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An efficient synthesis of *ortho*-*N*-Boc-arylmethyl ketone derivatives

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Abstract—A new and efficient method for the preparation of *ortho*-*N*-Boc-arylmethyl ketone derivatives is reported. The reaction involves the intermediacy of a 4-methylene-3,1-benzoaxin-2-one *moiety* which smoothly converts to the target compounds under acidic conditions. The *ortho*-*N*-Boc-arylmethyl ketone derivatives can be formed in a *one-pot* reaction or alternatively the 4-methylene-3,1-benzoaxin-2-ones can be isolated and subsequently transformed into the desired products.
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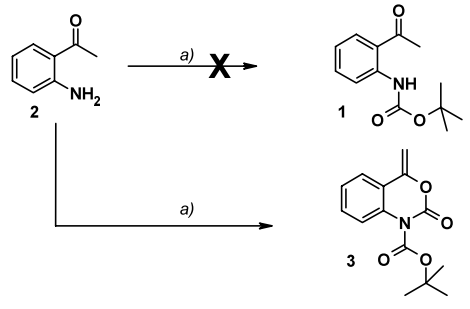
An efficient synthesis of *N*-Boc-acetophenone **1**, as a key strategic intermediate in a synthetic sequence, was sought.[1] However, when attempting the *N*-Boc-protection of *ortho*-aminoacetophenone **2** under standard conditions we were initially surprised to find that the desired product **1** was not formed and instead 4-methylene-3,1-benzoaxin-2-one **3** was isolated in 46% yield (Scheme 1).

The outcome of this reaction was undesired and was also found to be general for a small array of products **3a**–**d** (Table 1). However, encouraged by the fact that we had discovered a novel access to this scarcely studied heterocyclic ring-system we briefly investigated this new mild method for preparation of compounds of type **3**. Since two equivalents of Boc_2O are required in the transformation it was found that adding each equivalent portion-wise with either catalytic (10 mol%) or 1 equivalent of DMAP both offered acceptable reaction times and yields even at room temperature. At elevated temperatures the reactions were complete within a few minutes but the reaction yield was compromised somewhat.



Scheme 1. Formation of 4-methylene-3,1-benzoaxin-2-one; *Reagents and conditions*: (a) Boc_2O (1 equiv.), DMAP (10 mol%), CH_2Cl_2, rt, 1 h, silica gel chromatography, 46%.

A mechanism for the formation of the observed products **3** is proposed whereby the reaction proceeds through the bis-*N*-Boc derivative **4**. This infers enolisation of the methyl ketone **5** and intramolecular cyclisation via oxygen with concomitant loss of *t*-BuOH to afford the 4-methylene-3,1-benzoaxin-2-one **3** (Fig. 1).

This new route to 4-methylene-3,1-benzoaxin-2-ones **3** complements the known routes to molecules of such type which have been prepared from **6**[2] and **7**[3] in moderate to good yields using phosgene and acylisocyanates as the 'CO' source, respectively (Fig. 2).

All reactions were closely monitored by HPLC-MS which showed nearly quantitative formation of the 4-methylene-3,1-benzoaxin-2-ones **3**. Therefore we were frustrated and puzzled by the differences in the yields obtained after a silica-gel chromatographic purification step (Table 1). In closely examining the fractions collected post-purification we observed small amounts of a relatively non-polar product that appeared to form only during the chromatographic step. MS-analysis revealed this to be the desired *N*-Boc-acetophenone **1** and its formation was speculated to be due to decomposition

Keywords: 4-methylene-3,1-benzoaxin-2-one; polymer supported reagents; *ortho*-*N*-Boc-acetophenone; protecting groups.
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Table 1. Formation of 4-methylene-3,1-benzoaxin-2-ones **3a–d**

