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Lithiation and Electrophilic Substitution of Dimethyl Triazones

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Abstract

The lithiation and electrophilic substitution of dimethyl triazones is described. Directed lithiation or tin-lithium exchange of dimethyl triazones afforded the corresponding dipole stabilized nucleophiles that were trapped with various electrophiles. Keto-triazone derivatives accessed by acylation of such nucleophiles were readily converted to the corresponding imidazolone heterocycles.

Keywords

Triazone; Lithiation; Urea; Imidazolone; Synthesis

Complex-induced proximity effects have been utilized extensively to functionalize otherwise unactivated sites of a molecule.ⁱ In particular, the metalation and electrophilic substitution of carbon centers adjacent to a nitrogen bearing an electron withdrawing group has been studied extensively,ⁱⁱ and several examples of the directed lithiation of alkyl urea derivatives have been reported.ⁱⁱⁱ However, there have been no previous reports of the lithiation of alkyl triazone derivatives. While triazones have found great utility in protection of primary amines,^{iv} their potential use to mask urea functional groupings has received far less attention.^v In the context of our studies concerning the total synthesis of the agelastatin alkaloids,^{vi} we employed metalated triazone **1** as a synthetic equivalent of metalated urea **2** to access functionalized urea derivative **3** (Scheme 1). Herein, we report our observation on the directed lithiation and electrophilic substitution of 1,3-dimethyl triazones in addition to derivatization of related keto-triazones to the corresponding imidazolone heterocycles.

For these studies, we prepared several 1,3-dimethyl triazones by direct condensation of dimethyl urea (**4**), formalin, and various primary amines (Table 1).^{iva,ivb} Trimethyl triazone **6a** was prepared in 42% yield after purification by vacuum distillation (Table 1, entry 1). The isopropyl and mesityl triazones (**6b** and **6c**) were obtained in 20% and 21% yields, respectively (Table 1, entries 2 and 3). Notably, the benzyl and *p*-toluene triazones **6d** and **6e** were both readily prepared on greater than 30 gram scale in 91% and 71% yield, respectively (Table 1, entries 4 and 5), and could be efficiently purified by recrystallization from hexanes, rendering them particularly attractive urea surrogate from a preparative standpoint.

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We next examined the directed lithiation of 1,3-dimethyl triazones. Treatment of the 1,3-dimethyl triazone derivatives with one equivalent of *s*-butyl lithium at $-78\text{ }^{\circ}\text{C}$ in THF followed by quenching with deuterium oxide afforded the corresponding triazone products with complete deuterium incorporation at the methyl group α to the nitrogen (Table 2). Under optimal conditions the lithiation of the methyl and benzyl triazones **6a** and **6d**, respectively, with *s*-butyl lithium followed by quenching with deuterium oxide afforded the corresponding monodeuterated products in moderate yields (41% and 50%, respectively; Table 2, entries 1 and 3). Unfortunately, these reactions were plagued by the rapid formation of self-condensation byproducts via addition of the lithiated triazone to the C2-carbonyl of another triazone. The yields for the formation of the deuterated benzyl triazone were identical when quenched after 10, 30, or 60 min periods, which suggests that once formed, the lithiated triazone intermediates were stable at $-78\text{ }^{\circ}\text{C}$ for up to one hour (Table 2, entries 3–5). Interestingly, the mesityl and toluyl triazones **6c** and **6e**, respectively, underwent the lithiation and deuteration sequence with greater efficiency to afford the monodeuterated products **7c** and **7e** in 95% and 85% yield, respectively (Table 2, entries 2 and 6). Importantly, we observed that the formation of undesired self-condensation byproducts was significantly suppressed with these substrates. It should be noted that the use of *s*-butyllithium was found to be optimal for the lithiation of dimethyl triazones. Attempted use of *n*-butyllithium as the base additive predominantly led to undesired addition of the butyl group to the C2 carbonyl group of the urea. Alternatively, the use of *t*-butyllithium as the base additive resulted in formation of a complex mixture of products consistent with indiscriminate lithiation of the triazone substrates at undesired positions. Furthermore, metal amides were ineffective as the base additive at $-78\text{ }^{\circ}\text{C}$ and their use at higher temperatures was complicated by decomposition of lithiated triazone intermediates. Finally, inclusion of other common additives such as tetramethylethylenediamine (TMEDA) or hexamethylphosphoramide (HMPA) in combination with *s*-butyllithium gave no clear advantage.

