Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Ring Formylation of Bromobenzoate Esters by Direct Metalation

Andrew S. Kende [a] & Min Zhong [a]

[a] Department of Chemistry , University of Rochester , Rochester, NY, 14627

Published online: 17 Sep 2007.

To cite this article: Andrew S. Kende & Min Zhong (1999) Ring Formylation of Bromobenzoate Esters by Direct Metalation, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:19, 3401-3407, DOI: 10.1080/00397919908085967

To link to this article: http://dx.doi.org/10.1080/00397919908085967

SYNTHETIC COMMUNICATIONS, 29(19), 3401-3407 (1999)

RING FORMYLATION OF BROMOBENZOATE ESTERS BY DIRECT METALATION

Andrew S. Kende* and Min Zhong

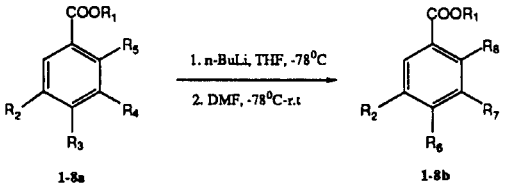
Department of Chemistry, University of Rochester
Rochester, NY 14627

ABSTRACT A study on the synthesis of a benzaldehyde containing an ester function directly from *tert*-butyl 4-lithiobenzate was described. *t*-Butyl 4-bromobenzoate reacted with butyllithium at -78°C in THF, followed by immediate addition of DMF to give the desired benzaldehyde in moderate yield. The scope of this reaction was examined.

The introduction of a CHO group to aromatic rings containing a preexisting COOH or COOR group is not readily achieved by mild electrophilic substitution such as the Vilsmeier Reaction.[1] In connection with our synthetic approach to Spirolactam I,[2] we sought to prepare the trisubstituted aldehyde **1b**. To this end, we followed the procedure of Lampe *et al* [3] starting with *t*-butyl 4-bromo-3,5-dibenzyloxybenzoate (**1a**), followed by lithiation in THF at -78°C and subsequent quenching by DMF to give aldehyde **1b** in 58% yield (**Scheme 1**).

* To whom correspondence should be addressed

Because of our need to prepare several related aldehydes, we explored the scope of this useful reaction. Specifically, we examined whether the observed stability of the *t*-butyl 4-lithio-3,5-dibenzyloxybenzoate at -78°C against self-condensation was the result of the hindered carbonyl of the *t*-butyl ester [4] or of the steric shielding by the two dibenzyloxy group flanking the metalated site.



Scheme 1

Table 1. Results of the formylation reactions by bromide-lithium exchange

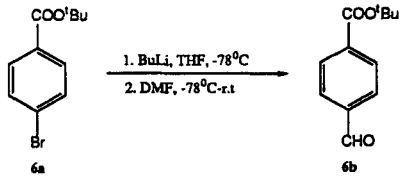
Entry	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Yield
1	OBn	Br	OBn	H	CHO	OBn	H	58%
2	OMe	Br	OMe	H	CHO	OMe	H	58%
3*	OBn	Br	OBn	H	CHO	OBn	H	14%
4	H	Br	OBn	H	CHO	OBn	H	39%
5	H	Br	OMe	H	CHO	OMe	H	43%
6	H	Br	H	H	CHO	H	H	47%
7	H	H	Br	H	H	CHO	H	32%
8	H	H	H	Br	H	H	CHO	0%

* For entry 3, R_1 was benzyl group; for entry 1-2 and 4-8, R_1 were *t*-butyl group.

As shown in Table 1, replacement of the two benzyloxy substituents by methoxy groups led by this sequence to the desired aldehyde **2b** in 58% yield. However, the 3,5-dibenzyloxy benzyl ester gave the aldehyde **3b** in only 14% yield. That the role of the *t*-butyl ester is primary is further demostrated by the

extension of this sequence to a variety of *t*-butyl bromobenzoates including two substrates lacking any alkoxy substituent (**6b, 7b**). Curiously, *t*-butyl 2-bromobenzoate failed to give any aldehyde (**8b**) under these conditions, even though the 3-bromo analog gave a 32% yield of **7b**.

We have also investigated the effects of varying the alkyllithium (**Table 2**), the solvent (**Table 3**) and the amount of base (**Table 4**) in the transformation below.



