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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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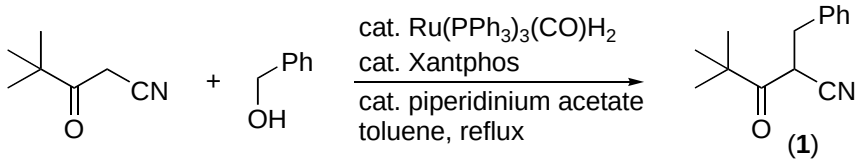
BENZYL ALCOHOL AS AN ALKYLATING AGENT USING THE RUTHENIUM-CATALYZED BORROWING HYDROGEN STRATEGY
(4,4-Dimethyl-3-oxo-2-benzylpentanenitrile)

Submitted by Tracy D. Nixon, Paul A. Slatford, Michael K. Whittlesey and Jonathan M. J. Williams.[1]
Checked by David A. Candito and Mark Lautens.[2]



1. Procedure

*4,4-Dimethyl-3-oxo-2-benzylpentanenitrile (**1**).* A 250-mL two-necked round-bottomed flask (Note 1) equipped with a magnetic stir bar, a rubber septum and a reflux condenser connected to an inert gas supply (Note 2) is flushed with inert gas for five minutes by venting through a needle in the rubber septum. The rubber septum is removed and the flask is charged with 4,4-dimethyl-3-oxopentanenitrile (5.82 g, 46.5 mmol, 1.0 equiv.), $Ru(PPh_3)_3(CO)H_2$ (0.21 g, 0.23 mmol, 0.005 equiv.) (Note 3), Xantphos (0.13 g, 0.23 mmol, 0.005 equiv.), piperidinium acetate (0.34 g, 2.3 mmol, 0.05 equiv.) (Note 4), anhydrous toluene (50 mL) (Note 5) and benzyl alcohol (4.82 ml, 5.03 g, 46.5 mmol, 1.0 equiv.) (Note 6). The rubber septum is replaced and the equipment flushed with inert gas for a further five minutes before replacing the rubber septum with a glass stopper. While still under an inert gas atmosphere, the solution is stirred and heated to reflux using an oil bath (Note 7). Heating is continued for 4 h after which the reaction is deemed to be complete by monitoring the consumption of starting material via TLC (Note 8). The resulting mixture is cooled to ambient temperature and transferred to a one-necked 250-mL round-bottomed flask (Note 9). Solvent evaporation using a rotary evaporator affords crude (**1**) as a yellow oil (Note 10). The crude product is purified by flash chromatography on silica gel (Note 11) to yield the product as a pale yellow oil (8.37 g, 84%) (Notes 12 and 13).

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2. Notes

1. All glassware was oven-dried at 120 °C overnight prior to use.

2. Nitrogen or argon are both suitable. In this experiment, nitrogen was used.

3. $Ru(PPh_3)_3(CO)H_2$ was purchased from Strem Chemicals Inc. and used as received (99% purity). $Ru(PPh_3)_3(CO)H_2$ can also be prepared via literature methods .[3]

4. Piperidinium acetate was purchased from TCI and used as received. Piperidinium acetate can also be prepared via literature methods.[4]

5. The submitters utilized dry toluene, which was dried using an anhydrous Engineering drying column. They also note that one equivalent of water is generated in the course of the reaction without any adverse effects. The Checkers utilized toluene which was distilled from sodium/benzophenone ketyl prior to use.

6. 4,4-Dimethyl-3-oxopentanenitrile (99% purity), Xantphos (97% purity) and benzyl alcohol (≥ 99% purity) were purchased from Aldrich. All chemicals were used as received.

7. The oil bath temperature rose from ambient temperature to 120 °C over approximately 10 minutes. Furthermore, the solution darkens over the first 30 minutes of heating to give a dark yellow-colored solution, which remains throughout.

8. Reaction monitoring was carried out by observing the consumption of starting material (R_f= 0.32, 1:1 ether:hexanes, visualized by $KMnO_4$ stain, Silia*Plate*™ silica gel plates, 250 μm, F254, available from Silicycle).

9. Portions of dichloromethane (3 x 20 mL) were used to rinse the reaction flask and were added to the transferred solution.

10. The bulk of the toluene was removed by rotary evaporation (80 °C, 100-200 mmHg). Furthermore, the crude material (12.84 g) showed minor impurities in the ^{1}H NMR spectrum.