Compound	R	R	Boc_2O (equiv.)	DMAP (equiv.)	Temperature (°C)	Reaction time (min)	Yield (%)	
							Conv.	Isol.
3a	H	H	1.0	0.1	25	60	46	40
3a	H	H	2.0	0.1	25	60	80	65
3a	H	H	2×1.0	1.0	25	30	82	46
3b	OMe	OMe	2.0	0.1	25	60	80	65
3b	OMe	OMe	2.0	1.0	25	30	86	56
3c	OCH_2O	OCH_2O	2.0	1.0	25	30	99	85
3c	OCH_2O	OCH_2O	2.0	2.0	25	30	80	50
3c	OCH_2O	OCH_2O	2.0	0.1	40	10	65	50
3d	Cl	Cl	2.0	1.0	25	30	99	81

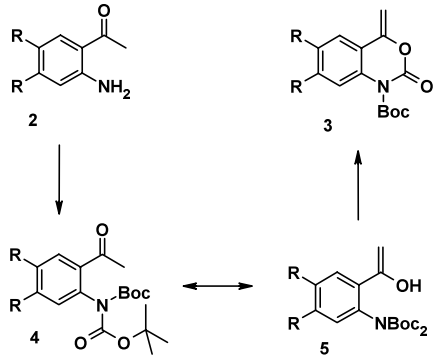


Figure 1. Proposed mechanism for the formation of **3**.

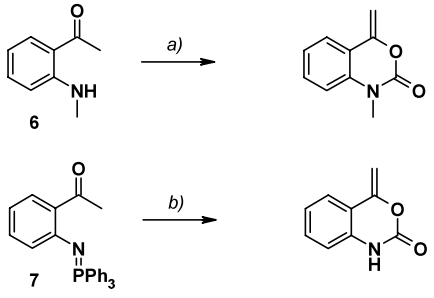


Figure 2. *Reagents and conditions*: (a) $COCl_2$, collidine, toluene, 0°C, 96%; (b) PhCON=C=O, CH_2Cl_2, rt, 30%.

of **3** under the slightly acidic conditions of the silica gel column. Upon testing this hypothesis by (a) stirring the crude reaction mixture in a 1N HCl in THF solution and (b) performing a time-delayed TLC by leaving a 'TLC-spot' on the silica gel TLC-plate for 2 h before 'running the TLC', we observed the near-complete conversion of 4-methylene-3,1-benzoaxin-2-ones **3** into **1** when monitored by TLC and HPLC-MS.

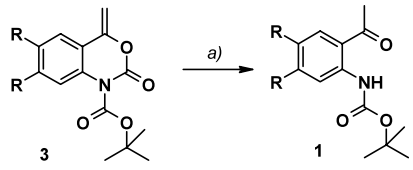
This serendipitous discovery prompted performing these reactions on a preparative scale and, pleasingly, yields up to 95% were recorded for this transformation when screening a small range of acids (Scheme 2).

Silica gel allowed the product to be isolated in good yields albeit with extended reaction times but notably Amberlyst-15 (a strongly acidic polymer supported sulfonic acid) offered much better yields and in shorter reaction times (Table 2). In addition the use of silica-gel or polymer supported acids to catalyse the decomposition of **3** into **1** required no further purification of the products after simple filtration and evaporation of solvent therefore offering an improved access to the desired *N*-Boc-acetophenones **1**.

The growing acceptance of polymer supported reagents[4] as standard reagents in organic synthesis encouraged us to design a *one-pot* method to allow direct access to the desired *N*-Boc-acetophenones **1** without chromatographic purification. Our initial attempt to employ polymer supported DMAP followed by filtration and evaporation of the reaction solvent afforded the 4-methylene-3,1-benzoaxin-2-one **3c** in good yield (75%). Subsequent reaction of **3c** *without purification* using A-15 in CH_2Cl_2 yielded the desired product **1c** in 60% yield.

A *one-pot* reaction was also possible and in the stepwise addition of the reagents [polymer supported DMAP, Boc_2O then after formation of the intermediate **3c** (monitored by TLC and HPLC-MS)] followed by addition of A-15 to the reaction mixture allowed the isolation of the desired product **1c** in 72% yield. A further development of the *one-pot* method was also possible where all reagents were added at the same time. In this case the reaction needed excess of reagents and extended reaction time but, pleasingly, the desired product **1c** was isolated in 56% yield without any purification steps involved (Scheme 3).

