

## Carbon–Carbon Bond Formation by Intramolecular 1,4-Dipolar Cycloaddition: Heterocyclic Betaines generated *in situ* from Amides and N-substituted Amides

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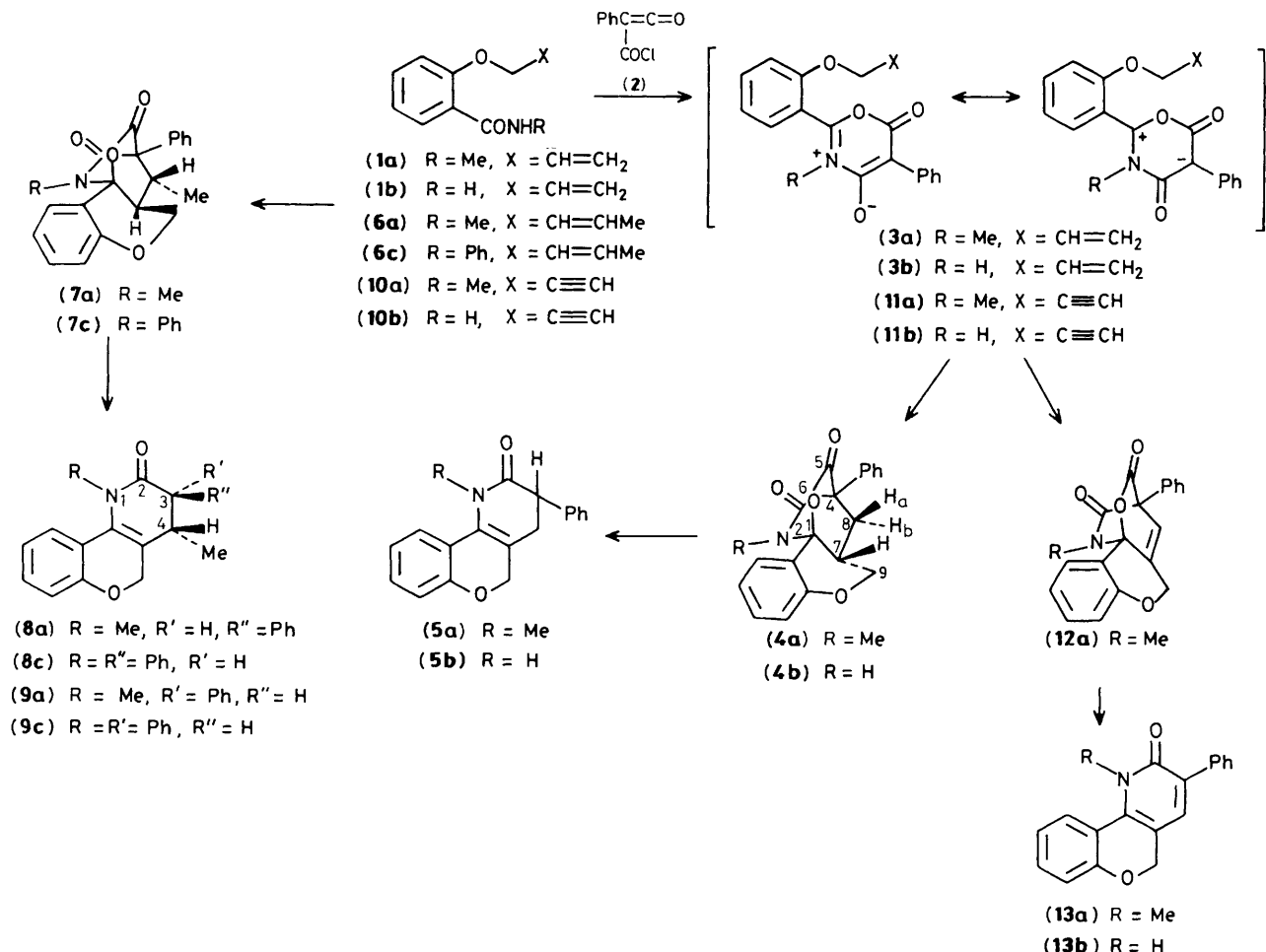
Reaction of benzamides and N-substituted benzamides with appropriate *o*-alkenyl and -alkynyl side-chains and (chlorocarbonyl)phenyl ketene gives transient *anhydro*-1,3-oxazinium hydroxides which readily undergo intramolecular 1,4-dipolar cycloaddition; loss of CO<sub>2</sub> from these 1 : 1-cycloadducts, isolable with N-substituted systems and alkenyl side-chains, gives chromeno[4,3-*b*]pyridin-2-ones.

