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A Scalable Protocol for the Regioselective Alkylation of 2-Methylcyclohexane-1,3-dione with Unactivated sp^3 Electrophiles

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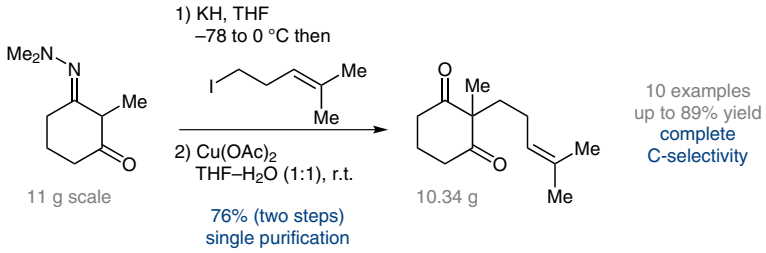

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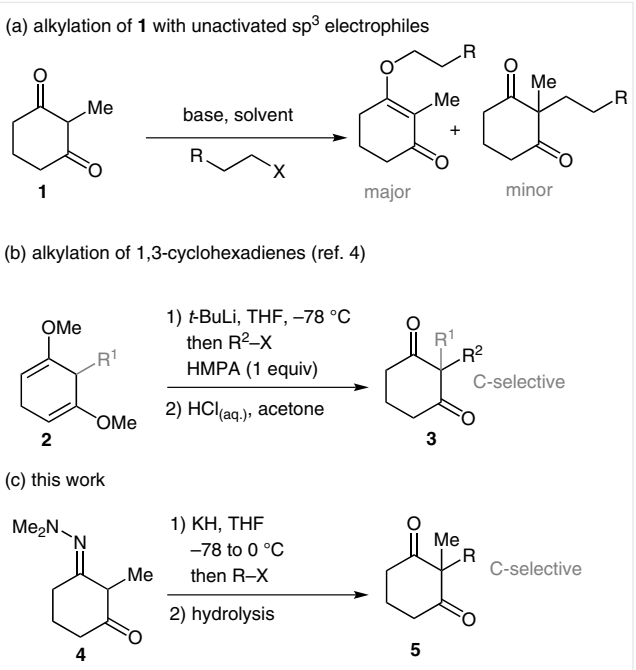
Abstract A method for the C-selective alkylation of 2-methylcyclohexane-1,3-dione with unactivated sp^3 electrophiles is accomplished via alkylation and subsequent deprotection of the derived ketodimethyl hydrazones. The present method provides a high-yielding entry to dialkyl cycloalkanones that cannot be accessed via direct alkylation of 2-methylcyclohexane-1,3-dione. The title reaction may be useful in the scalable preparation of terpene and steroidal building blocks in the arena of natural product synthesis.

Key words alkylation, regioselectivity, hydrazones, ketones, alkyl halides, steroids, terpenoids

The 2,2-dialkylcyclohexane-1,3-dione subunit has seen widespread use as a building block in the preparation of terpene and steroidal natural products.[1] The preparation of these compounds is often accomplished via the alkylation of 2-methylcyclohexane-1,3-dione (**1**, Scheme 1) with activated sp^3 electrophiles (e.g., MeI, $H_2C{=}CHCH_2Br$, BnBr, etc.) or π-electrophiles (e.g. α,β–unsaturated carbonyls). While alkylation with these electrophiles is efficient, the alkylation of **1** with unactivated sp^3 electrophiles is a significant challenge due to preferential O-alkylation in these cases, limiting the effectiveness of this method in target-oriented synthesis.[2] While a number of methods directed toward C-selective alkylation of **1** have been described,[3] these methods have been primarily limited to activated alkyl electrophiles. Piers and others have described preparation of 2,2-dialkylcyclohexane-1,3-diones **3** via alkylation and hydrolysis of 1,5-dimethoxy-1,4-cyclohexadienes **2**;[4] however, the stoichiometric requirements of *t*-BuLi and HMPA limit scalability and practicality of this protocol.