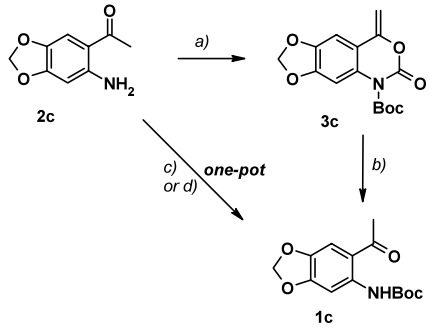
In conclusion a new efficient method for the preparation of *ortho-N*-Boc-arylmethyl ketone derivatives has been developed which involves the intermediacy of 4-methylene-3,1-benzoaxin-2-ones which smoothly convert into the target compounds under acidic conditions.



Scheme 2. *Reagents and conditions*: (a) see Table 2.

Table 2. Acid mediated transformation of **3** to **1**

Adduct	Acid (100 wt%)	Product	Reaction time (h)	Yield (%)
3a	SiO_2	**1a**	48	41
3a	A-15	**1a**	2	75
3a	HCl (1N)	**1a**	2	58
3b	SiO_2	**1b**	24	65
3b	A-15	**1b**	1	95
3c	SiO_2	**1c**	24	60
3c	A-15	**1c**	1	75
3d	SiO_2	**1d**	24	73
3d	A-15	**1d**	1	70



Scheme 3. *Reagents and conditions*: (a) PS-DMAP (2 equiv.), Boc_2O (2 equiv.), CH_2Cl_2, rt, 90 min, 75%; (b) A-15 (100 wt%), CH_2Cl_2, rt, 1 h, 60%; (c) PS-DMAP (2 equiv.), Boc_2O (2 equiv.), CH_2Cl_2, rt, 90 min then A-15 (100 wt%), CH_2Cl_2, rt, 1 h, 72%; (d) PS-DMAP (4 equiv.), Boc_2O (2 equiv.), A-15 (100 wt%), CH_2Cl_2, rt, 12 h, 56%.

This method was found to be applicable to the iterative parallel synthesis of a diverse array of *N*-Boc-acetophenone derivatives and further use of these synthetic intermediates within chemistry programmes will be reported in due course.

Typical experimental procedures and data for representative examples

*Standard methods for cyclisation to 4-methylene-3,1-benzoaxin-2-ones **3** and conversion to ortho-N-Boc-acetophenone **1** derivatives*

1(a) To a solution of 6′-amino-3′,4′-(methylenedioxy) acetophenone **2c** (1.0 g, 5.6 mmol) in CH_2Cl_2 (10 mL) at room temperature under an Argon-flow was added Boc_2O (2.4 g, 11.2 mmol) followed by DMAP (0.7 g, 5.6 mmol) with immediate 'bubbling' in the reaction mixture. After 30 min, the reaction mixture was washed with HCl (1N, 2×10 mL), and the organic layer, separated, dried and evaporated to leave a light yellow oil. Purification by chromatography on silica gel eluting with diethyl ether:hexane (1:1) afforded 8-methylene-6-oxo-8*H*-1,3,7-trioxa-5-aza-cyclopenta[*b*]naphthalene-5-carboxylic acid *tert*-butyl ester **3c** (1.45 g, 85%) as a white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.88 (1H, s), 6.80 (1H, s), 4.78 (2H, m) and 1.61 (9H, s); *m*/*e* (EI) 305.2 (M, 7%), 205.2 (100).

1(b) To a solution of 8-methylene-6-oxo-8*H*-1,3,7-trioxa-5-aza-cyclopenta[*b*]naphthalene-5-carboxylic acid *tert*-butyl ester **3c** (1.0 g, 3.3 mmol) in CH_2Cl_2 (100 mL) was added silica gel (100 g) and the reaction mixture shaken in a rotary shaker for 24 h. The reaction mixture was then filtered, washed with CH_2Cl_2 (20 mL) and the combined organic fractions were evaporated to afford (6-acetyl-benzo[1,3]dioxol-5-yl)-carbamic acid *tert*-butyl ester **1c** (0.55 g, 60%) as a white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.4 (1H, br s), 8.10 (1H, s), 7.20 (1H, s), 5.98 (2H, s), 2.57 (3H, s), 1.51 (9H, s); *m*/*e* (EI) 279.2 (M, 45%), 179.2 (100).