Intramolecular 1,3-dipolar cycloadditions have become an established method for heterocycle construction;<sup>1</sup> intramolecular 1,4-dipolar cycloadditions have received less attention, with difficulties encountered in generating the 1,4-dipole being avoided by incorporating the 1,4-dipole in a heterocyclic betaine.<sup>2</sup> We now describe an approach in which the heteroaromatic betaine is generated *in situ* and the use of tautomerism in this is exploited.

*N*-Methylsalicylamide and allyl bromide in acetone–K<sub>2</sub>CO<sub>3</sub> readily gave the allyl derivative<sup>‡</sup> (**1a**) {colourless needles, hexane, 93%, m.p. 41–42 °C, [*M* + 1] 192 (100%)} which, with (chlorocarbonyl)phenyl ketene<sup>3</sup> (**2**) in dry benzene–Et<sub>3</sub>N at 50 °C, formed (50 min) in a regio- and stereo-selective cycloaddition colourless cubes of (**4a**) {CH<sub>2</sub>Cl<sub>2</sub>–Et<sub>2</sub>O, 44%, m.p. 154–155 °C (decomp.); ν<sub>CO</sub> 1685, 1765 cm<sup>-1</sup>; [*M* + 1]

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<sup>‡</sup> All new compounds reported gave satisfactory analytical data (±0.4% C, H, N).



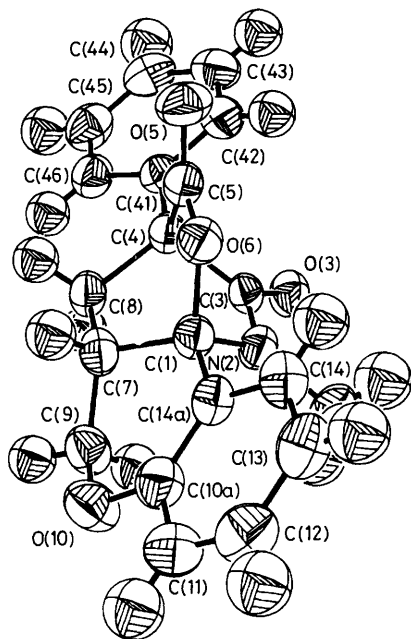
336 (3%). The n.m.r. data<sup>§</sup> and the single crystal *X*-ray determination (Figure 1)<sup>¶</sup> established the structure of the

<sup>§</sup> <sup>1</sup>H n.m.r. data (CDCl<sub>3</sub>, 200 MHz): (4a), δ 1.99 [dd, 1, *J*(H<sub>8a</sub>H<sub>8b</sub>) 12.0 Hz, *J*(H<sub>7a</sub>H<sub>8b</sub>) 5.30 Hz, H<sub>8b</sub>], 2.81 (s, 3, NMe), 2.99 [m, 2, *J*(H<sub>7a</sub>H<sub>8a</sub>) 10 Hz (coupling determined in CD<sub>3</sub>NO<sub>2</sub> owing to overlap in CDCl<sub>3</sub>), H<sub>7a</sub>, H<sub>8a</sub>], 3.86 [t, 1, *J*(H<sub>9</sub>H<sub>9</sub>) 11.8 Hz, *J*(H<sub>7a</sub>H<sub>9</sub>) 11.9 Hz, H<sub>9</sub>], 4.55 [dd, 1, *J*(H<sub>7a</sub>H<sub>6</sub>) 4.3 Hz, H<sub>6</sub>], 6.99–7.74 (m, 9, aromatic); (7a), δ 1.21 [d, 3, *J*(H<sub>8a</sub>Me) 6.7 Hz, Me], 2.48 [m, 1, *J*(H<sub>7b</sub>H<sub>8a</sub>) 5.8 Hz, H<sub>8a</sub>], 2.64 (m, 1, H<sub>7b</sub>), 2.78 (s, 3, NMe), 3.95 [t, 1, *J*(H<sub>9</sub>H<sub>7b</sub>) 12.2 Hz, *J*(H<sub>9</sub>H<sub>9</sub>) 11.9 Hz, H<sub>9</sub>], 4.51 [dd, 1, *J*(H<sub>9</sub>H<sub>7b</sub>) 4.5 Hz, H<sub>9</sub>], 6.96–7.65 (m, 9, aromatic); (7c), δ 1.24 [d, 3, *J*(MeH<sub>8a</sub>) 6.7 Hz, Me], 2.64 [m, 1, *J*(H<sub>8a</sub>H<sub>7b</sub>) 6.1 Hz, H<sub>8a</sub>], 2.70 (m, 1, H<sub>7b</sub>), 4.47 [t, 1, *J*(H<sub>9</sub>H<sub>7b</sub>) 13.3 Hz, H<sub>9</sub>], 4.66 [dd, 1, *J*(H<sub>9</sub>H<sub>7b</sub>) 7.1 Hz, H<sub>9</sub>], 6.66–7.77 (m, 14, aromatic).

