Regioselective O-Alkylations of Indazolinone Using (Cyanomethylene)triphenylphosphorane

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Received 23 April 2009

Abstract: Regioselective O-alkylation of indazolinones using (cyanomethylene)triphenthylphosphorane (CMPP) as a Mitsunobu-type reagent is described with a variety of aliphatic alcohols. This method was also successfully applied to the N-alkylation of O-protected indazolinone. Selective N1 and N2 alkylations on indazolinone have previously been described; our methodology is therefore orthogonal to the previous precedent.

Key words: alkylations, heterocycles, ylides, Mitsunobu, trialkylphosphoranes

The indazolinone ring system (Figure 1) is a versatile core that can be functionalized on both the oxygen and nitrogen atoms. There is a limited amount of literature on transformations involving indazolinones with the main areas of focus being N-alkylation with halides,[1] reaction with activated carbonyl compounds,[2] and activation of the oxygen.[3] Temporary protecting groups have also been employed on this system to control selectivity.[4]

Figure 1 Indazolinone

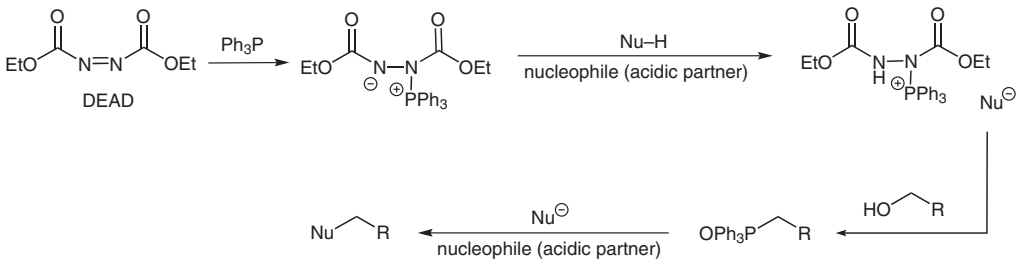
To our knowledge only one example of a selective O-alkylation on this system has been published.[5] This was a Mitsunobu reaction; the yield obtained was fairly poor and heating was required in the presence of thermally unstable azodicarbonyldipiperidine (ADDP). We were interested to see if we could expand the scope and safety of this single example utilizing recent developments in Mitsunobu protocols.

Initially we looked at the reaction of indazolinone with cyclopentanol, revisiting some of the standard Mitsunobu protocols,[6] but despite exhaustive screening of conditions this resulted in only trace quantities of the desired compound. Even modified reagents [e.g., *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD), tributylphosphine (TBP[7])] which allow deprotonation of less acidic nucleophiles showed no improvement.[8]

To determine why these reactions were problematic at room temperature we considered the mechanism of the Mitsunobu reaction (see general reaction scheme in Scheme 1). The key steps include the deprotonation of the nucleophile (acidic partner) and the displacement of phosphine oxide by the nucleophilic anion.

The 'nucleophile' in a standard Mitsunobu reaction has to have a pK_a less then 11 in order for the reaction to proceed well, and once it is above 13 the reaction will not occur. Due to the thermal instability of the reagents these reactions are also usually carried out at room temperature. We have estimated the pK_a of indazolinone to be 8.31,[16] and so in this case deprotonation should not be an issue. However, unlike Selwood,[5] our reactions were not heated, and this could be the reason that we see no reaction.

Stabilized trialkylphosphoranes, such as (cyanomethylene)trimethylphosphorane (CMMP[9]), were designed specifically to mediate Mitsunobu-type reactions on nucleophiles with a pK_a up to 23. However, unlike traditional Mitsunobu reagents, trialkylphosphoranes are also thermally stable,[10] allowing reactions to be carried out at elevated temperatures. Their structural similarity to the



Scheme 1 Mitsunobu reaction pathway[9] under standard conditions. pK_a of nucleophile must be less then 11 to allow deprotonation step to occur

SYNLETT 2009, No. 16, pp 2673–2675
Advanced online publication: 04.09.2009
DOI: 10.1055/s-0029-1217954; Art ID: D10209ST

traditional Mitsunobu intermediates (Figure 2) suggests they proceed by a similar reaction mechanism.

