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3-ACYLAMINO FURANS

MALCOLM M. CAMPBELL*, ASTON D. KAYE and MALCOLM SAINSBURY*

School of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY.

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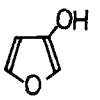
Abstract - 3-Acylaminofurans are readily prepared from 3-furoic acid. Their Diels Alder reactions and electrophilic substitutions at C-2 have been investigated.

The chemistry of 3-hydroxyfuran (1)[1] is relatively unexplored, and it is possibly best represented as 3(2H)-furanone, behaving as a vinylogous lactone rather than as a furan.[2] 3-Aminofuran (2) is unknown, although simple derivatives such as 3-acetamido- and 3-benzamidofuran are well characterized.[3] These were prepared from 3-furoic acid by the classical acyl azide sequence, leading to the isocyanates which were reacted with methyl or phenyl magnesium bromides.



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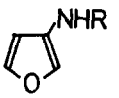
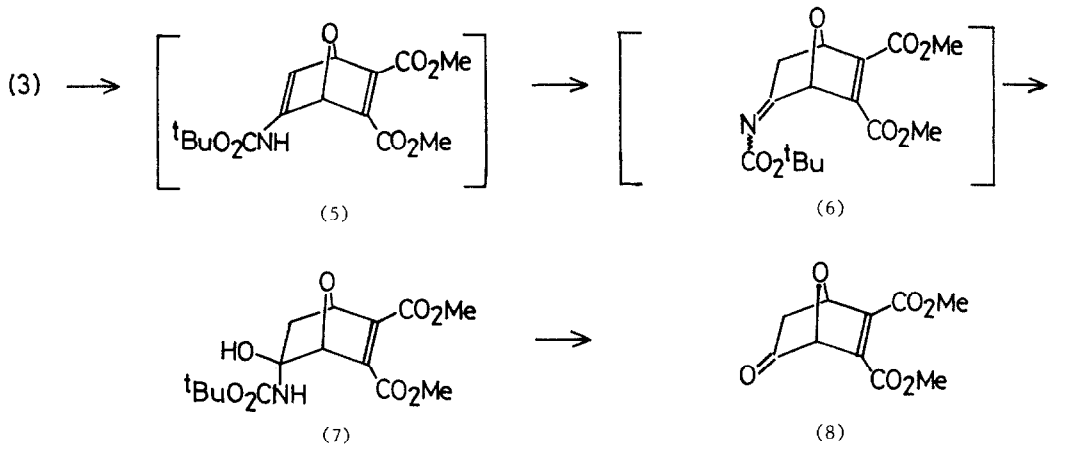


(2) R = H
(3) R = $CO_2{}^tBu$
(4) R = CO_2Me

Herein we report a simple synthesis of 3-alkoxycarbonylaminofurans, and describe some aspects of the chemistry of these novel compounds. Thus, 3-alkoxycarbonylaminofurans (3) and (4) can be prepared readily by treating 3-furanoic acid with diphenylphosphoryl azide[4] in the presence of triethylamine and the appropriate alcohol. Although the yields are modest (~50%), and the compounds lacking in stability, the approach is direct and more convenient than the Curtius route. We confirm that 3-aminofuran is unisolable, since all attempts to remove the acyl group under a wide range of standard conditions led to decomposition.

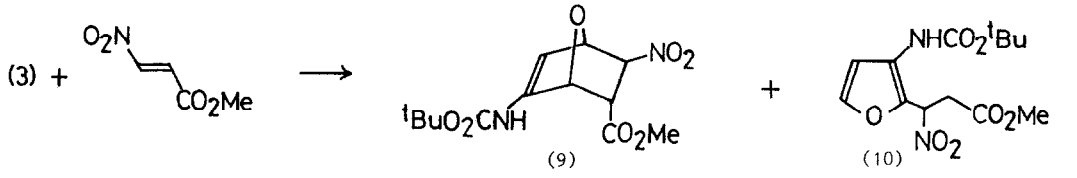
The ^1H n.m.r. spectrum of 3-(tert-butoxycarbonylamino)furan exhibited three furan aromatic signals, consistent with structure (3) rather than a 3(2H)-furanimine structure. The ^{13}C n.m.r. spectrum also showed the aromatic carbons as doublets in the range 105-141 p.p.m., and the quaternary C-3 carbon as a singlet at 125.2 p.p.m. Interestingly, the addition of D_2O to the ^1H n.m.r. sample caused the gradual disappearence of the NH and the H-2 signal. Moreover, the ^{13}C n.m.r. spectrum of the deuterated sample only exhibited two methine doublets, that for C-2 becoming a low intensity singlet. Similar phenomena were noted for 3-methoxycarbonylaminofuran (4). These facts indicated a degree of enamine character for (3) and (4), and encouraged us to examine, not only the Diels Alder chemistry of these derivatized 3-aminofurans, but also the possibility of regioselective electrophilic reactions at C-2.

