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Dialkylhydrazides for directed orthometalations

Scott A. Pratt, Michael P. Goble, Michael J. Mulvaney and Peter G. M. Wuts *

Chemical Process Research and Development, 1500-91-201, Pharmacia and Upjohn, Kalamazoo, MI 49001, USA

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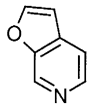
Abstract

Dimethylhydrazides are shown to be excellent substrates for the directed orthometalation reaction. The advantage of using the hydrazide is that it is easily removed by treatment with H_5IO_6 or $CuCl_2$ to give the carboxylic acid under very mild conditions, in contrast to other amides that generally require harshly acidic conditions to achieve hydrolysis. © 2000 Elsevier Science Ltd. All rights reserved.

The process of directed orthometalation is one of the better known methods for the construction of aryl containing molecular frameworks.[1] Among the many groups that have been used in the Dom reaction, the dialkylamides appear to have taken center stage. The primary disadvantage of this group is that harsh conditions are often required for its hydrolysis. The overall problem of hydrolysis of the directing group has recently been addressed by Hawkins who has developed the neopentyl ester as a useful group for the preparation of arylboronic acids, but the application to other derivatives was not described.[2]

During our work on approaches to the synthesis of new clinical candidates we became interested in an approach to the basic furanopyridine skeleton that would rely on the orthofunctionalization of 2-furoic acids. Initial studies with the *t*-Bu amide resulted in products that could not be hydrolyzed even in the presence of a participating hydroxyl group.[3]



The problem with the hydrolysis of the amide stimulated our interest in the possibility of using a dialkylhydrazide as an orthodirecting group,[4] as well as a report that they could be oxidatively cleaved under relatively mild conditions using reagents such as $Pb(OAc)_4$, MnO_2 and $NaIO_4$.[5] They also look much like primary amides, which are excellent orthodirecting groups. Furthermore, chiral hydrazides could be prepared and thus an asymmetric version of the Dom reaction was envisioned.

The concept was tested by preparing the *N*,*N*-dimethylhydrazide of benzoic acid and treating it with *s*-BuLi and TMEDA in THF at −78°C followed by silylation with TMSCl (Scheme 1). We found that the reaction proceeds smoothly giving the desired 2-trimethylsilylhdyrazide in excellent yield. *n*-BuLi

* Corresponding author.

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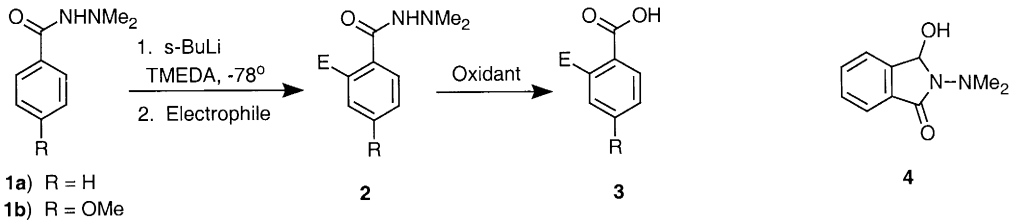
was also tested, but it would not deprotonate the hydrazide at temperatures below −10°C which was determined by reaction calorimetry.[6] A brief survey of a number of standard electrophiles shows that the generality of the process is consistent with the prior art on the use of simple amides. In the case of aldehydes and ketones, lactonization often occurs during the isolation.[7] This result augurs well for the use of this chemistry in the elaboration of furans. A small solvent effect has been observed in the reaction in that in some cases the use of ether results in better yields than when THF is used (Table 1).



1a) R = H
1b) R = OMe

2 **3** **4**

Scheme 1.

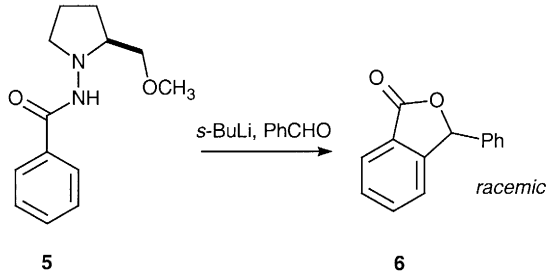
Table 1
Dom reaction of hydrazides and their oxidative cleavage[8]

Entry	Electrophile	Solvent	Yield of 2	Oxidant	% Yield of Acid 3
1a	TMSCl (a)	THF	84-93	$CuCl_2$	15
1a				H_5IO_6	72
1a	DMF (b)	THF	78	-	*
1b	TMSCl (c)	THF	81	-	-
1a	Anisaldehyde (d)	THF	57‡	$CuCl_2$	95
1a				H_5IO_6	93
1a		Ether	N/A	None	94 †
1b	3-Furaldehyde (e)	THF	34	-	-
1a	Cyclohexanone (f)	THF	N/A	None	68 †
1a		Ether	N/A	none	62 †
1a	Methyl iodide (g)	THF	85	$CuCl_2$	83
1a				H_5IO_6	80
1a	Ethyl iodide (h)	THF	62	-	-
1a				H_5IO_6	80
1a	Allyl Bromide (I)	THF	54	H_5IO_6	78
1a		Ether	24	$CuCl_2$	-
1a	Methyl disulfide (j)	THF	74	$CuCl_2$	85
1a		Ether	90.5		-
1a	Chloromethyl methyl ether (k)	THF	64		-