11. The submitters purified the product in the following manner: Column chromatography was carried out on an 8-cm diameter column packed with 220 g of Davisil LC 60 A silica gel using petroleum ether (bp. 40 – 60 °C) and diethyl ether (19:1) as the eluent. The column fractions were collected in 20 mL portions in boiling tubes. TLC analysis of the fractions (using 0.25 mm Macherey-Nagel silica gel G/UV_{254} visualising at 254 nm; R_f 0.21) showed that fractions 22-90 contained product and solvent

was removed from these fractions on a rotary evaporator to give product. The Checkers purified the product in the following manner: Column chromatography was carried out on a 6 x 60 cm column with a fused reservoir. The column was packed with 240 g of silica gel (Silia-P Flash silica gel, particle size 40-63 μm, pore diameter 60 Å) as a slurry using the eluent (1:9 ether:hexanes). The crude material was loaded onto the column and portions of the eluent were utilized to rinse the flask containing the crude (3 x 2 ml) and these washings were then transferred onto the column. Fractions were collected in 25 x 200 mm test tubes and analysis of the fractions via TLC (R_f= 0.31, 1:9 ether:hexanes, visualized by $KMnO_4$ stain, Silia*Plate*™ silica gel plates, 250 μm, F254, available from Silicycle) revealed that fractions 7-17 contained pure product. These fractions were collected and the solvent removed by rotary evaporation (45 °C, 100-200 mmHg) followed by 12 hours under vacuum (22 °C, 6.5-7.0 mmHg) in order to yield the desired product.

12. The checkers conducted a trial in which significant modifications were made to the stated procedure. The run was carried out on half the scale of the stated procedure and no previous drying of glassware or solvent was employed. An attempt was made to purify the crude material via kugelrohr distillation. An early fraction was collected (161 °C, 5.10 mmHg) containing a clear oil which was later discarded. The product was distilled at a temperature of 190 °C and pressure of 7.20 mmHg, to leave behind an orange residue. It was observed that the distilled product was obtained in a purity of 86 %. Subsequent column chromatography provided the pure product in a yield of 78 %. The result obtained is not significantly different from the original yield reported by the submitters indicating that previous drying of glassware and solvent is unnecessary.

13. Spectroscopic and analytical data are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09 (s, 9 H), 3.11-3.23 (m, 2 H), 4.01 (t, J = 7.6 Hz, 1 H), 7.18-7.23 (m, 2 H), 7.24-7.35 (m, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 25.4, 35.8, 38.6, 45.3, 116.9, 127.4, 128.6, 128.9, 136.0, 204.8. IR (neat, cm^{-1}): 3036, 2979, 2946, 2879, 2244, 1723, 1605, 1501, 1482, 1458, 1401, 1373. Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.03; H, 7.89; N, 6.50. Found: C, 77.83; H, 8.05; N, 6.55. MS (EI) *m*/*z* (rel. intensity): 215(18, M^+), 187(38), 131(10), 103(33), 91(65), 85(52), 57(100). HRMS [M^+] calcd for $C_{14}H_{17}NO$: 215.1310. Found: 215.1311. UV (hexane, 25 °C) λ_{max}, 307 nm (ε): 25.57 (L $mol^{-1}cm^{-1}$). A run on half of the reported scale (3.0 g of 4,4-

dimethyl-3-oxopentanenitrile) was conducted, which provided 4.41 g (85%) of the desired product.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

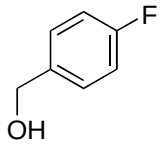
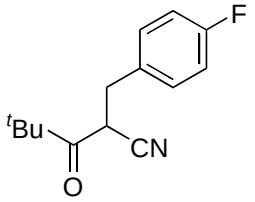
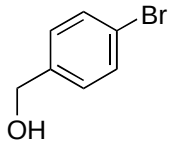
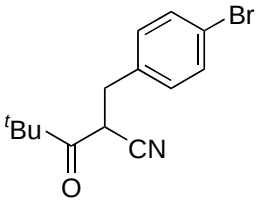
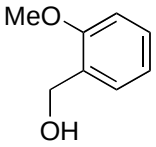
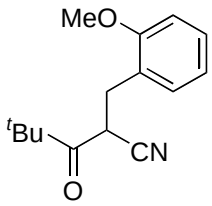
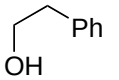
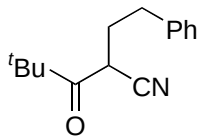
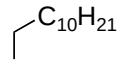
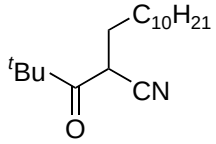
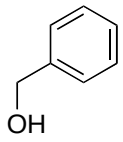
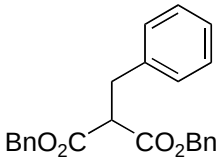
The borrowing hydrogen strategy allows alcohols to be used as alkylating agents for the alkylation of suitable carbon nucleophiles. Transition metal catalysts, including ruthenium and iridium complexes,[5,6] have been developed that temporarily remove hydrogen from the alcohol substrate to generate an intermediate aldehyde. The aldehyde is converted *in situ* into an intermediate alkene via a Wittig reaction or a condensation reaction. The hydrogen is then returned by the catalyst to the alkene, affording a new C-C bond. A similar approach for the alkylation of amines with alcohols is also known. In these reactions, the intermediate aldehyde is converted into an imine prior to return of the hydrogen to generate the amine.[7] The use of alcohols as alkylating agents avoids the use of traditional alkylating agents such as alkyl halides which can be toxic or mutagenic.

