An Azido–Hanessian Reaction

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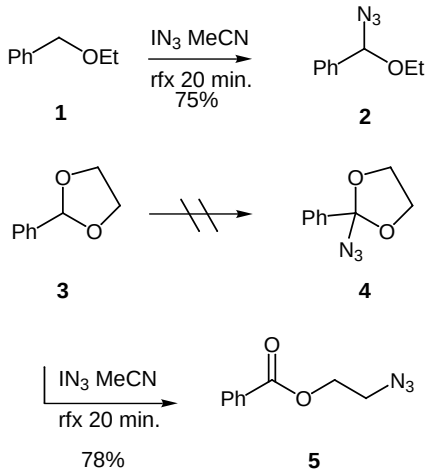
Abstract: Benzal acetals have been found to react with iodine azide to provide 2-azidoethyl- or 3-azidopropyl benzoates.

Key words: azide, azidonation, radicals, proctection group conversion

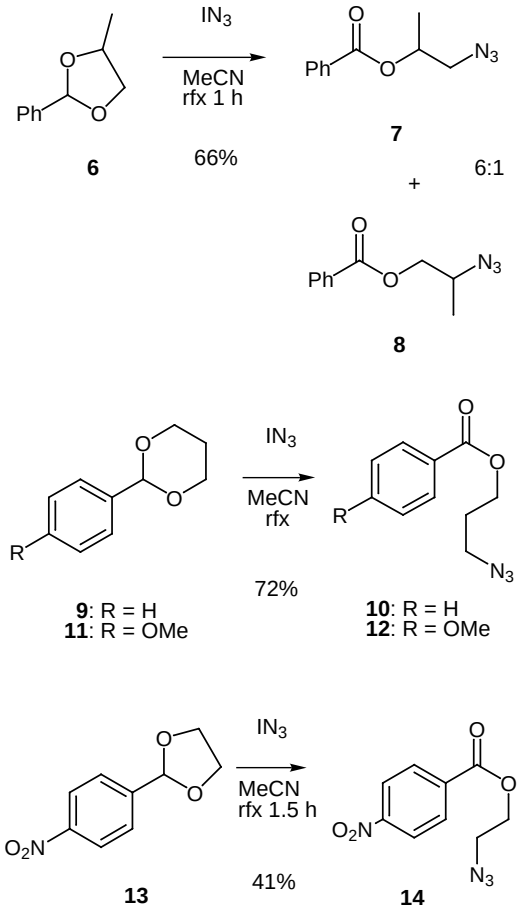
The Hanessian reaction,[1] which involves the reaction of a benzal acetal with *N*-bromosuccinimide to give a 1,2- or 1,3-bromobenzoate presumably in a radical reaction, is relatively unique in that it allows a protection group to be converted into a reactive functionality. This transformation has proven itself useful in synthesis.[2] While analogous benzal acetal opening reactions with a halogen atom are known,[3] other functional groups have apparently not been introduced in this manner. In this communication we report a benzal acetal opening reaction involving azide.



Scheme 1

Recently, we reported that IN_3[4] reacts with benzyl ethers, such as **1,** to form α-azido benzyl ethers, such as **2** (Scheme 1).[5] The idea was conceived that reaction of a benzal acetal **3** would give a similar reaction to form **4**. However when the reaction of **3** was carried out with IN_3 in refluxing MeCN not **4** but the azidobenzoate **5**[6] was obtained in a yield of 66%. No trace of **4** could be detected, but the product contained 10–15% of the corresponding alcohol, ethyleneglycol monobenzoate. However, with more thorough drying of the reagent solution and of the solvent this byproduct could be suppressed so that the yield of **5** was improved to 78%.[7,8]

This new reaction appear quite useful: A benzal acetal is directly transformed to a nitrogen functionality, since the azide can be readily converted to an amine or heterocycle, so when nitrogen-containing targets are desired a step is saved compared with the Hanessian type transformation.



Scheme 2

The reaction has been explored employing the benzal acetals **6**, **9**, **11** and **13** (Scheme 2).[9] Reaction of **6** led to a 6:1 mixture of the isomeric azides **7** and **8**[10] in 66% yield. It is clear from this experiment that the reaction has a considerable preference for substitution at the primary carbon. The 1,3-dioxane **9** gave the 3-azidobenzoate **10** in 72% yield. The *p*-methoxy analogue **11** gave a similar yield of **12**, but the reaction was faster. While the transformation of **9** to **10** took 1.5 h, formation of **12** was complete

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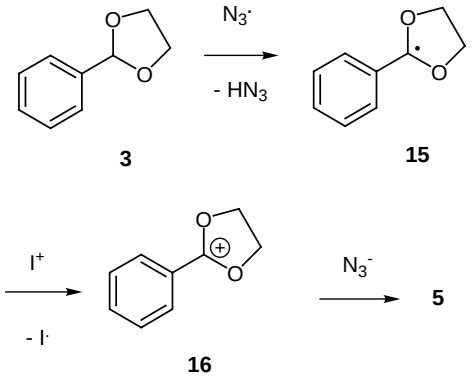
in 45 min. The faster rate of reaction of the *p*-methoxybenzal acetal **11** suggests that a positive charge is being formed at the benzylic position in the rate determining step. The nitrobenzylidene derivative **13** on the other hand gives, as expected, a rather sluggish reaction and a poor yield (Scheme 2).