Scheme 2

Table 2. Effect of alkylithium structure on the formylation reaction

Entry	Substrate/ Base (eq.)	Base	Yield (%)
1	1.0/1.0	*n*-BuLi	43
2	1.0/1.0	*s*-BuLi	48
3	1.0/1.0	*t*-BuLi	42

• THF as solvent

Thus while the role of THF appears to be critical, the other variables above were not significant.

We conclude that the low temperature metalation of a variety of *t*-butyl 3-

Table 3. Effect of solvents on the formylation reaction

Entry	Substrate/ Base (eq.)	Solvent	Yield (%)
1	1.0/1.0	THF	43
2	1.0/1.0	Ether	0
3	1.0/1.0	*n*-Hexane	0

* *n*-BuLi as base

Table 4. Effect of amount of base on the formylation reaction

Entry	Substrate (eq.)	*n*-BuLi (eq.)	Yield (%)
1	1.0	1.1	47
2	1.0	1.0	43
3	1.0	0.9	48

* THF as solvent

bromo and 4-bromobenzoates is a general synthetic route which leads to the corresponding new benzaldehydes in a one-pot reaction in moderate yields.

Experimental

All melting points were determined on MEL-TEMP and are uncorrected. IR and ^{1}H NMR were recorded on Perkin Elmer 1600 and QE 300 GE-Nicolet instruments respectively. Mass spectra were recorded on VG 7070 and HP 5989A by UCR Mass Spectrometry Laboratories. Microanalyses were due by GALBRAITH® Laboratories, Inc..

General Procedure To a solution of the *t*-butyl bromobenzoate (1.0 mmol) in 10 mL dry THF at -78°C under argon was added into *n*-BuLi (1.6 M in hexane,

1.0 mmol), followed immediately by addition of dry DMF (2.0mmol) . The resulting mixture was stirred at -78°C for 30 min and then warmed to r.t and stirred for another hour. Subsequently, the mixture was stirred with 1mL 1M aqueous HCl for 10 min, then the mixture was concentrated and the residue was dissolved in ethyl acetate. The organic phase was washed with sat. $NaHCO_3$ aqueous solution, brine, and dried over $MgSO_4$. The solvent was removed and the residue was purified by chromatography, using silica gel as support, and hexanes/ethyl acetate (10/1(*v/v*)) as mobile phase to give the desired benzaldehyde as described in **Table 1**.

1b. m.p 87-88°C (lit.[3] white foam); IR ($CHCl_3$) 1713, 1686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.64 (*s*, 1H, -C<u>H</u>O), 7.26-7.50 (*m*, 12H,12 × Ar-<u>H</u>), 5.23 (*s*, 4H, 2 × -C<u>H</u>$_2$Ph), 1.60 (*s*, 9H, -C(C<u>H</u>$_3$)$_3$); MS (*m/z*) 418(M^+), 345, 327, 310, 271, 254, 181, 91(100), 65; Anal. Calcd. for $C_{26}H_{26}O_5$: C, 74.62; H, 6.26. Found: C, 74.68; H, 6.44.

2b. m.p 124-125°C; IR ($CHCl_3$) 1716, 1686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.52 (*s*, 1H, -C<u>H</u>O), 7.20 (*s*, 2H, 2 × Ar-<u>H</u>), 3.95 (*s*, 6H, 2 × -C<u>H</u>$_3$), 1.62 (*s*, 9H, -C(C<u>H</u>$_3$)$_3$); MS (*m/z*) 266(M^+), 210, 193, 181, 168, 149, 134, 120, 107, 91, 77, 66, 57(100), 41; HRMS Calcd. for $C_{14}H_{18}O_5$ 266.115424, found 266.115002.

3b. m.p 101-102°C; IR ($CHCl_3$) 1718, 1689 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.64 (*s*, 1H, -C<u>H</u>O), 7.33-7.48 (*m*, 17H,17 × Ar-<u>H</u>), 5.37 (*s*, 2H, -C<u>H</u>$_2$Ph), 5.23 (*s*,

4H, 2 × -C<u>H</u>$_2$Ph); MS (*m/z*) 452(M^+), 361, 344, 253, 181, 91(100), 65; Anal. Calcd. for $C_{29}H_{24}O_5$: C, 76.96; H, 5.35. Found: C, 76.87; H,5.48.