† Isolated as the lactone directly ‡ Some lactonization occurred during isolation * Isolated as **4**

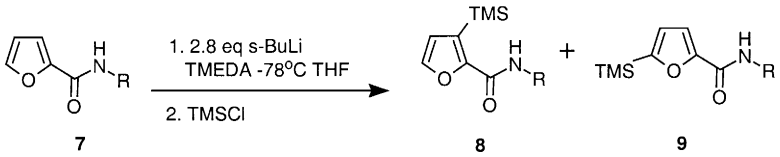
With the availability of Enders' chiral hydrazines, we examined the possibility of inducing asymmetry in a lactone synthesis. Unfortunately, when the hydrazide **5** was metalated and treated with anisaldehyde only the racemic lactone **6** could be isolated from this reaction (Scheme 2).

Barton's original work on the cleavage of the hydrazides utilized primarily $Pb(OAc)_4$ for this type of cleavage. Environmental concerns directed our attention to other oxidants such as periodic acid and



5 6

Scheme 2.



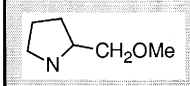
7 8 9

Scheme 3.

$CuCl_2$. The use of $CuCl_2$ to cleave the dimethylhydrazide is new to this study and proceeds with excellent efficiency as illustrated in Table 1.

With the viability of this reaction established, we began to explore the use of the furanyl hydrazides as substrates (Scheme 3). A number of hydrazides were prepared and the regioselectivity of deprotonation was examined by quenching the anions with TMSCl. The results of this study are outlined in Table 2. The observed ratios are quite dependent upon the hydrazide and the base used to effect deprotonation. Dimethyl and diisopropyl hydrazides favor deprotonation at the 5-position with increasing selectivity as the steric bulk of the hydrazine increases. The SAMP hydrazide drives the selectivity more toward the 3-position, which may be a result of the coordinating methoxymethyl group. Currently, the best result is obtained with the morpholine derivative which gives a reasonable 4.3:1 ratio favoring the 3-position when BuLi is used as a base. Changing the base to LDA, which then leads to a 1:4.7 ratio favoring the 5-position, can effectively reverse this.

Table 2
Silylation of 2-furylhydrazides

Hydrazide R =	Ratio(8:9)	Base	Yield
Me_2N (a)	1:2.7*	BuLi	-
$(i\text{-}Pr)_2N$ (b)	1:4.4‡	BuLi	70%
Morpholine (c)	4.3:1‡	BuLi	64%
Morpholine (c)	1:4.7‡	LDA	43%
 (d)	1:1.3‡	BuLi	70.5%

* Ratio determined by NMR ‡ Ratio determined by isolation

Representative procedure: Dissolve **1a** (1.0 g, 6.09 mmol) in diethyl ether (10 mL) under nitrogen, cool to −78°C and add TMEDA (0.708 g, 6.09 mmol), then add *s*-BuLi (1.3 M, 11.7 mL, 15.22 mmol) keeping the temperature below −74°C. After stirring for 3.5 hours, methyl disulfide (1.15 g, 12.18 mmol)

was added. After stirring for 2 more hours, the reaction was allowed to warm to 22°C. Water (10 mL) was added and the layers were separated. The aqueous phase was extracted with methylene chloride (2×10 mL). The organic phases were combined, and washed with water (1×10 mL). The organic phase was dried with magnesium sulfate, filtered and concentrated to afford 1.16 g (90.5%) of the thioether. ^{1}H NMR ($CDCl_3$, 400 MHz at 300 K) δ 2.47 (s, 3H, CH_3), 2.73 (s, 6H, CH_3), 6.92 (s, 1H, NH), 7.20 (t, *J*=7.6, 1H), 7.29 (d, *J*=7.6, 1H), 7.38 (t, *J*=7.6, 1H), 7.51 (d, *J*=7.6, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, 300 K) δ 16.72, 47.46, 125.35, 127.29, 128.74, 130.67, 134.44, 136.36, 166.01. Mp: 125–126°C. HRMS calcd for $C_{10}H_{14}N_2OS+H^+$: 211.0905. Found: 211.0909.

$CuCl_2$ induced cleavage of dimethylhydrazides: To a 50 mL round-bottomed flask with a magnetic stirrer was charged *N*,*N*-dimethyl-2-(methylthio)benzoic hydrazide (250 mg, 1.19 mmol), $CuCl_2$ (480 mg, 3.56 mmol), water (10 mL), and dioxane (10 mL). The reaction was heated to 96°C for 24 hours. The reaction was acidified to a pH of 2 with 10% (v/v) HCl. After adding 10 mL of CH_2Cl_2, the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The organic layers were combined, and washed with water (2×10 mL). After drying the organic layer with $MgSO_4$, and filtering, the organic layer was evaporated by rotary evaporation to yield 170 mg (85%) of a white solid. ^{1}H NMR and ^{13}C NMR analysis confirmed the product to be the known acid. All products of this cleavage were compared to known standards by comparison with spectral data of known compounds.

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6. We wish to thank Don K. Knoechel for this determination.
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8. Analytical data was obtained for all new compounds.