Direct Carbon–Carbon Bond Formation via Soft Enolization: A Facile and Efficient Synthesis of 1,3-Diketones

2007 Vol. 9, No. 21 4139–4142

ORGANIC LETTERS

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Received July 7, 2007

ABSTRACT

MgBr₂·OEt₂, *i*-Pr₂NEt,

$R \xrightarrow{O} + X \xrightarrow{R^2} R^2 \xrightarrow{CH_2Cl_2 (untreated),} O \xrightarrow{O} O \xrightarrow{O} O$ $R \xrightarrow{H^1} + X \xrightarrow{R^2} R^2 \xrightarrow{CH_2Cl_2 (untreated),} O \xrightarrow{O} O \xrightarrow{O} O$

Ketones undergo soft enolate formation and acylation on treatment with MgBr₂·OEt₂, *i*-Pr₂NEt, and various acylating agents to give 1,3diketones. The process is particularly efficient for *N*-acylbenzotriazoles and *O*-Pfp esters, and, in these cases, is conducted with untreated, reagent-grade CH₂Cl₂ open to the air, thus providing an exceptionally simple approach to the synthesis of this important class of compounds.

1,3-Diketones are important compounds in synthetic organic chemistry.^{1,2} They are widely represented in natural products, pharmaceuticals, and other biologically relevant compounds, or are key intermediates en route to such species.¹ Indeed, their interesting and at times unusual chemical properties are often used to facilitate other synthetic methods, including the preparation of heterocycles and other aromatic compounds.² Many naturally occurring 1,3-diketones exhibit biological activity including antioxidant, antitumor, antimicrobial, antiviral, and antifungal activity.¹ Despite their prevalence, the synthesis of 1,3-diketones remains problematic. As part of an ongoing program aimed at developing operationally simple approaches to key carbon-carbon bondforming reactions via soft enolization, we have developed a method for 1,3-diketone synthesis that resolves the longstanding problems associated with their preparation. In our approach, a ketone and either an N-acylbenzotriazole or O-Pfp ester are combined with MgBr₂•OEt₂ and *i*-Pr₂NEt in untreated, reagent-grade CH₂Cl₂ open to the air. Prior enolate formation and the use of a large excess of enolate and acylating agent are avoided, making the method both facile and efficient compared to conventional approaches.

Considerable research has been conducted over the years on the development of methods for the synthesis of 1,3diketones.¹ The classic procedure, which is a modification of the well-known Claisen condensation,³ involves acylation of a ketone by an ester in the presence of an alkoxide base.¹ This method has limited substrate scope, gives only modest to good yield, requires a large excess of the acylating agent, and often requires elevated temperatures and/or removal of the alcohol produced. Coupling yields are generally improved through the use of at least 2 equiv of sodium or lithium hydride in place of the alkoxide, but this approach is not applicable to substrates having even weakly acidic functionality elsewhere in the reactants. The current procedure of choice for 1,3-diketone synthesis uses a strong, nonnucleophilic base such as LDA to preform the required enolate, which is followed by addition of the acylating agent, typically as an acid chloride. Yields generally improve under these conditions, but the presence of acidic functionality elsewhere in the reactants remains an issue. Furthermore, competing *O*-acylation and bis-acylation are common.³ The major drawback of this method is that at least 2-3 equiv of the enolate are required, making it inherently inefficient.³ This stems primarily from the fact that the 1,3-diketone product is significantly more acidic ($pK_a \approx 9$) than the parent ketone (p $K_a \approx 20$), so, as it forms, it protonates the unreacted ketone enolate preventing acylation.

Kel'in, A. V. Curr. Org. Chem. 2003, 7, 1691–1711.
 Kel'in, A. V.; Maioli, A. Curr. Org. Chem. 2003, 7, 1855–1886.

⁽³⁾ Smith, M. B.; March, J. March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 6th ed.; Wiley & Sons: Hoboken, NJ, 2007; Chapter 16.

