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_2 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;[1] 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.[2] 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_2CO_3 readily gave the allyl derivative‡ (**1a**) {colourless needles, hexane, 93%, m.p. 41—42 °C, [*M* + 1] 192 (100%)} which, with (chlorocarbonyl)phenyl ketene[3] (**2**) in dry benzene–Et_3N at 50 °C, formed (50 min) in a regio- and stereo-selective cycloaddition colourless cubes of (**4a**) {CH_2Cl_2–Et_2O, 44%, m.p. 154—155 °C (decomp.); ν_{CO} 1685, 1765 cm^{-1}; [*M* + 1]

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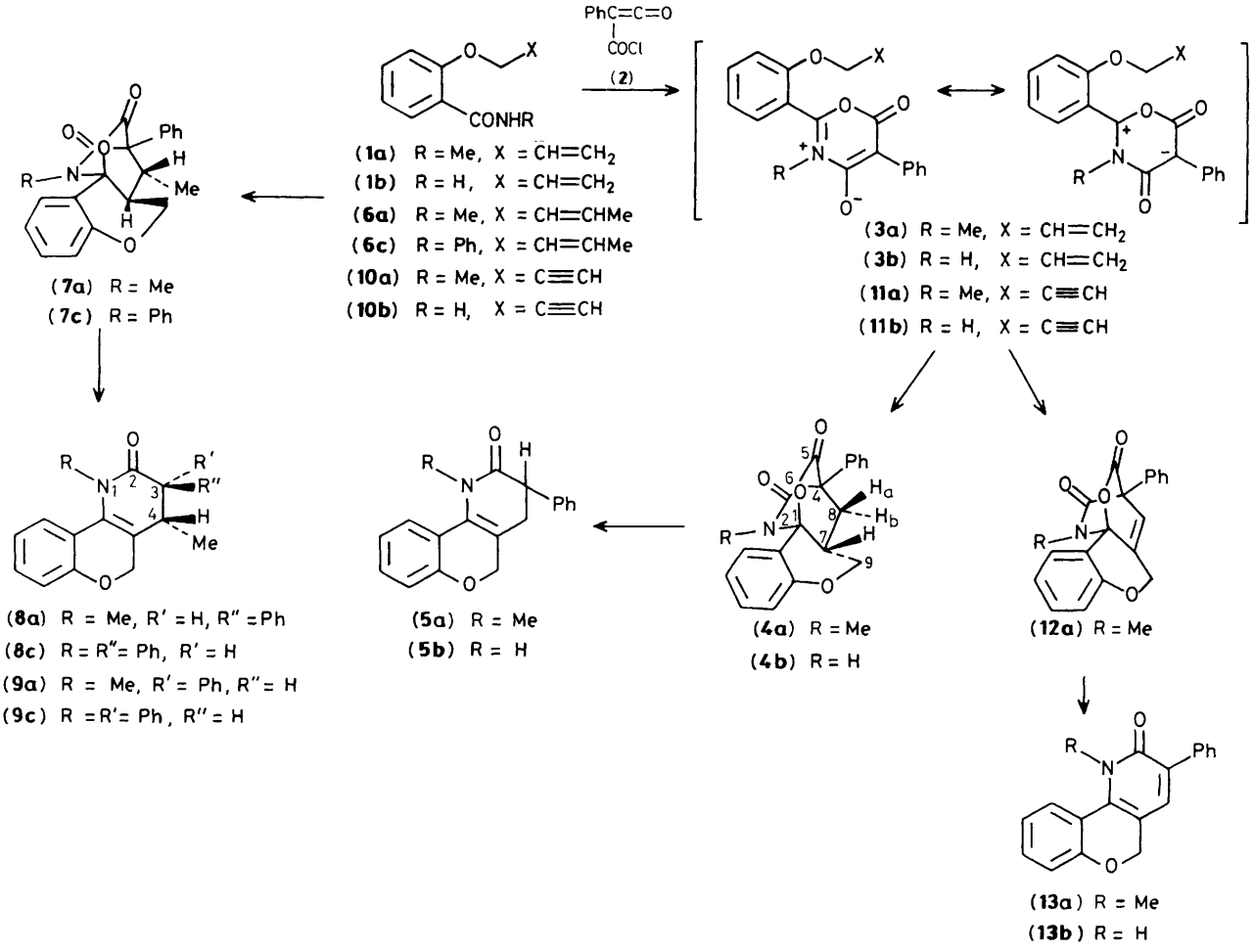
‡ All new compounds reported gave satisfactory analytical data (±0.4% C, H, N).