The above experiments show two characteristics of the reaction: The azide preferentially adds to a primary position, which suggests that it is introduced by a nucleophilic substitution reaction and not by a radical reaction. Secondly, the rate enhancing/reducing effect of electron-donating or withdrawing substituents suggests an ionic intermediate. Nevertheless the reaction is likely to involve radical abstraction as was found in the transformation of **1** to **2**. We therefore propose the mechanism outlined in Scheme 3. Attack of an azide radical at the benzylic hydrogen leads to a benzylic radical **15**, which is subsequently oxidised to a phenyl dioxolanium ion **16** by an iodonium ion. This cation is finaly substituted by N_3^- to give the product.



Scheme 3

This new reaction will be further explored in this laboratory.

Acknowledgement

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(4) IN_3 is a potentially explosive compound. We have never encountered any problems, but it is advisable to destroy the reagent after the reaction using $Na_2S_2O_3$ wash.

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(6) The 1-monodeuterated analogue of **5** has been reported: Hammerschmidt, F. *Liebigs Ann. Chem.* **1988**, 955.

(7) A typical reaction to prepare **5** was carried out as follows: To a stirred solution of NaN_3 (107 mg, 1.4 mmol) in dry CH_3CN (3 mL) at –10 °C was added a dry solution of iodine monochloride (101 mg, 0.6 mmol) in CH_3CN (2 mL) through a syringe under nitrogen atmosphere. After stirring 20 min the cooling bath was removed, and 2-phenyl-1,3-dioxolane (45 mg, 0.3 mmol) was added. The mixture was refluxed for 45 min. Upon completion (monitored by TLC), the reaction mixture was cooled to r.t., then CH_2Cl_2 (25 mL) was added, and the solution was washed with 5% $Na_2S_2O_3$ solution (20 mL). The dried (Na_2SO_4) organic phase was concentrated in vacuo, and the residue was purified by flash chromatography (silica gel, pentane–EtOAc 10:1, R_f = 0.58) to give 2-azidoethyl benzoate **5** (44 mg, 78%) as a colourless oil.

(8) Spectral data for **5** (ref.[4]): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.61 (t, *J* = 5 Hz, 2 H, CH_2N), 4.45 (t, *J* = 5 Hz, 2 H, CH_2O), 7.40–7.52 (m, 3 H, Ar), 8.10 (m, 2 H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 50.1 (CH_2N), 63.8 (CH_2O), 128.6, 129.9, 133.4 (Ar), 166.4 (COO); MS (ES): 214.1 [M + Na^+]. For **7**: ^{1}H NMR: δ = 1.40 (d, *J* = 6.5 Hz, 3 H, CH_3), 3.38 (dd, *J* = 6.1, 12.9 Hz, 1 H, HCHN), 3.43 (dd, *J* = 3.8, 12.9 Hz, 1 H, HCHN), 5.25 (m, 1 H, CHO), 7.50 (m, 3H, Ar), 8.10 (m, 2 H, Ar); ^{13}C NMR: δ = 17.6 (CH_3), 55.2 (CH_2N), 70.3 (CH_2O), 128.5, 129.8, 133.3 (Ar), 166.6 (COO); MS (ES): 228.1 [M + Na^+]. For **8** (ref.[8]): ^{1}H NMR: δ = 1.24 (d, *J* = 6.5 Hz, 3 H, CH_3), 3.82 (m, 1 H, CHN), 4.20 (dd, *J* = 3.8, 11.4 Hz, 1 H, HCHO), 4.30 (dd, *J* = 7.4, 11.4 Hz, 1 H, HCHO), 7.50 (m, 3 H, Ar), 8.10 (m, 2 H, Ar). For **10**: ^{1}H NMR: δ = 2.10 (p, 2 H, CH_2), 3.40 (t, *J* = 7 Hz, 2 H, CH_2N), 4.36 (t, *J* = 6.3 Hz, 2 H, CH_2O), 7.30–7.60 (m, 3 H, Ar), 8.10 (m, 2 H, Ar). ^{13}C NMR: δ = 28.4 (CH_2), 48.4 (CH_2N), 62.0 (CH_2N), 128.6, 129.7, 133.2 (Ar), 166.2 (COO); MS (ES): 228.0 [M + Na^+]. For **12**: ^{1}H NMR: δ = 2.10 (m, 2 H, CH_2), 3.40 (t, *J* = 7 Hz, 2 H, CH_2N), 3.80 (s, 3 H, OMe), 4.27 (t, *J* = 6.3, 2 H, CH_2O), 6.82 (m, 2 H, Ar), 7.90 (m, 2 H, Ar); MS (ES): 258.05 [M + Na^+]. For **14**: ^{1}H NMR: δ = 3.64 (t, *J* = 5.1 Hz, 2 H, CH_2N), 4.50 (t, *J* = 5 Hz, 2 H, CH_2O), 8.20–8.40 (m, 4 H, Ar). ^{13}C NMR: δ = 49.9 (CH_2N), 64.6 (CH_2O), 123.8, 127.6, 131.1 (Ar), 164.5 (COO).

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(10) Compound **8** is known: Ariza, X.; Urpi, F.; Viladomat, C.; Vilarrasa, J. *Tetrahedron Lett.* **1998**, *39*, 9101.