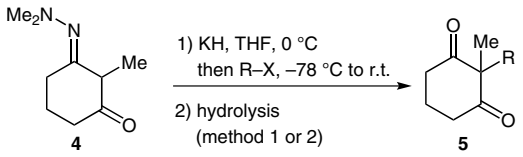


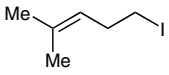
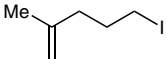
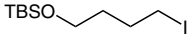
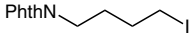
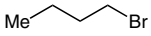
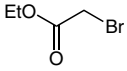
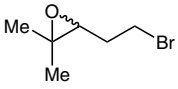
Scheme 1 C-Selective alkylations of 2-alkylcyclohexane-1,3-diones and their derivatives

As part of a research problem in our previously described total synthesis of the indole diterpenoid paspaline,[5] we required an efficient and scalable alkylation of **1** or its derivatives. We were encouraged by the work of Enders and co-workers,[3d,6] which demonstrated C-selective alkylation of cyclic ketohydrazones **4** with activated electrophiles (MeI, $HC{\equiv}CCH_2Br$, BnBr, EtO_2CCH_2Br) and EtI. We found that ketohydrazone **4** gave exclusively C-alkylation even with more hindered and functionalized electrophiles; subse-

quent hydrolysis gave the desired diones **5**. Herein, we describe this extension as a scalable protocol for the preparation of 2,2-dialkylcyclohexane-1,3-diones for use in the arena of natural product synthesis.

Table 1 Substrate Scope of the Alkylation/Hydrolysis of Ketohydrazone **4**[a]

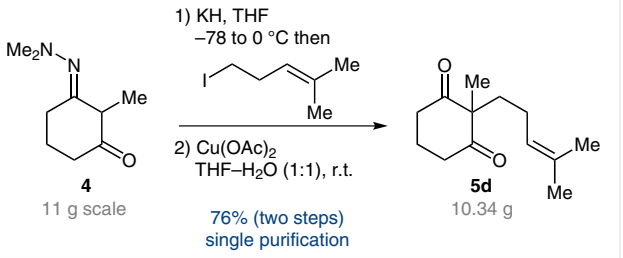


Entry	Alkyl halide	Product	Alkylation yield (%)[b]	Hydrolysis method (yield, %)[c]
1		**5a**	92	1[d] (97)
2		**5b**	81	1 (81)
3		**5c**	90	1 (81)
4		**5d**	78	1 (91)
5		**5e**	92	1 (80)
6		**5f**	90	1 (81)
7		**5g**	0	–
8		**5h**	67	2[e] (63)
9		**5i**	68	1 (78)
10		**5j**	94	2 (80)
11		**5k**	67	1 (77)

[a] Yields refer to isolated analytically pure products. Yields are reported as averages of at least two experiments.
[b] Reactions were carried out with 1.0 mmol alkyl halide, 1.5 mmol **4**, and 1.5 mmol of KH.
[c] Reactions were carried out with 0.5 mmol of intermediate ketohydrazone.
[d] Method 1: $Cu(OAc)_2$ (2.0 equiv), THF–H_2O (1:1), r.t.
[e] Method 2: Oxone (4.0 equiv), acetone–H_2O (1:3), r.t.

A screen of reaction conditions revealed the optimal protocol: Deprotonation of ketohydrazone **4** with KH in THF followed by addition of the electrophile provided access to the intermediate dialkyl ketohydrazones in good yields (Table 1). Hydrolysis of the intermediate alkylation products was completed via Corey's method [$Cu(OAc)_2$, aq THF][7] or upon treatment with Oxone in aqueous acetone.[8] Employing these conditions, alkylation of **4** with 1-iodooctane (entry 1) gave exclusively C-alkylation in 92% yield, which upon hydrolysis, gave diketone **5a** in 97% yield (89%, two steps). Extending the carbon chain in the alkyl iodide (entries 2 and 3) gave the same C-alkylation selectivity in slightly decreased yields. Alkenyl halides (entries 4 and 5) also performed well (78% and 92%, respectively), which upon hydrolysis provided diketones **5d**,**e** bearing valuable functional handles. Alkylation of **4** with an iodide bearing a protected hydroxyl group (entry 6) also underwent efficient alkylation (73%, two steps), although the analogous protected aminoiodide (entry 7) failed to react with **4** under any conditions examined. Secondary alkyl halides (entry 8) also underwent alkylation with complete C-regioselectivity, albeit in decreased yields (42%, two steps) to give diketone **5h**. Furthermore, alkyl bromides (entries 9–11) also underwent C-selective alkylation. The alkyl bromide bearing an electrophilic epoxide functionality (entry 11) underwent alkylation (and not the undesired epoxide opening) to give the corresponding diketone upon hydrolysis (52%, two steps).