336 (3%)}. The n.m.r. data§ and the single crystal *X*-ray determination (Figure 1)¶ established the structure of the cycloadduct as (**4a**). These chemical shifts and coupling constants were also consistent with those of the corresponding adduct obtained from the analogous thiazinium betaine.[2] Although oxazinium betaines of type (**3**) are stable,[4] 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[4b] (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_2O (85%), m.p. 169—171 °C; ν_{CO} 1655 cm^{-1}; [*M* + 1] 292 (100%); ^1H n.m.r. ($CDCl_3$, 200 MH_2) δ 2.64 (m, 2, H_4), 3.30 (s, 3, NMe), 3.83 [t, 1, *J*(H_3,H_4) 7.3 Hz, H_3], 4.59 (dd, 2, J_{gem} 14.7 Hz, OCH_2), 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_2CO_3, {colourless needles, hexane, 66%, m.p. 59—60 °C; ^1H n.m.r. ($CDCl_3$, 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_2) 5.4 Hz, OCH_2], 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_3N at 50 °C (2 h) (**6a**) gave colourless microneedles of (**7a**) [61%, m.p. 192 °C (decomp.); ν_{CO} 1760, 1680 cm^{-1}; [*M* + 1]

§ ^1H N.m.r. data ($CDCl_3$, 200 MHz): (**4a**), δ 1.99 [dd, 1, *J*($H_{8a}H_{8b}$) 12.0 Hz, *J*($H_{7a}H_{8b}$) 5.30 Hz, H_{8b}], 2.81 (s, 3, NMe), 2.99 [m, 2, *J*($H_{7a}H_{8a}$) 10 Hz (coupling determined in CD_3NO_2 owing to overlap in $CDCl_3$), H_{7a}, H_{8a}], 3.86 [t, 1, *J*(H_9H_9) 11.8 Hz, *J*($H_{7a}H_9$) 11.9 Hz, H_9], 4.55 [dd, 1, *J*($H_{7a}H_9$) 4.3 Hz, H_9] 6.99—7.74 (m, 9, aromatic); (**7a**), δ 1.21 [d, 3, *J*(H_{8a}Me) 6.7 Hz, Me], 2.48 [m, 1, *J*($H_{7b}H_{8a}$) 5.8 Hz, H_{8a}], 2.64 (m, 1, H_{7b}), 2.78 (s, 3, NMe), 3.95 [t, 1, *J*(H_9H_{7b}) 12.2 Hz, *J*(H_9H_9) 11.9 Hz, H_9], 4.51 [dd, 1, *J*(H_9H_{7b}) 4.5 Hz, H_9], 6.96—7.65 (m, 9, aromatic); (**7c**), δ 1.24 [d, 3, *J*(MeH_{8a}) 6.7 Hz, Me], 2.64 [m, 1, *J*($H_{8a}H_{7b}$) 6.1 Hz, H_{8a}], 2.70 (m, 1, H_{7b}), 4.47 [t, 1, *J*(H_9H_{7b}) 13.3 Hz, H_9], 4.66 [dd, 1, *J*(H_9H_{7b}) 7.1 Hz, H_9), 6.66—7.77 (m, 14, aromatic).

¶ *Crystal data* for (**4a**): $C_{20}H_{17}NO_4$, *M* = 335.36, space group $P2_1/n$ (No. 14), *a* = 10.235(2), *b* = 10.825(2), *c* = 14.920(2) Å, β = 104.59(1)°, *U* = 1599.7(4) Å^3, *Z* = 4, D_c = 1.39 g cm^{-3}. Data were collected on a Nicolet R3m diffractometer using Cu-K_α radiation (graphite monochromator; λ = 1.54178 Å) in a ω-scan mode (ω range: 2° + [2θ ($K_{\alpha1}$) −2θ ($K_{\alpha2}$)]; 2θ range: 3° to 110°). 2447 Reflections were collected (incl. standards), of which 1725 were unique and considered observed [$F > 3\sigma F$)]. The programs of SHELXTL (Rev. 5.1) were used for data reduction and all other calculations. No absorption correction was applied [μ(Cu-K_α = 8.1 cm^{-1}]. 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_w = 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.