3-Acylaminofuran (3) was expected to react with dimethylacetylenedicarboxylate (DMAD) to give the adduct (5), but instead, the hydroxy compound (7) was formed, presumably through tautomerism to the imine (6) and capture of water during work-up. The stereochemistry of



(7), a single isomer, is uncertain although the carbonyl unit may well be endo with respect to the oxygen bridge. Apart from this ambiguity, the adduct structure (7) is clearly defined by the ^{1}H n.m.r. spectrum, and is an obvious manifestation of relief of ring strain in (6). Attempted aromatization of (7) (1M HCl) gave, surprisingly, the new 7-oxabicycloheptene (8). This reaction sequence is therefore formally equivalent to the Diels Alder reaction of 3-hydroxyfuran with DMAD, which is impracticable.† The bicyclic system (8) showed no tendency to hydrate, unlike (6), providing a contrast in behaviour.

coupling of 4Hz.) It is noteworthy that (9) exists in the enamine form, in contrast to adduct (6), but here, of course, there is only one endocyclic double bond and consequently less ring strain. The ^{1}H n.m.r. spectrum of the 2-substituted furan (10) showed H-4 at δ6.71 and H-5 at δ7.32, the former being broadened by coupling with NH. The 2-substituent exhibited a clear fourteen-line ABX spin system (J_{AB}=15Hz, J_{AX}=7Hz and J_{BX}=4.5Hz). In a similar experiment with diethyl azodicarboxylate, only the 2-substituted furan (11), in very low yield, was isolable, H-4 and H-5 being coupled (4Hz) in the simpler H n.m.r. spectrum. Reactions with

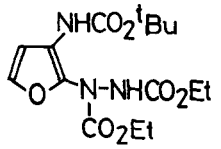


Other Diels Alder attempts with electron deficient dienophiles led to complex mixtures from which low yields of cycloaddition adducts and C-2 substituted furans were isolated with difficulty. Methyl 3-nitroacrylate, for example, gave 2-(tert-butoxycarbonylamino)-6-endo-methoxycarbonyl-5-exo-nitro-7-oxabicyclo-[2.2.1]hept-2-ene (9) and 3-[3](tert-butoxy-carbonylamino)furan-2-yl]-3-nitropropionate (10). The structure and stereochemistry of (9) were apparent from the ^{1}H n.m.r. spectrum. Thus, H-6 (dd, δ4.02 p.p.m.) coupled both with H-5 (J=4Hz) and with H-1 (J=2.5Hz). H-4 obviously was exo, because of the lack of coupling with H-4, consistent with structure (9), and a dihedral angle of ~90°. (The alternative endo-configuration would have shown

other dienophiles such as E-1,2-diacetoxyethene were unsuccessful under a wide range of conditions, including high pressure, but it was noted that diethylaluminium chloride catalysis resulted in trans-acylation, amide (12) being the only non-polar product.

In summary, protected 3-aminofurans (3) and (4) are readily prepared, and although slightly unstable will undergo Diels Alder cycloadditions with electron-withdrawing dienophiles, and also exhibit a tendency to undergo electrophilic attack at C-2. Additionally, a facile route to the 2-oxo-7-oxabicyclo[2.2.1]hept-5-ene system, albeit in low yield, has been developed.