We have previously reported that while $Ru(PPh_3)_3(CO)H_2$ is not a very active catalyst for the alkylation of keto nitriles by alcohols, the addition of the bidentate ligand Xantphos[8] provides a catalyst which can be used at 0.5 mol% loading.[9]

The $Ru(PPh_3)_3(CO)H_2$ / Xantphos combination has also been used to catalyze related reactions involving the alkylation of 4,4-dimethyl-3-oxopentanenitrile with other alcohols. As shown in Table 1, this chemistry is most effective with benzylic alcohols, although aliphatic alcohols can be successfully used at higher catalyst loadings. The exact role of Xantphos in these reactions has not been fully established, although the reaction of Xantphos with $Ru(PPh_3)_3(CO)H_2$ affords $Ru(Xantphos)(PPh_3)(CO)H_2$ which is slightly more catalytically active than the *in situ* combination, and a crystal structure of $Ru(Xantphos)(PPh_3)(CO)H_2$ has been obtained. Other bidentate ligands can also enhance the reactivity of the parent complex, and details of these studies have been published elsewhere.[9,10]

The $Ru(PPh_3)_3(CO)H_2$ / Xantphos combination has been found to be effective for other reactions including the dehydration of oxime ethers to give nitriles[11] and the isomerisation of 1,4-alkynediols with further reaction to give furans[12] or pyrroles.[13]

Table 1. Alkylation of 4,4-Dimethyl-3-oxopentanenitrile with alcohols.[a]

Alcohol	Product	Ru cat.[b] (mol%)	Yield[c] (%)
		0.5	89
		0.5	79
		0.5	82
		2.5	87
		0.5	85
		5.0	78[d]

[a]Reactions were run in toluene at reflux for 4 h, using piperidinium acetate as a co-catalyst (5 mol% for reactions using 0.5 mol% Ru, and 25 mol% for reactions using 2.5 or 5 mol% Ru). [b]Ru cat = $Ru(PPh_3)_3(CO)H_2$ / Xantphos (1:1). [c]Isolated yield. [d]Dibenzylmalonate was used in place of the ketonitrile in this experiment.

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2. Department of Chemistry, University of Toronto, Toronto, Ontario, M5S 3H6, Canada
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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Benzyl alcohol; (100-51-6)
4,4-Dimethyl-3-oxopentanenitrile; (59997-51-2)
4,5-bis(Diphenylphosphino)-9,9-dimethylxanthene (Xantphos); (161265-03-8)
Piperidinium acetate; (4540-33-4)
Carbonyl(dihydrido)tris(triphenylphosphine)ruthenium (II); (25360-32-1)