<sup>¶</sup> *Crystal data* for (4a): C<sub>20</sub>H<sub>17</sub>NO<sub>4</sub>, *M* = 335.36, space group *P*2<sub>1</sub>/*n* (No. 14), *a* = 10.235(2), *b* = 10.825(2), *c* = 14.920(2) Å, β = 104.59(1)°, *U* = 1599.7(4) Å<sup>3</sup>, *Z* = 4, *D*<sub>c</sub> = 1.39 g cm<sup>-3</sup>. Data were collected on a Nicolet R3m diffractometer using Cu-*K*<sub>α</sub> radiation (graphite monochromator; λ = 1.54178 Å) in a ω-scan mode (ω range: 2° + [2θ(*K*<sub>α1</sub>) - 2θ(*K*<sub>α2</sub>)]); 2θ range: 3° to 110°). 2447 Reflections were collected (incl. standards), of which 1725 were unique and considered observed [*F* > 3σ(*F*)]. The programs of SHELXTL (Rev. 5.1) were used for data reduction and all other calculations. No absorption correction was applied [μ(Cu-*K*<sub>α</sub>) = 8.1 cm<sup>-1</sup>]. Direct phase determination followed by three Fourier cycles allowed all 25 non-hydrogen atoms to be recognized. Atomic co-ordinates and anisotropic temperature factors were refined for all non-hydrogen atoms. Hydrogen atoms were included in the refinement in calculated positions. The refinement converged at *R* = 4.24%; *R*<sub>w</sub> = 5.25%. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

cycloadduct as (4a). These chemical shifts and coupling constants were also consistent with those of the corresponding adduct obtained from the analogous thiazinium betaine.<sup>2</sup> Although oxazinium betaines of type (3) are stable,<sup>4</sup> no attempt was made to isolate (3a) as partial cycloaddition had occurred under these reaction conditions which are in marked contrast to those required for intermolecular cycloaddition of oxazinium betaines with alkynes<sup>4b</sup> (130 °C, 60 h). With alkenes no intermolecular cycloaddition occurs. N.m.r. analysis of the crude reaction mixture showed no other isomers of (4a) to be present, and material balance is accounted for by unreacted amide (1a) and a small amount of the tricyclic ring system (5a). When the cycloadduct (4a) was heated overnight in boiling benzene, (5a) was obtained exclusively {colourless microprisms, Et<sub>2</sub>O (85%), m.p. 169–171 °C; ν<sub>CO</sub> 1655 cm<sup>-1</sup>; [*M* + 1] 292 (100%); <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>, 200 MHz) δ 2.64 (m, 2, H<sub>4</sub>), 3.30 (s, 3, NMe), 3.83 [t, 1, *J*(H<sub>3</sub>,H<sub>4</sub>) 7.3 Hz, H<sub>3</sub>], 4.59 (dd, 2, *J*<sub>gem</sub> 14.7 Hz, OCH<sub>2</sub>), 6.93–7.36 (m, 9, aromatic)}. Heating (1a) and (2) in boiling xylene (90 min) led directly to (5a) in 43% yield.