† Early claims[1] for the synthsis of (1) have been refuted by subsequent workers.[5]



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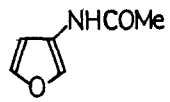

(12)

EXPERIMENTAL

3-(^{t}Butoxycarbonylamino)furan (3). tert-Butanol (2g) and triethylamine (2.8cm³) were added to a solution of 3-furoic acid (2g) in dry toluene (30cm³) and the mixture heated at reflux for 7h. After cooling to room temperature, ethyl acetate (50cm³) was added and the organic phase washed with water (2 x 50cm³), dried over magnesium sulphate, and evaporated to give a gum which was then chromatographed on silica (250g). Elution with dichloromethane : 60-80° petrol (1:1) gave the title compound as colourless prisms (1.74g, 53.5%), m.p. 128-130°, λ_{max} (ε) 220 (3310) nm. νmax (Nujol) 3320, 1690 cm^{-1} ^{1}H n.m.r. ($CDCl_3$) 1.52 (9H,s,C(CH_3)$_3$), 6.3 (1H,m,4-H), 6.4 (1H,bs, NH), 7.28 (1H,m,5-H), 7.72 (1H,bs,2-H) p.p.m. The last signal, together with that at δ6.4, is eliminated when the ^{1}H n.m.r. sample is shaken overnight with deuterium oxide. ^{13}C n.m.r. δ($CDCl_3$), 28.40 (s,OC(Me)$_3$), 80.65 (s,OC(Me)$_3$), 105.15 (d,C-4), 125.17 (s,C-3), 131.02 (d,C-2), 141.67 (d,C-5), 153.11 (s,$HNCO_2$) p.p.m. (After deuterium exchange the doublet at 131.02 becomes a singlet of much reduced intensity.) [Found: C, 59.2; H, 7.15; N, 7.5. $C_9H_{13}NO_3$ requires C, 59.0; H, 7.15; N, 7.7%].

Dimethyl-5-(^{t}butoxycarbonylamino)-5-hydroxy-7-oxabicyclo[2.2.1]hept-2-ene-2,3-dicarboxylate (7). Dimethylacetylene dicarboxylate (0.4g) was added to a solution of 3-(^{t}butoxycarbonylamino)furan (0.5g) in dry toluene (25 cm³) protected by an atmosphere of nitrogen. After 3h at reflux, the solvent was removed and the residue chromatographed on silica. Elution with ethyl acetate : 60-80° petrol (3:2) afforded the title compound as an off-white solid which recrystallised from diethylether-60-80° petrol as colourless prisms (0.23g, 24%), m.p. 94-95°, λ_{max} (ε) 231 (5,400) nm. ν_{max} (Nujol) 3320, 1732, 1715, 1692 cm^{-1}, δ($CDCl_3$) 1.46 (9H,s,C(CH_3)$_3$), 1.80 (1H,d,J=12Hz,6$_\beta$-H), 2.41 (1H,dd,J_1=12Hz,J_2=4Hz,6$_\alpha$-H), 3.86 (6H,s, OCH_3), 4.83 (1H,bs,NH), 5.31 (1H,dd,J_2=4Hz,J_3= 1.5Hz,1-H), 5.36 (1H,d,J=1.5Hz,4-H), 5.93 (1H, bs,OH). The resonances at 4.83 and 5.93 are eliminated by deuterium exchange. m/e 343 (M$^+$ weak), 185.0437 ($C_8H_9O_5$=185.0450, 24%), 184.0391 ($C_8H_8O_5$=184.0372, 12.5%), 153.0189 ($C_7H_5O_4$= 153.0187, 100%). [Found: C, 52.6; H, 6.2; N, 4.3. $C_{15}H_{21}NO_8$ requires C, 52.5; H, 6.1; N, 4.1%].