4b. m.p 95-96°C; IR ($CHCl_3$) 1711, 1686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.58 (*s*, 1H, -C<u>H</u>O), 7.88 (*d*, 2H, *J*= 6.0 *Hz*, 2 × Ar-<u>H</u>), 7.72 (s, 1H, Ar-<u>H</u>), 7.63 (*d*, 2H, *J*= 6.0 *Hz*, 2 × Ar-<u>H</u>), 7.37-7.48 (*m*, 5H,5 × Ar-<u>H</u>), 5.25 (*s*, 2H, -C<u>H</u>$_2$Ph), 1.61 (*s*, 9H, -C(C<u>H</u>$_3$)$_3$); MS (*m/z*) 312(M^+), 239, 199, 165, 91(100), 57; Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H,6.45. Found: C,72.96; H,6.57.

5b. m.p 63-64°C; IR ($CHCl_3$) 1711, 1686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.50 (*s*, 1H, -C<u>H</u>O), 7.85 (*d*, 2H, *J*= 6.0 *Hz*, 2 × Ar-<u>H</u>), 7.62 (*s*, 1H, -Ar-<u>H</u>), 7.61 (*d*, 2H, *J*= 9.0 *Hz*, 2 × Ar-<u>H</u>), 3.98 (*s*, 3H, -C<u>H</u>$_3$) 1.61 (*s*, 9H, -C(C<u>H</u>$_3$)$_3$); MS (*m/z*) 236(M^+), 180, 163, 148, 135, 119, 105, 77, 57(100), 41; Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.53; H,7.02.

6b. m.p 48-49°C; IR ($CHCl_3$) 1706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.10 (*s*, 1H, -C<u>H</u>O), 8.16 (*d*, 2H, *J*= 6.0 *Hz*, 2 × Ar-<u>H</u>), 7.95 (*d*, 2H, *J*= 9.0 *Hz*, 2 × Ar-<u>H</u>), 1.62 (*s*, 9H, -C(C<u>H</u>$_3$)$_3$); MS (*m/z*) 207(MH^+), 191, 151, 133, 105, 77, 65, 57(100), 41; Anal. Calcd. for $C_{12}H_{15}O_3$: C, 69.89; H, 6.84. Found: C, 70.20; H, 6.97.

7b. m.p 31-32°C; IR ($CHCl_3$) 1702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.07 (*s*, 1H, -C<u>H</u>O), 8.45 (*s*, 1H, Ar-<u>H</u>), 8.25 (*d*, 1H, *J*= 9.0 *Hz*, Ar-<u>H</u>), 8.05 (*d*, 1H, *J*= 6.0 *Hz*, Ar-<u>H</u>), 7.60 (*t*, 1H, *J*= 7.5 *Hz*, Ar-<u>H</u>), 1.62 (*s*, 9H, -C(C<u>H</u>$_3$)$_3$); MS (*m/z*) 207(MH^+), 191, 151, 133, 105, 77, 65, 57(100), 41; Anal. Calcd. for $C_{12}H_{15}O_3$: C, 69.89; H, 6.84. Found: C, 70.03; H, 6.89.

References and Notes

1. Jones, G.; Stanforth, S. P., in "Organic Reaction" , ed. Paquette, L. A., John Wiley & Sons, Inc., New York, **1997**, *Vol 49*, pp 1-330.

2. Roggo, B. E.; Hug, P.; Moss, S.; Stämpfli, A.; Kriemler, H.-P.; Peter, H. H., *J. Antibiotics*, **1996**, *49*, 374

3. Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H. and Hu, H., *J. Org. Chem.*, **1994**, *59*, 5417

4. Some *t*-Butyl lithiobenzoates were stable and resistant to attack by a wide range of nucleophiles under specific conditions. See, (a). Parham, W. E. and Jones, L. D., *J. Org. Chem.*, **1976**, *41*, 2704. (b). Miller, J. A. *J. Org. Chem.* **1987**, *52*, 322. (c). Frey, L. F.; Tillyer, R. D.; Caille, A.-S.; Tschaen, D. M.; Dolling, U.-H., Grabowski, E. J. J. and Reider, P. J., *J. Org. Chem.*, **1998**, *63*, 3120. (d). Xu, F.; Tillyer, R. D.; Tschaen, D. M.; Grabowski, E. J. J. and Reider, P. J., *Tetrahedron: Asymm.*, **1998**, *9*, 1651

(Received in the USA 17 February 1999)