The stereochemistry of the 1,5-hydrogen shift was studied using the (*E*)-isomer of (6a) prepared from *N*-methylsalicylamide and (*E*)-but-2-enyl chloride in acetone-K<sub>2</sub>CO<sub>3</sub>, {colourless needles, hexane, 66%, m.p. 59–60 °C; <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>, 200 MHz) δ 1.79 [d, 3, *J*(CH,Me) 6.1 Hz, Me], 3.00 (d, 3, *J*(NH,Me) 4.9 Hz, NMe], 4.60 [d, 2, *J*(CH,OCH<sub>2</sub>) 5.4 Hz, OCH<sub>2</sub>], 5.86 [m, 2, *J*(CH,CH) 15.5 Hz, CHCH], 6.94–8.26 (m, 5, aromatic and NH)}. With (2) in benzene-Et<sub>3</sub>N at 50 °C (2 h) (6a) gave colourless microneedles of (7a) [61%, m.p. 192 °C (decomp.); ν<sub>CO</sub> 1760, 1680 cm<sup>-1</sup>; [*M* + 1]



**Figure 1.** Molecular structure of (4a) (mirror image). Some selected bond lengths (Å) and angles (°): C(1)–N(2), 1.464(3); C(1)–C(7), 1.519(3); N(2)–C(21), 1.460(4); N(2)–C(3), 1.355(3); C(3)–O(3), 1.221(3); C(3)–C(4), 1.553(3); C(4)–C(8), 1.553(3); C(7)–C(8), 1.527(3); C(1)–O(6), 1.463(3); C(5)–O(6), 1.359(3); C(5)–O(5), 1.194(3); C(4)–C(5), 1.534(3); C(4)–C(41), 1.512(3); C(7)–C(9), 1.503(3); C(1)–C(14a), 1.506(3); N(2)–C(1)–O(6), 106.7(2); O(6)–C(1)–C(7), 107.2(2); O(6)–C(1)–C(14a), 109.0(2); C(1)–N(2)–C(21), 124.7(2); C(21)–N(2)–C(3), 119.9(2); N(2)–C(3)–C(4), 111.2(2); C(3)–C(4)–C(41), 111.7(2); C(41)–C(4)–C(5), 113.0(2); C(41)–C(4)–C(8), 114.9(2); C(4)–C(5)–O(5), 126.7(2); O(5)–C(5)–O(6), 119.7(2); C(1)–C(7)–C(8), 108.7(2); C(8)–C(7)–C(9), 114.8(2); C(7)–C(9)–O(10), 111.0(2); N(2)–C(1)–C(7), 110.2(2); N(2)–C(1)–C(14a), 113.3(2); C(1)–N(2)–C(3), 115.4(2); N(2)–C(3)–O(3), 124.6(2); C(3)–C(4)–C(5), 104.5(2); C(1)–O(6)–C(5), 113.0(1).

350 (2%)}. The absence of a chemical shift at *ca.*  $\delta$  1.99, corresponding to an *endo* proton at H<sub>8</sub> [cf. chemical shift of H<sub>8b</sub> at  $\delta$  1.99 in (4a)], is strong evidence in support of structure (7a).

Thermal elimination of CO<sub>2</sub> from (7a) gave a mixture of stereoisomers (8a) and (9a) which was difficult to separate. However, the *N*-phenyl analogue (6c) [colourless needles, hexane, 65%, m.p. 77–78 °C; <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>, 200 MHz)  $\delta$  1.85 [d, 3, *J*(CH,Me) 6.5 Hz, Me], 4.67 [d, 2, *J*(CH,OCH<sub>2</sub>) 5.6 Hz, OCH<sub>2</sub>], 5.98 [m, 2, *J*(CH,CH) 15.6 Hz, CHCH], 7.06–8.34 (m, 9, aromatic), 10.17 (br. s, 1, NH)] under the above conditions gave cycloadduct (7c) [colourless prisms, Et<sub>2</sub>O, 28%, m.p. 168 °C (decomp.);  $\nu_{\text{CO}}$  1695, 1765 cm<sup>-1</sup>; [M + 1] 412 (100%)]. Heating (7c) at 180 °C in *o*-dichlorobenzene gave a 2.2 : 1 mixture of (8c) : (9c), determined by <sup>1</sup>H n.m.r. data. The isomers were readily separated by preparative layer chromatography (silica gel, 20% EtOAc–hexane) and recrystallization from hexane afforded (8c) {colourless microneedles, m.p. 164–166 °C;  $\nu_{\text{CO}}$  1675 cm<sup>-1</sup>; <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>, 200 MHz)  $\delta$  1.36 [d, 3, *J*(Me,H<sub>4</sub>) 7.2 Hz, Me], 2.62 (m, 1, H<sub>4</sub>), 3.85 [d, 1, *J*(H<sub>3</sub>,H<sub>4</sub>) 3.1 Hz, H<sub>3</sub>], 4.51 (d, 1, *J*<sub>gem</sub> 14.7 Hz, OCH<sub>2</sub>), 4.67 (d, 1, OCH<sub>2</sub>), 6.52–7.34 (m, 14, aromatic); [M + 1] 368 (100%)} and (9c) [colourless microneedles, m.p. 162–164 °C;  $\nu_{\text{CO}}$  1675 cm<sup>-1</sup>; <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>, 200 MHz)  $\delta$  1.14 [d, 3, *J*(Me,H<sub>4</sub>) 7.2 Hz, Me], 2.49