Dimethyl-5-oxo-7-oxabicyclo[2.2.1]hept-2-ene-2,3-dicarboxylate (8). The product (0.31g) from the previous experiment in diethylether (15cm³) was stirred with 1M hydrochloric acid (6cm³). After 24h the ether layer was separated, dried, and evaporated to give an oil (0.20g) which as chromatographed on silica (25g). Elution with ethyl acetate : 60-80° petrol (1:1) yielded the title compound as an oil (0.09g, 53%). λ_{max} 230 nm. ν_{max} (liq. film) 1780, 1743, 1722 cm^{-1} δ($CDCl_3$) 2.09 (1H,d,J=17Hz,6-H$_\alpha$), 2.44 (1H,dd,J_1=17Hz,J_2=4.5Hz,6-H$_\beta$), 3.83 (6H,s, 2xOCH_3), 4.92 (1H,dd,J_3=1.2Hz,J_4=0.6Hz,4-H), 5.52 (1H,m,J_2=4.5Hz,J_3=1.2Hz,J_4=0.6Hz,1-H). m/e 226 (M$^+$ very weak), 194.0217 (M-MeOH; $C_9H_6O_5$= 194.0215, 7%), 185.0437 ($C_8H_9O_5$=185.0424, 24%), 184.0391 ($C_8H_8O_5$=184.0362, 12%), 153.0189 ($C_7H_5O_4$=153.0187, 100%).

2-(^{t}Butoxycarbonylamino)-5-exo-nitro-6-endo-methoxycarbonyl-7-oxabicyclo[2.2.1]hept-2-ene (9) and methyl 3-[3-(^{t}butoxycarbonylamino)furan-2-yl]-3-nitropropionate (10). 3-^{t}Butoxycarbonylaminofuran (500mg) and methyl 3-nitroacrylate (380mg) in dry diethylether (50cm³) were stirred for 2 days. The solvent was then removed and the residue chromatographed on silica (100g). Elution with ethyl acetate : 60-80° petrol (2:3) afforded an oil from which the nitropropionate ester (10) was obtained as colourless prisms on trituration with petrol and partial evaporation of the solvent (82mg, 9.6%), m.p. 127-129°, λ_{max} (ε) 230 (6000) nm. ν_{max} ($CHCl_3$) 3440, 1740, 1644, 1560 cm^{-1} ^{1}H n.m.r. ($CDCl_3$) 1.52 (9H,s,C(CH_3)$_3$), 3.80 (3H, s,OCH_3), ∿4.7 (2H,m,J_{AB}=15Hz,J_{AX}=7Hz,J_{BX}=4.5Hz, $CH_XNO_2CH_AH_B$), 5.21 (1H,dd,J_{XA}=7Hz,J_{XB}=4.5Hz, $CH_XNO_2CH_AH_B$), 6.46 (1H,bs,NH), 6.71 (1H,m,H-4), 7.32 (1H,m,H-5). m/e 314.1133 ($C_{13}H_{18}N_2O_7$= 314.1114, 2%), 211.0481 ($C_9H_9NO_5$=211.0481, 44%), 167.0607 ($C_8H_9NO_3$=167.0591, 54%), 57 (100%). [Found: C, 49.7; H, 5.8; N, 8.9. $C_{13}H_{18}N_2O_7$ requires C, 49.7; H, 5.7; N, 8.9%]. The residual oil slowly crystallised in contact with diethylether : 60-80° petrol to yield the bicycloheptene (9) as colourless plates (23mg, 3%), m.p. 112-114°, λ_{max} (ε) 230 (8100) nm. ν_{max} ($CHCl_3$) 3440, 1744, 1648, 1560 cm^{-1} δ ($CDCl_3$) 1.5 (9H,s,C(CH_3)$_3$), 3.72 (3H,s,OCH_3), 4.02 (1H,dd,J_1=4Hz,J_2=2.5Hz,H-6), 4.95 (1H,d, J_1=4Hz,H-5), 5.38-5.48 (2H,m,H-1,H-4), 5.82 (1H,d,J_3=2Hz,H-3), 6.56 (1H,bs,NH). m/e 313.111 ($C_{13}H_{18}N_2O_7$=314.1113, 0.3%), 241.0461 ($C_9H_9N_2O_6$=241.0460, 3%), 127 (32%), 83 (29%), 57 (100%). [Found: C, 49.75; H, 5.6; N,9.2. $C_{13}H_{18}N_2O_7$ requires C, 49.7; H, 5.7; N, 8.9%].