We then evaluated the reactivity of various electrophiles with the lithiated triazones (Table 3). The lithiated triazones underwent nucleophilic addition to α,β -unsaturated aldehydes (Table 3, entry 1–3) and benzaldehyde (Table 3, entry 4) in moderate yields (47–70%). Methyl ester derivatives were suitable electrophiles for this chemistry and afforded the corresponding keto-triazone products (Table 3, entries 5–13). The use of 2.5 equivalents of the triazone nucleophile resulted in full and efficient conversion of methyl benzoate (**12**) to ketone **22** (Table 3, entry 5). In more challenging cases, an increase in the equivalents of the nucleophile led to an increase in the yield of the desired adduct (Table 3, entries 6–8, and 11–12). The use of excess lithiated triazone allowed for the generation of the desired keto-triazones **25c** and **25e** from methyl ester **15**, which contains an acidic lactam N–H proton (Table 3, entry 11–13). However, when a large excess of lithiated triazone was used, we sometimes observed the formation of minor double-addition byproducts. The lithiated triazone could also be trapped with trialkyltin chlorides to afford versatile and stable α -stannylated triazones **26d–e** and **27d–e** (Table 3, entry 14–17)–substrates that allowed for a more practical C–C bond formation (*vide infra*).^{vii,viii}

Despite the successful direct lithiation of 1,3-dimethyl triazones described above, the formation of triazone self-condensation byproducts complicated the reaction, and an excess of the triazone was needed to form the desired products efficiently (Table 3, entries 8 and 10). In order to address this issue, we evaluated whether tin-lithium exchange could generate the lithiated triazones with greater efficiency.^{ix} When stannyl triazone **26d** was treated with one equivalent of *n*-butyllithium at $-78\text{ }^{\circ}\text{C}$ in THF, the desired lithiated triazone intermediate was obtained quantitatively. *Importantly, the rapid rate of tin-lithium exchange completely suppressed the formation of self-condensation byproducts.* This method required only two equivalents of lithiated triazone (via tin-lithium exchange) to convert methyl ester

14 to ketone **24d** in 74% yield (Table 4, entry 1) as compared to the six equivalents required using the direct lithiation route (Table 3, entry 10). Additionally, conversion of methyl ester **15** to the corresponding keto-triazone **25** using reagents generated through tin-lithium exchange afforded the desired keto-triazone products in higher yields than the direct lithiation protocol previously described (Table 4, entries 2–4).

Finally, we investigated the synthesis of imidazolones from keto-triazones.^{vi,x} To our delight, the triazone moiety in **28** could be readily hydrolyzed in the presence of aqueous hydrochloric acid in methanol at 23 °C. The 2,3-disubstituted imidazolone **30** was obtained in 83% yield through a condensative cyclization of a putative keto-urea intermediate **29** (Scheme 2).^{vi,xi}

The alkylation of these versatile keto-triazones provides an expedient route to trisubstituted imidazolones. For example, the methylation of keto-triazone **31** occurred efficiently via its deprotonation with sodium hydride followed by treatment of the corresponding enolate with methyl iodide to afford keto-triazone **32** in 91% yield (Scheme 3). When the methylated keto-triazone **32** was treated with aqueous hydrochloric acid in methanol at 63 °C, 2,4-dimethyl-3-phenyl imidazolone **33** was obtained in 100% yield.