We reasoned that the inefficiency of these conventional methods could be overcome if the required enolates were formed under soft rather than hard conditions. In hard enolization the required enolates are preformed by treatment with a strong, non-nucleophilic base such as LDA (Scheme 1). While effective, these stepwise procedures are time-



consuming, particularly if enolate trapping is involved, and require that all manipulations be conducted under anhydrous conditions and, when strong bases are used, at low temperatures. An alternative is soft enolization (Scheme 1), which does not employ a strong base and, consequently, can be conducted under less stringent conditions (e.g., open to the air, untreated solvent, rt)⁴ than are required of hard enolization. In soft enolization, a weak base and a Lewis acid act in concert to effect deprotonation reversibly. Here, the Lewis acid interacts with the carbonyl oxygen to polarize it beyond its normal state, resulting in a substantial increase in the acidity of the α -proton, to the extent that it can be removed appreciably by the weak base. Since enolization in this case is reversible, it is conducted in a direct fashion in the presence of the electrophilic species, further simplifying the procedure. In addition, when applied in acylation reactions the β -dicarbonyl product (3, $E = COR^2$, Y = alkyl/aryl, Scheme 1) that forms would not be expected to interfere in a detrimental way, as in situations employing hard enolization. Deprotonation of this species by the ketone enolate (cf. 5, Y = alkyl/aryl) would undoubtedly occur, but in a reversible sense such that the intended ketone enolate could reform and eventually undergo the desired acylation. Given the relatively weak nucleophilic nature of the dicarbonyl enolate, bis-acylation should not occur with appropriate choice of acylating agent.

We recently reported the initial stages of development of an efficient MgBr₂•OEt₂-promoted direct aldol addition of simple thioesters based on soft enolization.⁴ The reaction is conducted with inexpensive MgBr₂•OEt₂ in untreated, reagentgrade solvent open to the air, and produces innocuous byproducts on workup. Given the efficiency, mildness, and operational simplicity of this reaction, we felt that it might provide the basis for workable solutions to the aforementioned problems associated with the synthesis of 1,3diketones.

To explore the use of soft enolization in 1,3-diketone synthesis, acetophenone (6) was combined with benzoyl chloride (7), MgBr₂·OEt₂, and *i*-Pr₂NEt in CH₂Cl₂ (Scheme 2). The desired 1,3-diketone (8) was indeed isolated from



this reaction in very good yield (83%) after only 1 h. A control experiment was carried out in which acetophenone and benzoyl chloride were combined in CH₂Cl₂ in the presence of *i*-Pr₂NEt but in the absence of MgBr₂•OEt₂, with no coupled product observed after 24 h, thus confirming the essential nature of the Lewis acid in enolization. Encouraged by the result with MgBr₂·OEt₂, we conducted a similar reaction with the aliphatic system, 3,3-dimethylbutanoyl chloride (9). In this case the desired product (10) was also obtained, but in a somewhat lower yield (65%). Use of pentanoyl chloride (11) as the acylating agent also gave the desired β -diketone (12), albeit in a much lower yield (30%) due to formation of the α,α -bis-acylation byproduct (13), as is typical when acid chlorides are used in enolate acylations. None of the reactions showed any improvement in yield when left for greater than 1 h.

Significantly, in the two reactions involving **9** and **11**, no products were detected corresponding to self-acylation of the acid chloride (**14** or **15**, respectively, Scheme 3). This is

Scheme 3. Mechanistic Considerations in the MgBr₂·OEt₂-Promoted Direct Acylation with Acid Chlorides $R \rightarrow CO_2H$ $R \rightarrow R$ $R \rightarrow R$

understandable if it is assumed that the reaction is facilitated by coordination of Mg²⁺ to the carbonyl oxygen $(1 \rightarrow 16)$, followed by deprotonation to form the enolate $(16 \rightarrow 17)$, rather than on the basis of α -proton acidity alone. In such a case, despite greater acidity predicted for the acid chloride α -protons (1, Y = Cl) compared to the ketone (1, Y = alkyl/ aryl), its relatively electron deficient carbonyl oxygen would be less prone to coordination to the electrophilic metal salt (1 \rightarrow 16, Y = Cl) and, correspondingly, enolate formation,

⁽⁴⁾ Zhou, G.; Yost, J. M.; Coltart, D. M. Synthesis **2007**, 478–482. Yost, J. M.; Zhou, G.; Coltart, D. M. Org. Lett. **2006**, 8, 1503–1506.

compared to the ketone. This model is also consistent with the lack of reactivity observed in the control experiment described above, in which MgBr₂•OEt₂ was omitted for the reaction.