1-[3-(^{t}Butoxycarbonylamino)furan-2-yl]-1,2-diethylhydrazodicarboxylate (11). A solution of 3-(^{t}butoxycarbonyl)furan (200mg) and diethyldiazodicarboxylate (200mg) in dry diethylether (50cm³) was stirred for 2½h and the solvent then removed to leave a sticky solid which was chromatographed on silica (50g). Elution with ethyl acetate : 60-80° petrol (2:3) gave the title compound as colourless prisms (56mg, 14.3%), m.p. 99-101°, λ_{max} (ε) 231 (7800) nm. ν_{max} ($CHCl_3$) 3415, 3325, 1730, 1670 cm^{-1} ^{1}H n.m.r. δ ($CDCl_3$) ∿1.3 (6H,2xt,2xCH_2CH_3), 1.50 (9H,s,C(CH_3)$_3$), ∿4.2 (4H,2xq,2xCH_2CH_3), 6.97 (1H,m,H-4), 7.12 (1H,d,J=2.5Hz,H-5), 7.42 (1H,bs,$NHCO_2Et$), 7.91 (1H,bs,NHOCO^{t}Bu) (the last two signals are eliminated by deuterium exchange). ^{13}C n.m.r. ($CDCl_3$) 14.36 (q,2x CH_2CH_3), 28.39 (q,C(CH_3)$_3$), 62.79, 63.82 (2xt, 2xCH_2CH_3), 80.34 (s,C(CH_3)$_3$), 107.27 (d,C-4), 120.65 (s,C-3), 132.35 (s,C-2), 139.17 (d,C-5), 152.88, 154.78, 157.49 (3xs,3xNCO_2). m/e 357.1536 ($C_{15}H_{23}N_3O_7$=357.1536, 35%), 301 (20%), 229 (59%), 184 (41%), 138 (70%), 97 (79%), 57 (100%). [Found: C, 50.3; H, 6.5; N, 11.7. $C_{15}H_{23}N_3O_7$ requires C, 50.4; H, 6.5; N, 11.8%].

3-Methoxycarbonylaminofuran (12). 3-Furoic acid (0.5g) in dry toluene (30cm³) containing diphenylphosphoryl azide (1.4g) and methanol 0.2cm³) was treated with triethylamine (0.7cm³) and heated at reflux for 12h. The reaction mixture was then cooled, diluted with ethyl acetate (30cm³) and extracted with water (2x 20cm³). The organic phase was dried and

evaporated to give an oil which was chromatographed on silica. Elution with dichloromethane afforded the title compound as colourless prisms, which readily sublimed (0.17g, 27%), m.p. 75-76°, ν_{max} (Nujol) 3300, 1700 cm^{-1} δ ($CDCl_3$) 3.78 (3H,s,OCH_3), 6.32 (1H,m,4-H), 6.70 (1H,bs,NH), 7.26 (1H,m,5-H), 7.69 (1H,bs,2-H). On adding D_2O to the ^1H n.m.r. sample the signal at 6.70 was removed and that at 7.69 gradually reduced in intensity. m/e 141.0428 (M^+, $C_6H_7NO_3$=141.0425, 100%), 109.0190 ($C_5H_3NO_2$ =109.0183, 52%), 82.0322 (C_4H_4NO=82.0293, 20%).

3-Acetamidofuran (12). 3-(^{t}Butoxycarbonylamino)furan (0.10g) was treated with (E)-1,2-diacetoxyethene (0.08g) and diethylaluminium (III) chloride (0.13g) in dry dichloromethane (20cm^3), the reaction mixture being maintained throughout at 0°. After 2h, water (10cm^3) was added and the solvent layer separated, dried and evaporated to yield a gum which was chromatographed on silica. Elution with dichloromethane afforded a colourless solid, m.p. 91-92° (lit.,[3] 91-94°). ν_{max} (Nujol) 3450, 1680 cm^{-1}. δ ($CDCl_3$) 2.19 (3H,s,$COCH_3$), 6.38 (1H, bs,NH), 7.38 (2H,m,H-4,H-5), 8.08 (1H,s,H-2). m/e 125 (M^+, 75%), 83 (100%).

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