In summary, we have described the utility of 1,3-dimethyl triazones in the introduction of a urea functional grouping through directed lithiation to afford dipole-stabilized lithiated triazone intermediates that can be trapped with various electrophiles (Table 3). We have also shown that stannylated triazones prepared from such lithiated triazones provide a highly efficient source of the desired lithiated triazones and can lead to significant improvement in more complex unions (Table 4). The resulting keto-triazones not only provide further opportunity for introduction of additional substituents but they also serve as excellent precursors for the corresponding imidazolone heterocycles.

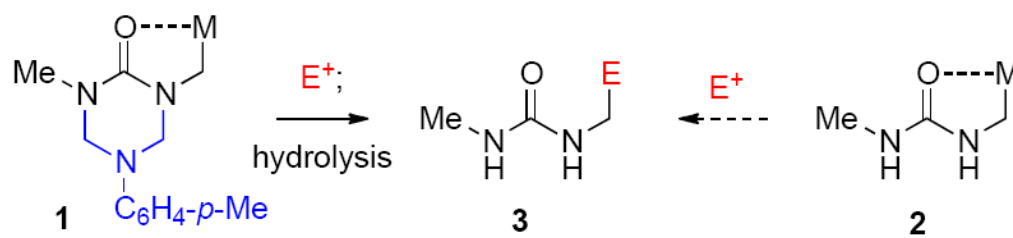
Acknowledgments

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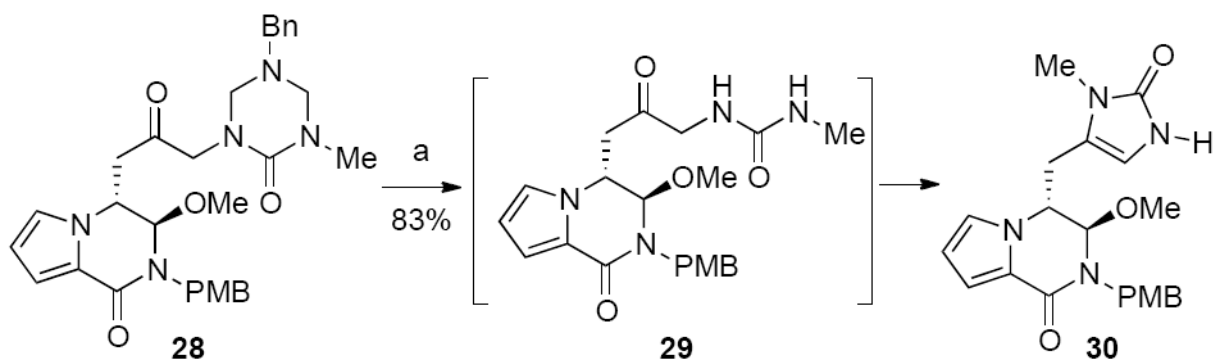
References

- i. Beak P, Meyers AI. *Acc Chem Res.* 1986; 19:356.. For a review, see: Whisler MC, MacNeil S, Snieckus V, Beak P. *Angew Chem Int Ed.* 2004; 43:2206.
- ii. Beak P, Zajdel WJ. *Chem Rev.* 1984; 84:471.
- iii. Hassel T, Seebach D. *Helv Chim Acta.* 1978; 61:2237. Resek J, Beak P. *J Am Chem Soc.* 1994; 116:405. Anderson DR, Faibish NC, Beak P. *J Am Chem Soc.* 1999; 121:7553. Clayden J, Turner H, Pickworth M, Adler T. *Org Lett.* 2005; 7:3147. [PubMed: 16018607] Clayden J, Dufour J, Grainger DM, Helliwell M. *J Am Chem Soc.* 2007; 129:7488. [PubMed: 17521189] Bach R, Clayden J, Hennecke U. *Synlett.* 2009:421. Smith K, El-Hiti GA, Hegazy AS, Kariuki B. *Beilstein J Org Chem.* 2011; 7:1219. [PubMed: 21977206] . For an example of directed lithiation of DMPU, see: Sun X, Collum DB. *J Am Chem Soc.* 2000; 122:2459.
- iv. (a) Knapp S, Hale JJ, Bastos M, Gibson BF. *Tetrahedron Lett.* 1990; 31:2109. (b) Knapp S, Hale JJ, Bastos M, Moline A, Chen KY. *J Org Chem.* 1992; 57:6239. (c) Knight SD, Overman LE, Pairaudeau G. *J Am Chem Soc.* 1993; 115:9293. (d) Pearson WH, Lee IY, Mi Y, Stoy P. *J Org Chem.* 2004; 69:9109. [PubMed: 15609944]
- i. (a) Shimizu LS, Smith MD, Hughes AD, Shimizu KD. *Chem Comm.* 2001:1592. [PubMed: 12240397] (b) Xu Y, Smith MD, Krause JA, Shimizu LS. *J Org Chem.* 2009; 74:4874. [PubMed: 19462988] (c) Tian L, Wnag C, Dawn S, Smith MD, Krause JA, Shimizu LS. *J Am Chem Soc.* 2009; 131:17620. [PubMed: 19908868]
- vi. Movassaghi M, Siegel DS, Han S. *Chem Sci.* 2010; 1:561. [PubMed: 21218186]