To improve the yield for the aliphatic systems, we undertook an investigation into the effect of the acylating component on the outcome of the reaction. To do this we screened a variety of known acylating agents both with and without added DMAP⁵ as a nucleophilic acylation catalyst. The results are summarized in Table 1. Addition of DMAP



\prec	$ \bigvee_{X + Ph}^{O} Ph \frac{Mg}{i \cdot Pr_2 N} $	Br ₂ ·OEt ₂ , NEt, CH ₂ Cl ₂		D ↓ Ph
	1	nucleophilic	time	yield
entry	acylating agent	acylation catalyst	(h)	(%)
1	$9, \mathbf{X} = \mathbf{Cl}$		1	63
2	9, $X = Cl$	DMAP	1	65
3	18 , $X = O$ -succinimide			\mathbf{NR}
4	$19, X = SC_6H_4-4-NO_2$		24	40
5	$19, X = SC_6H_4-4-NO_2$	DMAP	24	39
6	20 , $X = OC_6F_5$		12	79
7	$20, \mathbf{X} = \mathbf{OC}_6\mathbf{F}_5$	DMAP	12	80
8	$20, \mathrm{X} = \mathrm{OC}_6\mathrm{F}_5$		24	92
9	$21, \mathbf{X} = $ benzotriazole		3	96
10	$21, \mathbf{X} = $ benzotriazole	DMAP	3	92

was uniformly of no benefit with regard to either the time required for the reaction or the yield produced (entries 2, 5, 7, and 10). *O*-Succinimide ester **18** failed to react altogether, and while thioester **19** did produce the desired product, yields were lower than for the corresponding acid chloride (**9**). *O*-Pfp ester **20** proved to be a suitable acylating agent, giving 79% yield of the β -diketone within 12 h and 92% within 24 h. Even better yields and shorter reaction times resulted from the use of *N*-acylbenzotriazole **21**. Thus, both *O*-Pfp esters⁶ and *N*-acylbenzotriazoles were investigated in our subsequent studies.

Another compelling reason for the use of *O*-Pfp esters and *N*-acylbenzotriazoles in this reaction is that, unlike acid chlorides, they are relatively insensitive to moisture. This trait would potentially allow us to conduct the coupling reactions open to the air using untreated, reagent-grade CH₂-Cl₂, resulting in even greater simplification of the procedure. To test this, *N*-acylbenzotriazole **21** and *O*-Pfp ester **20** were each combined with acetophenone, MgBr₂·OEt₂, and *i*-Pr₂-NEt with use of untreated, reagent-grade CH₂Cl₂ open to the air. Under these conditions the desired 1,3-dicarbonyl product (**10**) was obtained with no change in either the isolated yield or reaction time, in comparison to the use of

Table 2.	MgBr ₂ ·OEt ₂ -Promoted Coupling with Untreated
Solvent O	pen to the Air

R	C ↓ X + ∕	O MgB I <i>i</i> -Pr ₂ NE	$\begin{array}{ccc} r_2 \cdot OEt_2, & OEt_2\\ \hline Et, \ CH_2 Cl_2 \\ \hline \hline \end{array} \\ \hline \end{array} \\ \begin{array}{c} B \end{array}$	D O Pr	n
entry	X	R	1,3-diketone	time (h)	yield (%)
1	Bt	CH₂ <i>t</i> -Bu	10	2.5	96
2	<i>O</i> -Pfp	CH ₂ t-Bu	10	24	92
3	Bt	t-Bu	22	4	99
4	<i>O</i> -Pfp	t-Bu	22	24	81
5	Bt	Ph	8	2.5	95
6	<i>O</i> -Pfp	Ph	8	24	87
7	Bt	TBSO	23	4	91
8	<i>O</i> -Pfp	l Ph	23	24	86
9	Bt	Bu	12	2.5	79
10	<i>O</i> -Pfp	Bu 🕋	12	24	61
11	O-Pfp	BocHN 🖰 Bn	24	24	73
12	Bt	CH ₂ CH ₂ CHC	CH ₂ 25	3	70
13	<i>O</i> -Pfp		CH ₂ 25	24	53
14	Bt	(<i>E</i>)-CHĈHPh	26	2.5	81

dry CH_2Cl_2 and an Ar atmosphere (see Table 2, entry 1). As such, this protocol was employed for the remainder of our work.

Having secured a mild and straightforward method for the synthesis of β -diketone **10**, we determined the scope of the method with respect to other *N*-acylbenzotriazoles and *O*-Pfp esters (see Table 2). In general, the *N*-acylbenzotriazoles outperformed the *O*-Pfp esters in terms of both reaction time and yield. The isolated yields were typically excellent when *N*-acylbenzotriazoles were used. Significantly, the coupling reaction could be carried out in the presence of an acidic urethane nitrogen protecting group (entry 11), and also in the presence of an enone (entry 14), without detrimental results, as would be expected in the corresponding hard enolization processes.