Following a similar method to ***1(a)*** using DMAP (10 mol%) provided 4-methylene-2-oxo-4*H*-benzo[*d*][1,3]-oxazine-1-carboxylic acid *tert*-butyl ester **3a** (0.95 g, 65%) which was isolated as a white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50 (1H, d), 7.35 (1H, t), 7.15 (2H, m), 4.95 (2H, m), 1.60 (9H, s); *m*/*e* (EI) 261.2 (M, 4%), 161.1 (100).

Following a similar method as ***1(b)*** using A-15 (1.0 g) provided (2-acetyl-phenyl)-carbamic acid *tert*-butyl ester **1a** (0.58 g, 75%) which was isolated as a white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.9 (1H, br s), 8.45 (1H, d), 7.87 (1H, dd), 7.51 (1H, t), 7.02 (1H, t), 2.63 (3H, s), 1.51 (9H, s); *m*/*e* (EI) 235.2 (M, 40%), 179.2 (60), 135.2 (100).

Polymer supported DMAP and A-15 method

To a solution of 6′-amino-3′,4′-(methylenedioxy) acetophenone **2c** (1.0 g, 5.6 mmol) in CH_2Cl_2 (10 mL) at room temperature under an Argon-flow was added Boc_2O (2.4 g, 11.2 mmol) followed by polymer supported DMAP (3.74 g, 11.2 mmol) with the immediate evolution of gas in the reaction mixture and the reaction mixture shaken in a rotary shaker for 1.5 h. The reaction mixture was then filtered, washed with CH_2Cl_2 (10 mL) and the combined organic fractions were evaporated to afford 8-methylene-6-oxo-8*H*-1,3,7-trioxa-5-aza-cyclopenta[*b*]naphthalene-5-carboxylic acid *tert*-butyl ester **3c** (1.28 g, 75%) as a white solid. The solid was then dissolved in CH_2Cl_2 (10 mL) and A-15 (1.3 g) added and the reaction mixture shaken in a rotary shaker for 1 h. The reaction mixture was then filtered, washed with CH_2Cl_2 (10 mL) and the combined organic fractions were evaporated to afford (6-acetyl-benzo[1,3]dioxol-5-yl)-carbamic acid *tert*-butyl ester **1c** (0.71 g, 60%) as a white solid. Data as above.

One-pot method with polymer supported DMAP and A-15

To a solution of 6′-amino-3′,4′-(methylenedioxy) acetophenone **2c** (0.1 g, 0.36 mmol) in CH_2Cl_2 (2 mL) at room temperature under an Argon-flow was added Boc_2O (0.16 g, 0.72 mmol) followed by polymer supported DMAP (82 mg, 2.88 mmol) and A-15 (0.1 g) and the reaction mixture shaken in a rotary shaker for 12 h. The reaction mixture was then filtered, washed with CH_2Cl_2 (2 mL) and the combined organic fractions were evaporated to afford (6-acetyl-

benzo[1,3]dioxol-5-yl)-carbamic acid *tert*-butyl ester **1c** (0.06 g, 56%) as a white solid. Data as above.

Acknowledgements

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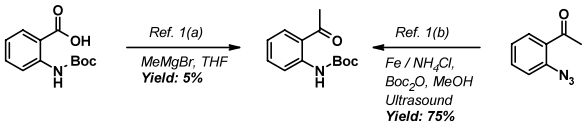
References

1. Two other methods for the preparation of *ortho*-*N*-Boc-acetophenone have been reported: (a) Zwang, P.; Terefenko, E. A.; Slavin, J. *Tetrahedron Lett*. **2001**, *42*, 2097; (b) Chandrasekhar, S.; Narsihmulu, Ch. *Tetrahedron Lett*. **2000**, *41*, 7969.



2. Visser, C. M.; Kellogg, R. M. *Bioorg. Chem*. **1977**, *6*, 79.
3. Molina, P.; Conesa, C.; Alias, A.; Arques, A.; Velasco, M. D. *Tetrahedron* **1993**, *49*, 7599.
4. Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815.