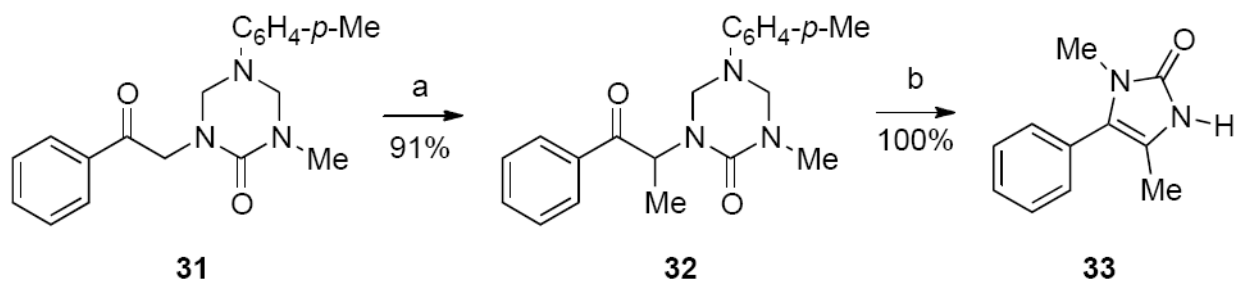
- vii. For the use of **27e** in the copper mediated cross-coupling reaction with a key thioester, see: reference 6.
- viii. Representative experimental procedure for lithiation and electrophilic trapping of a dimethyl triazone–synthesis of stannyltriazone **27e**: To a solution of triazone **6e** (10.0 g, 46.0 mmol, 1 equiv) in tetrahydrofuran (400 mL) at $-78\text{ }^{\circ}\text{C}$ under an argon atmosphere was added *s*-butyllithium (1.4 M in cyclohexane, 34.5 mL, 48.0 mmol, 1.05 equiv) rapidly via cannula. After 10 min, the resulting bright orange mixture was transferred via cannula over a 15 min period to a solution of tricyclohexyltin chloride (20.3 g, 50.0 mmol, 1.10 equiv) in tetrahydrofuran (400 mL) at $-78\text{ }^{\circ}\text{C}$. After 1.5 h, saturated aqueous ammonium chloride solution (100 mL) was added via syringe, and approximately 80% of the volatiles were removed by concentration of the mixture under reduced pressure. The residue was partitioned between dichloromethane (800 mL) and water (800 mL). The layers were separated, and the organic layer was washed with brine (800 mL), was dried over anhydrous sodium sulfate, and was concentrated under reduced pressure. The crude residue absorbed onto silica gel was loaded as a solid, and was purified by flash column chromatography (silica gel: diam. 6 cm, ht. 15 cm; eluent: hexanes then 10% ethyl acetate in hexanes) to afford stannyltriazone **27e** (12.1 g, 45%) as a white solid. ^1H NMR (500 MHz, CDCl_3 , $20\text{ }^{\circ}\text{C}$): δ 7.07 (app-dd, $J = 8.7, 0.7\text{ Hz}$, 2H), 6.89 (app-d, $J = 8.5\text{ Hz}$, 2H), 4.60 (s, 2H), 4.58 (s, 2H), 2.85 (s, 3H), 2.78 (t, $J = 12.2\text{ Hz}$, 2H), 2.27 (s, 3H), 1.82-1.74 (m, 6H), 1.65-1.56 (m, 9H), 1.52-1.13 (m, 18H). ^{13}C NMR (125.8 MHz, CDCl_3 , $20\text{ }^{\circ}\text{C}$): δ 156.3, 146.1, 132.2, 130.0, 119.5, 69.2, 67.3, 32.7, 32.3, 29.5, 28.7, 27.9, 27.4, 20.8. FTIR (neat) cm^{-1} : 2915 (s), 2844 (s), 1636 (s), 1515 (s), 1444 (s), 1407 (m), 1299 (s), 1201 (m), 991 (m). HRMS (m/z): calc'd for $\text{C}_{30}\text{H}_{50}\text{N}_3\text{OSn}$, $[\text{M}+\text{H}]^+$: 588.2987, found: 588.2982. TLC (15% ethyl acetate in hexanes), R_f 0.20 (CAM, UV).
- ix. (a) Peterson D. J Organometal Chem. 1970; 21:63.(b) Pearson WH, Lindbeck AC, Kampf JW. J Am Chem Soc. 1993; 115:2622.
- x. Zav'yalov SI, Ezhova GI, Kravchenko NE, Kulikova LB, Dorofeeva OV, Rumyantseva EE, Zavozin AG. Pharm Chem J. 2004; 38:256.
- xi. (a) Marckwald W. Chem Ber. 1892; 25:2354.(b) Duschinsky R, Dolan LA. J Am Chem Soc. 1946; 68:2350. [PubMed: 21002238]