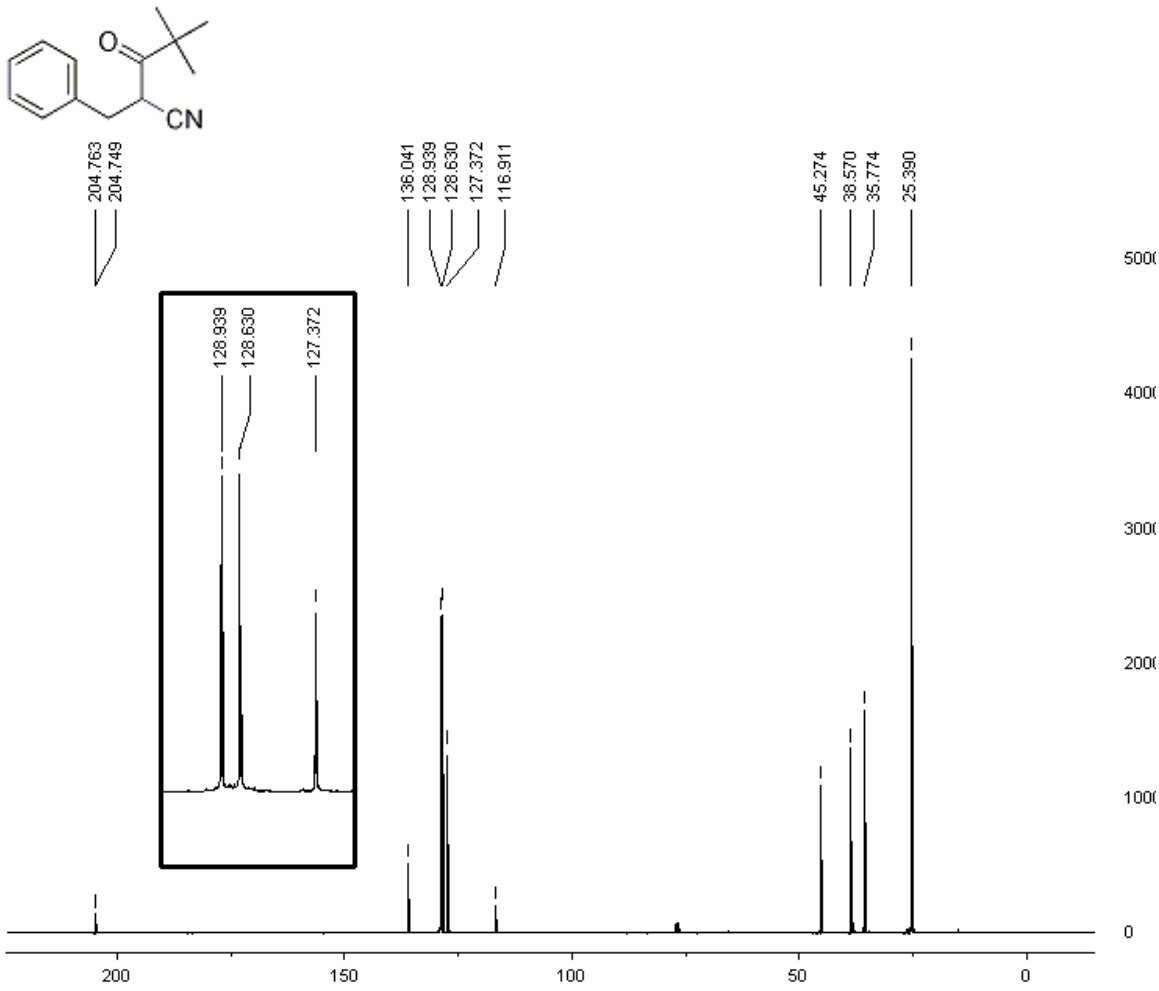
Jonathan Williams was born in Worcestershire, England, in 1964. He received a B.Sc. from University of York, a D.Phil. from University of Oxford (with Prof. S G Davies), and was then a post-doctoral fellow at Harvard with Prof. D. A. Evans (1989-1991). He was appointed to a Lectureship in Organic Chemistry at Loughborough University in 1991, and was then appointed as a Professor of Organic Chemistry at the University of Bath in 1996, where his research has mainly involved the use of transition metals for the catalysis of organic reactions.

Tracy Nixon was born in Newcastle-upon-Tyne in 1979 and graduated from the University of Leeds in 2001, where she then remained for her Ph.D. under the supervision of Dr. Terry Kee. After a two-year postdoctoral position with Dr. Jason Lynam at the University of York, she started work at the University of Bath in October, 2007, as a postdoctoral research associate in the group of Professor Jonathan Williams.