To demonstrate the scalability of this protocol, the reaction of ketohydrazone **4** with 5-iodo-2-methylpent-2-ene was carried out on an 11.00 gram (65 mmol) scale with complete C-alkylation selectivity (Scheme 2); the sequence provided >10 grams (76% yield) of diketone **5d** over two steps. Notably, purification of the intermediate alkylated hydrazone was omitted, enabling preparation of **5d** requiring only a single purification. Compound **5d** is a critical intermediate in our previously described total synthesis of paspaline.[5]



Scheme 2 Large-scale synthesis of dialkyldiketone **5d** (10 g scale)

In summary, a practical and scalable alkylation of 2-methyl-1,3-cyclohexanediones using unactivated electrophiles has been enabled via alkylation[9] and deprotection[10,11] of the corresponding ketohydrazones. The scalability and applicability of this protocol has been demonstrated via the 10 gram scale synthesis of diketone **5d**. This methodology may be useful to synthetic chemists in the preparation of 'quaternized' cyclohexane building blocks for natural product synthesis.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560186.

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(9) **Typical Procedure for Alkylation of 4**
KH (30% dispersion in oil, 0.20 g, 1.50 mmol, 1.50 equiv) was washed free of oil with PE and suspended in anhydrous THF (3.0 mL). The suspension was transferred to a flame-dried, 10 mL round-bottomed flask under an atmosphere of N_2, and the suspension was cooled to –78 °C. Hydrazone **4** (0.25 g, 1.50 mmol, 1.50 equiv) was dissolved in THF (1.0 mL) and added dropwise to the KH suspension. The resulting solution was warmed to 0 °C and stirred 4.5 h. The reaction was recooled to –78 °C, and 1-iodooctane (0.18 mL, 1.00 mmol, 1.00 equiv) was added dropwise. The mixture was allowed to stir overnight, allowing the reaction to slowly warm to r.t. as the dry ice bath evaporated. After 14 h, the reaction was quenched via addition of sat. NH_4Cl aq (4.0 mL), and the mixture was partitioned in a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried with $MgSO_4$ and concentrated in vacuo. The product was purified via flash chromatography (hexanes–EtOAc, 80:20 to 70:30) to afford the product ketohydrazone (0.25 g, 91% yield) as a yellow oil.

(10) **Typical Procedure for Hydrazone Hydrolysis (Method 1)**
A 10 mL round-bottomed flask was charged with $Cu(OAc)_2{\cdot}H_2O$ (0.20 g, 1.00 mmol, 2.00 equiv) and H_2O (3.3 mL), and the solution was allowed to stir until complete dissolution of $Cu(OAc)_2{\cdot}H_2O$ was observed, typically 2 min. The intermediate ketohydrazone derived from alkylation of **4** with 1-iodooctane (0.14 g, 0.50 mmol, 1.00 equiv) was dissolved in THF (3.3 mL) and added to the $Cu(OAc)_2{\cdot}H_2O$ solution. The resulting reaction mixture was allowed to stir until complete conversion of the starting material was observed by TLC analysis, typically 12 h. The reaction mixture was concentrated on a rotary evaporator to remove THF, and the remaining solution was quenched with sat. NH_4Cl aq (5 mL) and diluted with CH_2Cl_2 (5 mL). The mixture was partitioned in a separatory funnel, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo. The product was purified via flash chromatography (hexanes–EtOAc, 90:10 to 80:20) to afford diketone **5a** (0.12 g, 99% yield) as a yellow oil.

(11) **Typical Procedure for Hydrazone Hydrolysis (Method 2)**
A 20 mL scintillation vial was charged with acetone (2.0 mL) and Oxone (1.20 g, 2.00 mmol, 4.00 equiv) with magnetic stirring. The intermediate ketohydrazone derived from alkylation of **4** with 2-iodopropane (0.11 g, 0.50 mmol, 1.00 equiv) was dissolved in acetone (0.7 mL) and transferred to the Oxone solution at r.t., producing a white suspension. The resulting mixture was stirred 2 h, whereupon the solution was concentrated on a rotary evaporator to remove the acetone. The remaining solution was diluted with H_2O (5 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (2 × 7 mL) and CH_2Cl_2 (2 × 7 mL), and the combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo. The product was purified via flash chromatography (hexanes–EtOAc, 90:10 to 80:20) to afford diketone **5h** (0.051 g, 65% yield) as a yellow oil.