CMMP is the most common trialkylphosphorane found in the literature, and it has been used successfully on indazoles,[11] activated methylenes,[12] and secondary amines.[13] Unfortunately CMMP is very air and moisture sensitive and is currently not commercially available. Tsunoda et al. cited a single example of the use of (Cyanomethylene)triphenylphosphorane (CMPP),[14] and the yield obtained was comparable to CMMP. This reagent is commercially available and, although still partially air sensitive, should be easier to work with.

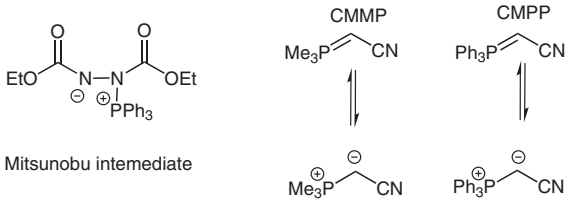
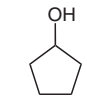
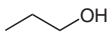
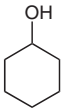
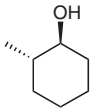
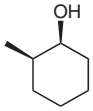
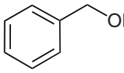
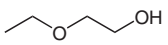
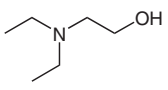
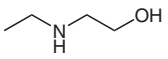
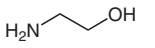
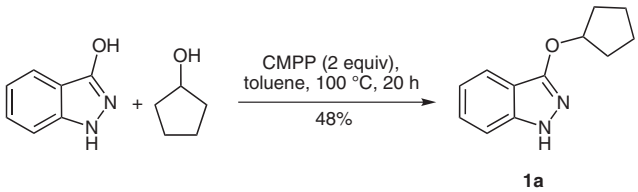


Figure 2 Comparison of traditional Mitsunobu intermediate to the ylides generated form CMMP and CMPP

Table 1 Results of Alkylations Using CMMP

Alcohol	Yield (%), O-alkylation	Yield (%), N-alkylation of **1a**
	48 **1a**	65 **1b**
	31 **2a**	54 **2b**
	42 **3a**	84 **3b**
	56 **4a**	28 **4b**
	36 **5a**	16 **5b**
	20 **6a**[17]	11 **6b**
	9 **7a**[17]	–
	32 **8a**	95 **8b**
	44 **9a**	74 **9b**
	47 **10a**	53 **10b**
	31 **11a**	0 **11b**
	13 **12a**	15 **12b**

We were interested in testing this reagent on indazolinone. An initial trial was carried out using cyclopentanol (2 equiv) and CMPP (2 equiv) in toluene at reflux for 20 hours (Scheme 2). The reaction proceeded well giving a 48% yield of O-alkylated product that was confirmed by NMR analysis (**1a**, Table 1).



Scheme 2 O-alkylation (step A)

This was very encouraging, especially as secondary alcohols are traditionally more challenging in the Mitsunobu reaction then primary alcohols.[15] Interestingly, when the same reaction was carried out at room temperature no conversion was observed.

The scope of this reaction was investigated with a range of alcohols (Table 1, O-alkylation) and appears to be fairly general. Although yields are only moderate, the reactions appear clean with major impurities being starting material and bisalkylated byproduct (where reaction had first occurred on the oxygen and then on the nitrogen). No mono-N-alkylated products were observed (due to the large pK_a difference between OH and NH[16]). Ethers were well tolerated (**9a**) as were tertiary amines (**10a**), however, decreasing yields were observed for secondary and primary amines (**11a** and **12a**). Sterically hindered alcohols also showed a reduction in yield (**7a**). When more reactive alcohols were used (**8a**) reactions were pushed to completion and so little starting material was observed, however, yields were still only moderate as more bisalkylated byproduct was generated.

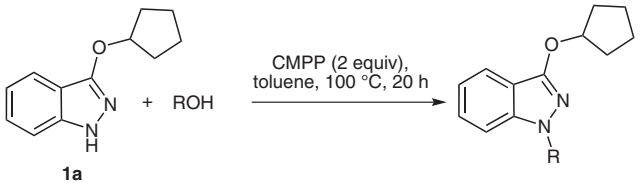
We also carried out this reaction with the alcohol used by Selwood (3-dimethylaminopropan-ol),[5] our reaction conditions offered an improvement in yield (40%).

The presence of bisalkylated byproduct suggested that a second alkylation should be fairly simple, so an initial trial was carried out on intermediate **1a** with ethanol using identical conditions to our O-alkylation, pleasingly it proceeded in a 54% yield (**2b**, Table 1).