**Scheme 1.**

Use of the metalated triazone **1** as a synthetic equivalent of a metalated urea **2**.

**Scheme 2.**

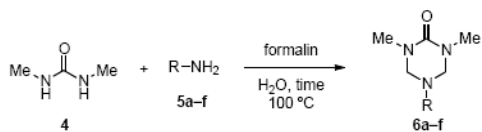
Formation of imidazolone **30** from keto-triazone **28**. Reagents and Conditions: (a) 0.5 N HCl (2 equiv), MeOH, 23 °C, 83%. PMB: *p*-methoxybenzyl

**Scheme 3.**

Formation of trisubstituted imidazolone **33**. Reagents and Conditions: (a) NaH (1.2 equiv), MeI (2 equiv), DMF, 0→23 °C, 91%; (b) 0.5 N HCl (2 equiv), MeOH, 63 °C, 100%.

Table 1

Synthesis of triazones



Entry	Amine	Time (h)	Yield of 6 (%)
1	5a , R = Me	24	42 ^a
2	5b , R = <i>i</i> -Pr	24	20 ^b
3	5c , R = Mesityl	48	21 ^b
4	5d , R = Bn	17	91 ^c
5	5e , R = C ₆ H ₄ - <i>p</i> -Me	19	71 ^c

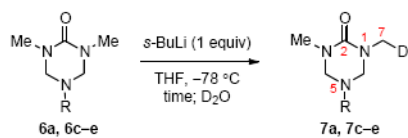
^aPurified by distillation.

^bPurified by silica gel flash column chromatography.

^cPurified by recrystallization from hexanes.

