioxo-3,5-diphenylpyrrolo[3,4-c]pyrrole-1-carboxylate (**3a)**: Yield 17%. M.p.: 70–71°C. IR (KBr, cm^{-1}): 1735, 1710, 1505, 1385, 1190, 700. ^{1}H-NMR ($CDCl_3$, δ ppm): 1.36 (3H, t, CH_3), 4.25 (1H, d, CHa), 4.30 (2H, q, OCH_2), 4.90 (1H, dd, CHb), 5.37(1H, t, CHc), 7.14–8.30 (10H, m, ArH). MS *m/z* (%): 362 (M^+, 100), 289 (85.5), 142 (42.5). Anal. calcd. for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73. Found: C, 69.60; H, 5.00; N, 7.73.

3b: Yield 16%. M.p.: 168–170°C. IR (KBr, cm^{-1}): 1730, 1705, 1515, 1200, 760. ^{1}H-NMR ($CDCl_3$, δ ppm): 1.36 (3H, t, CH_3), 3.80 (3H, s, OCH_3), 4.22 (1H, d, CHa), 4.30 (2H, q, OCH_2), 4.90 (1H, dd, CHb), 5.37 (1H, t, CHc), 6.83–8.30 (9H, m, ArH). MS *m/z* (%): 392 (M^+, 67.1), 219 (24.8), 142 (100). Anal. calcd. for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14. Found: C, 67.03; H, 5.01, N, 6.97.

4a: Yield 20%. M.p.: 119–120°C. IR (KBr, cm^{-1}): 1725, 1715, 1510, 1390, 1180, 680. ^{1}H-NMR ($CDCl_3$, δ ppm): 1.30 (3H, t, CH_3), 3.94 (1H, d, CHa), 4.25 (2H, q, OCH_2), 4.81 (1H, d, CHb), 5.40 (1H, t, CHc), 7.17-8.30 (10H, m, ArH). MS *m/z* (%): 362 (M^+, 6.5), 289 (11.7), 233 (100). Anal. calcd. for $C_{21}H_{18}N_2O_4$: C, 69.60;H, 5.01; N, 7.73. Found: C, 69.68; H, 4.90; N, 7.34.

4b: Yield 19%. M.p.: 95–96°C. IR (KBr, cm^{-1}): 1740, 1715, 1520, 1180, 755. ^{1}H-NMR ($CDCl_3$, δ ppm): 1.30 (3H, t, CH_3), 3.97 (3H, s, OCH_3), 4.00 (1H, d, CHa), 4.25 (2H, q, OCH_2), 4.81 (1H, dd, CHb), 5.40 (1H, d, CHc), 6.82-8.30 (9H, m, ArH). MS *m/z* (%): 392 (M^+, 62.4), 319 (18.7), 142 (100). Anal. calcd. for $C_{22}H_{20}N_2O_5$: C, 67.34; H 5.14; N, 7.14. Found: C, 66.99; H, 5.22; N, 7.38.

Ethyl dodecahydro-1,3,5,7-tetraoxo-2,6,8-triphenyl-4,8-iminopyrrolo[3,4-f]isoindole-4-carboxylate **5a**: Yield 22%. M.p.: 312–314°C. IR (KBr, cm^{-1}): 3310, 1720, 1710, 1500, 1390, 1210, 750. ^{1}H-NMR ($CDCl_3$, δ ppm): 1.38 (3H, t, CH_3), 3.96 (4H, s, 2CHCH), 4.30 (2H, q, OCH_2), 4.62 (1H, s, NH), 7.08–8.00 (15H, m, ArH). MS m/z (%): 535 (M^+, 0.2), 362 (84.4), 316 (100). Anal. calcd. for $C_{31}H_{25}N_3O_6$: C, 69.52; H, 4.71; N, 7.85. Found: C, 68.99; H, 4.74; N, 7.62.

5b: Yield 18%. M.p.: 300–302°C. IR (KBr, cm^{-1}): 3300, 1720, 1705, 1515, 1200, 780. ^{1}H-NMR ($CDCl_3$, δ ppm): 1.37 (3H, t, CH_3), 3.78 (3H, s, OCH_3), 3.93 (4H, s, 2CHCH), 4.36 (2H, q, OCH_2), 4.67 (1H, s, NH), 6.85-8.00 (13H, m, ArH). MS *m/z*: 596 $(M+H)^+$. Anal. calcd. for $C_{33}H_{29}N_3O_8$: C, 66.55; H, 4.91; N, 7.06. Found: C, 66.08; H, 5.34; N, 6.84.

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