We subsequently investigated the scope of the reaction with a range of alcohols on this cyclopentyl-substituted indazolinone (Scheme 3 and Table 1, N-alkylation). This second alkylation generally showed an improvement in yield, as bisalkylation was no longer an issue (**3a** vs.**3b**).

Similar trends in reactivity were observed, with the same functional groups being tolerated. The effects of steric hindrance seemed to be more pronounced possibly suggesting that S_N2 displacements are more challenging in this case (**4a** vs.**4b**).

The success of this work is presumably due to the thermal stability of CMPP which allows these reactions to be



Scheme 3 N-Alkylation of **1a** (step B)

heated. It also facilitates the use of nucleophiles (NuH) of higher pK_a allowing the second alkylation (on N1) to proceed. CMPP offers a simple method for the regioselective O-alkylation of indazolinone. Selective N1- and N2-alkylations on indazolinone have previously been described;[18] our methodology is therefore orthogonal to the previous precedent.

General Method for O-Alkylation (Compound 1a)
Indazolinone (100 mg, 0.746 mmol), cyclopentanol (203 μL, 2.24 mmol) and CMPP (450 mg, 1.49 mmol) were taken up in toluene (2 mL) and stirred at 100 °C in a Reacti-Vial for 12 h. Reaction mixture was then concentrated under vacuum and crude material purified by column chromatography [7 g silica, heptane (100%) through to heptane–EtOAc (91:1)] to give a yellow oil/foam (72 mg, 48%).

Characterization Data
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (2 H, m), 1.85 (2 H, m), 2.00 (4 H, m), 5.31 (1 H, quin, *J* = 4.7 Hz), 7.07 (1 H, m), 7.27 (1 H, d, *J* = 8.4 Hz), 7.35 (1 H, m), 7.69 (1 H, d, *J* = 8.0 Hz), 9.34 (1 H, br s). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 24.2, 33.2, 81.5, 109.8, 113.6, 119.8, 120.3, 127.9, 142.7, 157.3. ESI-MS: *m/z* = 203 $[M + H]^+$. MS: *m/z* calcd for $C_{12}H_{14}N_2O$ $[M + H]^+$: 203.1179; found: 203.1178.

General Method for N-Alkylation (Compound 2b)
3-Cyclopentyloxy-1*H*-indazole (100 mg, 0.5 mmol), EtOH (86 μL, 1.5 mmol) and CMPP (298 mg, 1.0 mmol) were taken up in toluene (2 mL) and stirred at 100 °C in a Reacti-Vial for 12 h. Reaction mixture was then concentrated under vacuum and crude material purified by column chromatography [7 g silica, heptane–EtOAc (95:5)] to give a yellow oil/foam (61 mg, 54%).

Characterization Data
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (3 H, t, *J* = 7.2 Hz), 1.67 (2 H, m), 1.87 (2 H, m), 2.00 (4 H, m), 4.24 (2 H, q, *J* = 7.2 Hz), 5.32 (1 H, quin, *J* = 4.5 Hz), 7.02 (1 H, m), 7.23 (1 H, d, *J* = 8.5 Hz), 7.34 (1 H, m), 7.66 (1 H, dt, *J* = 8.0, 0.9 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 15.1, 24.2, 33.2, 43.5, 81.4, 108.7, 113.8, 118.9, 120.5, 127.1, 141.1, 155.5. ESI-MS: *m/z* = 231 $[M + H]^+$. MS: *m/z* calcd for $C_{14}H_{18}N_2O$ $[M+H]^+$: 231.1508; found: 231.1492.

Acknowledgment

The authors would like to thank Paul Glossop and Dr Lyn Jones for advice and helpful discussions. We also thank Denise Burring for structural confirmation and Dr. David Blakemore and Dr. David Fenwick for reviewing the manuscript.

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(16) ACD pK_a predictor suggests (Figure 3)

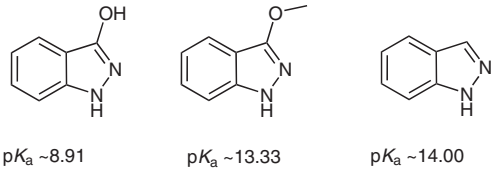

Figure 3

(17) NMR and LC-MS data confirm that **6a** and **7a** are diasteromers. Based on mechanism inversion in assumed, but this has not been confirmed experimentally.
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