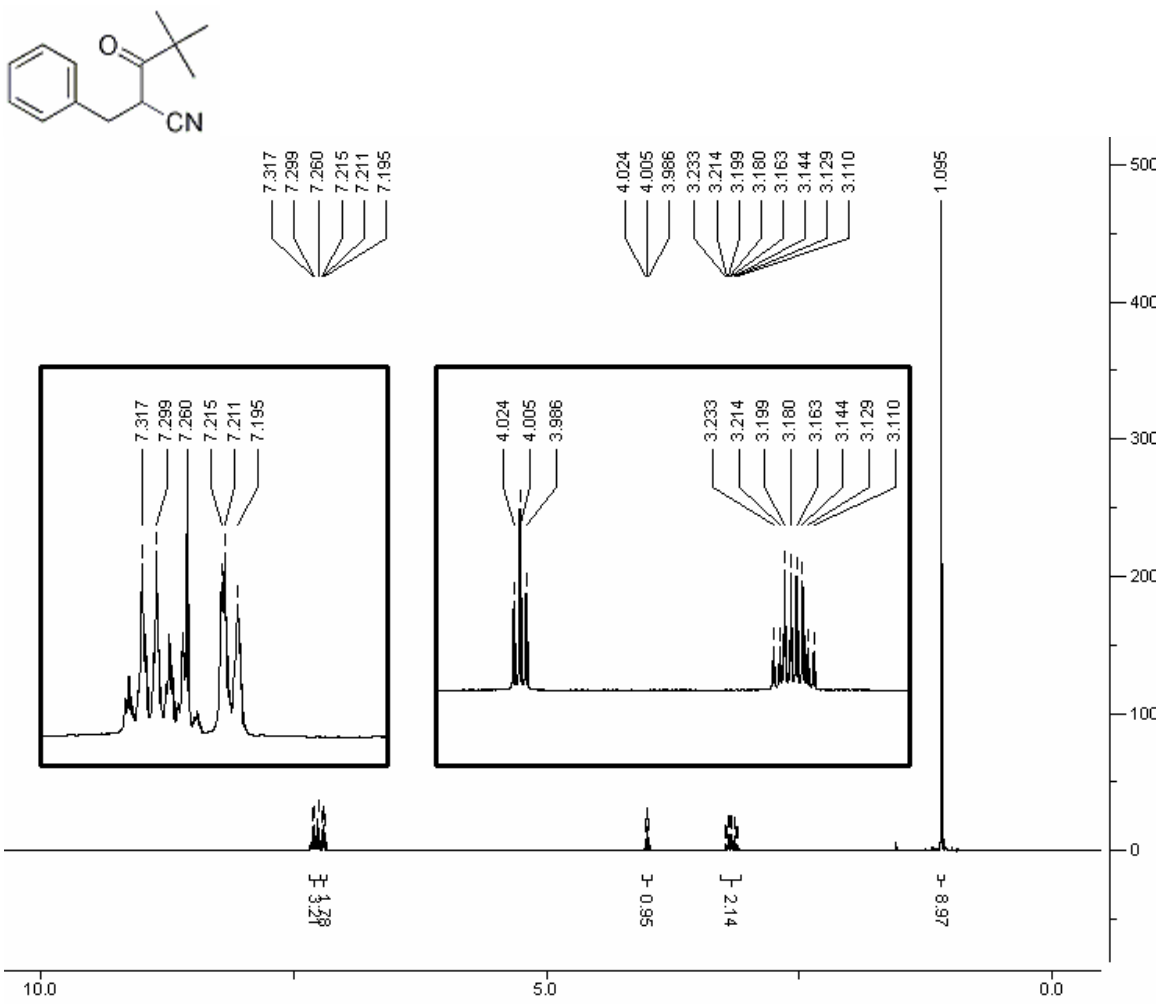
Paul Slatford was born in Hornchurch, England, in 1977, and graduated from the University of Bristol in 2000. He completed his Ph.D. under the supervision of Professor Guy Lloyd-Jones, also at the University of Bristol, in 2004. Following a three-year post-doc with Professor Jonathan Williams at the University of Bath, he is now pursuing a career in industry.

Mike Whittlesey (born Nottingham, England, 1966) received a D.Phil. for work in organometallic photochemistry with Professor Robin Perutz and Dr. Roger Mawby at the University of York, before moving to post-doctoral work in organic photochemistry with Professor Tito Scaiano at the University of Ottawa in Canada. He returned to inorganic chemistry, working with Perutz at York once more on metal induced C-F bond activation. After a fixed-term Lectureship at the University of East Anglia, he moved to Bath in 1999, where he is now a Senior Lecturer. His research interests focus on the reactivity of transition metal-N-heterocyclic carbene complexes.

David A. Candito completed his undergraduate degree in pharmaceutical and biological chemistry at York University in 2007. During his undergraduate thesis, he had the opportunity to work in the group of Professor Michael G. Organ where his research focused on the application of N-heterocyclic carbenes to palladium mediated cross-coupling reactions. He is currently pursuing a Ph.D. at the University of Toronto in the research group of Professor Mark Lautens where his research is focused upon Domino reactions involving norbornene mediated C-H activation.



^{13}C NMR (400 MHz, $CDCl_3$) Purified 4,4-Dimethyl-3-oxo-2-benzylpentanenitrile



^{1}H NMR (400 MHz, $CDCl_3$) Purified 4,4-Dimethyl-3-oxo-2-benzylpentanenitrile