Table 2

Directed lithiation and deuterium incorporation of 1,3-dimethyl triazone



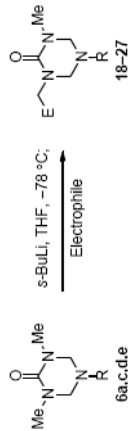
Entry	Substrate	Time (min)	Yield of 7^a (%)
1	6a , R = Me	10	41
2	6c , R = Mes	15	95
3	6d , R = Bn	10	50
4	6d , R = Bn	30	50
5	6d , R = Bn	60	50
6	6e , R = C ₆ H ₄ - <i>p</i> -Me	15	85

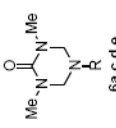
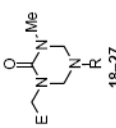

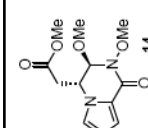
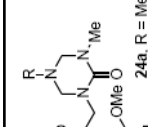
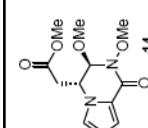
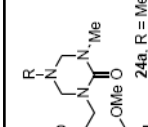
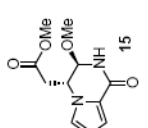
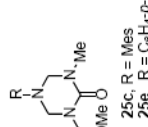
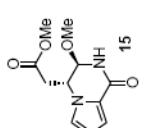
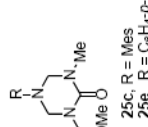
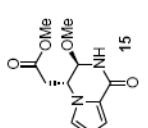
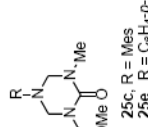

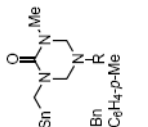

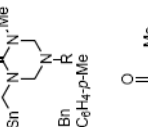

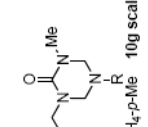

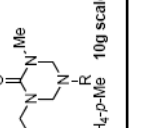
^aProducts showed complete monodeuterium incorporation at C7.

Table 3

Triazone addition to various electrophiles

Entry	Substrate	Electrophile	Triazone (equiv)	Product	Yield ^d (%)
1 ^b	6d		2		70
2 ^b	6d		2		17
3 ^b	6d		1.7		47
4 ^b	6d		1.7		65
5	6a		2.5		91
6 ^b	6d		2		21
7 ^b	6d		4		49
8 ^b	6d		6		70



Entry	Substrate	Electrophile	Triazone (equiv)	Product	Yield ^d (%)
9					
10 ^b	6a		2		37
	6d		6		80
11	6c		3.5		50
12	6c		4		72
13 ^c	6e		4		65
14 ^d	6d		1		45
15 ^e	6e		1		64
16	6d		2		90
17 ^e	6e		1		45

^a Isolated yield after purification.

^b TMEDA (2 equiv) was used as an additive.

^c HMPA (2 equiv) was used as an additive.

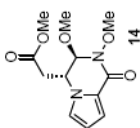
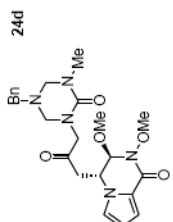
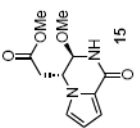
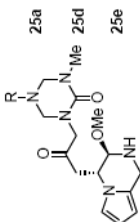
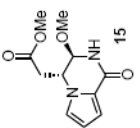
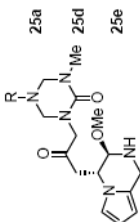
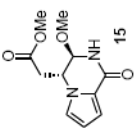
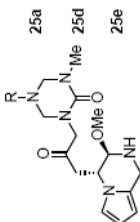
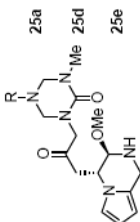
^d 1.5 equivalent of trialkyltin chloride was used.

^e 1.1 equivalent of trialkyltin chloride was used.

Mes: mesityl

Table 4

Nucleophilic addition of the lithiated triazone obtained by tin-lithium exchange

Entry	Substrate	Electrophile	Stannane(equiv)	Product	Yield ^a (%)
1	26d , R = Bn		2		74
2	26a , R = Me		3		62
3	26d , R = Bn		3.5		83
4	26e , R = C ₆ H ₄ - <i>p</i> -Me		3.5		80
			3.5		80

^a Isolated yield after purification.