(m, 1, H<sub>4</sub>), 4.10 [d, 1, *J*(H<sub>3</sub>,H<sub>4</sub>) 5.3 Hz, H<sub>3</sub>], 4.65 (d, 1, *J*<sub>gem</sub> 14.6 Hz, OCH<sub>2</sub>), 4.87 (d, 1, OCH<sub>2</sub>), 6.48–7.33 (m, 14, aromatic); [M + 1] 368 (100%)}. These data establish a *trans* coupling of 3.1 Hz between H<sub>3</sub> and H<sub>4</sub> of (8c) and a *cis* coupling of 5.3 Hz between H<sub>3</sub> and H<sub>4</sub> of (9c), consistent with the assigned structures. The two isomers were not interconvertible at the temperature required for CO<sub>2</sub> elimination, and a stepwise process was most likely involved in the hydrogen migration.

The benzamide (1b), prepared<sup>5</sup> from salicylamide and allyl bromide in acetone–K<sub>2</sub>CO<sub>3</sub>, and (2) in boiling xylene (90 min) led directly to (5b) {colourless microprisms, 20%, EtOAc, m.p. 176–178 °C;  $\nu_{\text{CO}}$  1655 cm<sup>-1</sup>; [M + 1] 278 (100%)}. The intermediate 1,3-oxazine-4,6-dione can undergo a tautomeric shift of the C<sub>5</sub>-H to generate the betaine (3b) in sufficient amount for cycloaddition to occur to give the 1 : 1-cycloadduct (4b) which, under the reaction conditions, lost CO<sub>2</sub> to give (5b). This type of tautomerism may account for the cycloaddition behaviour of several substituted pyrimidine-4,6-diones,<sup>6</sup> and has been observed<sup>7</sup> in intermolecular cycloadditions involving oxazole derivatives and also with 3-hydroxypyridines.<sup>8</sup>

Appreciably milder reaction conditions effected cycloaddition of alkyne side-chains to the oxazinium betaines. *N*-Methylsalicylamide and prop-2-ynyl bromide in acetone–K<sub>2</sub>CO<sub>3</sub> gave<sup>5</sup> (10a) which, with (2) in benzene–Et<sub>3</sub>N at 50 °C (4 h), gave (13a) {yellow needles, 59%, MeOH–Et<sub>2</sub>O, m.p. 144–145 °C;  $\nu_{\text{CO}}$  1615 cm<sup>-1</sup>; [M + 1] 290 (100%); <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>, 200 MHz)  $\delta$  3.86 (s, 3, NMe), 4.87 (s, 2, OCH<sub>2</sub>), 7.10–7.78 (m, 10, aromatic and vinyl)} formed by thermal extrusion of CO<sub>2</sub> from the intermediate 1 : 1-cycloadduct (12a). Similarly (10b), prepared<sup>5</sup> from salicylamide and prop-2-ynyl bromide, and (2) in boiling xylene (90 min) gave (13b) {yellow microprisms, EtOAc, 36%, m.p. 258 °C (decomp.);  $\nu_{\text{CO}}$  1605 cm<sup>-1</sup>; [M + 1] 276 (100%)}. In these cycloadditions with the unsubstituted amides, starting materials were always recovered from the reaction mixtures.

These intramolecular 1,4-dipolar cycloadditions utilizing heteroaromatic betaines generated *in situ* illustrate a hitherto undeveloped approach to carbon–carbon bond formation using readily available starting materials.

Received, 21st October 1986; Com. 1508

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- For a recent review of this topic see '1,3-Dipolar Cycloaddition Chemistry,' ed. A. Padwa, vol. 1–2, John Wiley, New York, NY, 1985.
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