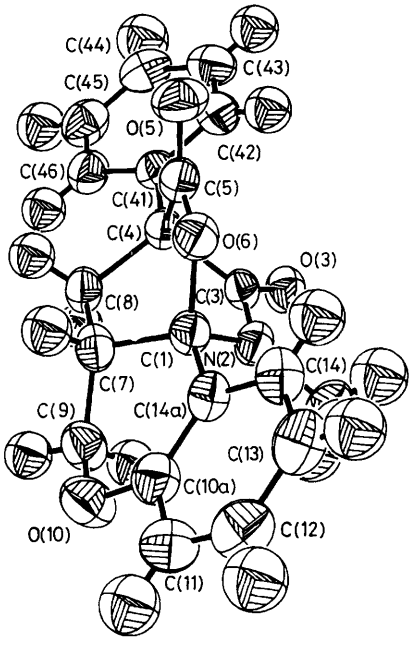


Figure 1. Molecular structure of (**4a**) (mirror image). Some selected bond lengths (Å) and angles (°): C(1)–N(2), 1.464(3); C(1)–C(7), 1.519(3); N(2)–C(21), 1.460(4); N(2)–C(3), 1.355(3); C(3)–O(3), 1.221(3); C(3)–C(4), 1.553(3); C(4)–C(8), 1.553(3); C(7)–C(8), 1.527(3); C(1)–O(6), 1.463(3); C(5)–O(6), 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.* δ 1.99, corresponding to an *endo* proton at H_8 [*cf.* chemical shift of H_{8b} at δ 1.99 in (**4a**)], is strong evidence in support of structure (**7a**).

Thermal elimination of CO_2 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; ^{1}H n.m.r. ($CDCl_3$, 200 MHz) δ 1.85 [d, 3, *J*(CH,Me) 6.5 Hz, Me], 4.67 [d, 2, *J*(CH,OCH_2) 5.6 Hz, OCH_2], 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_2O, 28%, m.p. 168 °C (decomp.); ν_{CO} 1695, 1765 cm^{-1}; [*M* + 1] 412 (100%)}.§ Heating (**7c**) at 180 °C in *o*-dichlorobenzene gave a 2.2 : 1 mixture of (**8c**) : (**9c**), determined by ^{1}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; ν_{CO} 1675 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$, 200 MHz) δ 1.36 [d, 3, *J*(Me,H_4) 7.2 Hz, Me], 2.62 (m, 1, H_4), 3.85 [d, 1, *J*(H_3,H_4) 3.1 Hz, H_3], 4.51 (d, 1, J_{gem} 14.7 Hz, OCH_2), 4.67 (d, 1, OCH_2), 6.52—7.34 (m, 14, aromatic); [*M* + 1] 368 (100%)} and (**9c**) [colourless microneedles, m.p. 162—164 °C; ν_{CO} 1675 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$, 200 MHz) δ 1.14 [d, 3, *J*(Me,H_4) 7.2 Hz, Me], 2.49 (m, 1, H_4), 4.10 [d, 1, *J*(H_3,H_4) 5.3 Hz, H_3], 4.65 (d, 1, J_{gem} 14.6 Hz, OCH_2), 4.87 (d, 1, OCH_2), 6.48—7.33 (m, 14, aromatic); [*M* + 1] 368 (100%)}. These data establish a *trans* coupling of 3.1 Hz between H_3 and H_4 of (**8c**) and a *cis* coupling of 5.3 Hz between H_3 and H_4 of (**9c**), consistent with the assigned structures. The two isomers were not interconvertible at the temperature required for CO_2 elimination, and a stepwise process was most likely involved in the hydrogen migration.

The benzamide (**1b**), prepared[5] from salicylamide and allyl bromide in acetone–K_2CO_3, and (**2**) in boiling xylene (90 min) led directly to (**5b**) {colourless microprisms, 20%, EtOAc, m.p. 176—178 °C; ν_{CO} 1655 cm^{-1}; [*M* + 1] 278 (100%)}. The intermediate 1,3-oxazine-4,6-dione can undergo a tautomeric shift of the C_5-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_2 to give (**5b**). This type of tautomerism may account for the cycloaddition behaviour of several substituted pyrimidine-4,6-diones,[6] and has been observed[7] in intermolecular cycloadditions involving oxazole derivatives and also with 3-hydroxypyridines.[8]

Appreciably milder reaction conditions effected cycloaddition of alkynic side-chains to the oxazinium betaines. *N*-Methylsalicylamide and prop-2-ynyl bromide in acetone–K_2CO_3 gave[5] (**10a**) which, with (**2**) in benzene–Et_3N at 50 °C (4 h), gave (**13a**) {yellow needles, 59%, MeOH–Et_2O, m.p. 144—145 °C; ν_{CO} 1615 cm^{-1}; [*M* + 1] 290 (100%); ^{1}H n.m.r. ($CDCl_3$, 200 MHz) δ 3.86 (s, 3, NMe), 4.87 (s, 2, OCH_2), 7.10—7.78 (m, 10, aromatic and vinyl)} formed by thermal extrusion of CO_2 from the intermediate 1 : 1-cycloadduct (**12a**). Similarly (**10b**), prepared[5] 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.); ν_{CO} 1605 cm^{-1}; [*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.

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