We next explored the scope of the coupling reaction using a variety of ketones with various N-acylbenzotriazoles and O-Pfp esters (see Table 3). Once again, in all cases the desired 1,3-diketone was obtained in good to excellent yield. Notably, the coupling could be conducted with cyclohexanone as the nucleophile to give the corresponding monosubstituted 1,3-diketone (33) in excellent yield (entry 13). Entries 11 and 12 reveal that the process is even compatible with the presence of phenolic functionality. Such a substrate would not be amenable to traditional coupling methods without prior incorporation of a phenol protecting group. A significant result is shown in entry 18 where 1-[(E)cinnamoyl]-1H-benzotriazole and 3-pentanone were coupled to give the desired 1,3-dicarbonyl (35) without subsequent cyclization to the corresponding 1,3-cyclohexanedione (36), as is typical of such systems.¹ To further explore the versatility of our method, we undertook the synthesis of 23 in an inverse sense by switching the respective ketone and acylbenzotriazole. Thus, methyl ketone 37 was prepared according to known procedures⁷ and was subjected to the coupling with 1-benzoylbenzotriazole. β -Diketone 23 was

⁽⁵⁾ Scriven, E. F. V. Chem. Soc. Rev. **1983**, *12*, 129–161. Spivey, A. C.; Arseniyadis, S. Angew. Chem., Int. Ed. **2004**, *43*, 5436–5441.

⁽⁶⁾ The pentafluoro phenol ($pK_a \approx 5$) produced in the coupling reaction can be recovered by extraction into saturated aqueous NaHCO₃, followed by neutralization (10% HCl) and back extraction (EtOAc).

⁽⁷⁾ Vries, E. F. S.; Steenwinkel, P. J. Org. Chem. 1993, 58, 4315-4325.

 Table 3.
 MgBr₂·OEt₂-Promoted Coupling with Untreated

 Solvent Open to the Air

			MgB <i>i</i> -Pr ₂ NB	r₂·OEt₂, Et, CH₂Cl₂			
		n R ¹		-	R ¹	n-	
entry	R	х	R ¹	R ²	1,3- diketone	time (h)	yield (%)
1	CH₂ <i>t</i> -Bu	Bt	н	2-OMe-C _e H	⊿ 27	2.5	92
2	CH₂t-Bu	<i>O</i> -Pfp	Н	2-OMe-C ₆ H	4 27	24	68
3	CH ₂ t-Bu	Bt	н	4-OMe-C ₆ H	4 28	4	99
4	CH₂t-Bu	<i>O</i> -Pfp	Н	4-OMe-C ₆ H	4 28	24	99
5	CH ₂ t-Bu	Bt	н	2-furanyl	29	2.5	91
6	CH ₂ t-Bu	<i>O</i> -Pfp	н	2-furanyl	29	24	72
7	CH ₂ t-Bu	Bt	Me	Ph	30	4	92
8	CH ₂ t-Bu	<i>O</i> -Pfp	Me	Ph	30	24	65
9	CH ₂ t-Bu	Bt	OTBS	Ph	31	2.5	65
10	CH ₂ t-Bu	<i>O</i> -Pfp	OTBS	Ph	31	24	68
11	CH ₂ t-Bu	Bt	Н	2-OH-C ₆ H ₄	32	24	50
12	CH ₂ t-Bu	<i>O</i> -Pfp	H ~	2-OH-C ₆ H ₄	32	24	65
13	CH ₂ t-Bu	Bt	້		33	3	99
14	CH ₂ t-Bu	<i>O</i> -Pfp	\sim	s. /	33	24	58
15	CH ₂ t-Bu	Bt	Ŷ	Ť	34	3	66
16	CH ₂ t-Bu	<i>O</i> -Pfp	~	\checkmark	34	24	62
17	Ph	Bt	Me	(E)-CHCHP	h 26	3	81
18	(<i>E</i>)-CHCHPh	Bt	Me	Et	35	16	72

indeed produced from this reaction, and in a yield (88%) comparable to that obtained when prepared from acetophenone and **38** (91%) (Table 2, entry 7).

Finally, we examined the impact of the coupling reaction on the stereochemical integrity of the starting materials. As mentioned above, conventional methods for β -dicarbonyl synthesis are limited to substrates lacking acidic functionality. This includes compounds having base epimerizable stereogenic centers α to a carbonyl group. To test the effect of our coupling conditions on such compounds, compound 23, prepared from 38 and acetophenone and from 37 and 1-benzoylbenzotriazole, was compared to the corresponding racemic material by HPLC using a chiral, nonracemic stationary phase. No racemization had occurred during either of the synthetic procedures, thus demonstrating that our method is also compatible with substrates prone to baseinduced epimerization under conventional hard enolization conditions.

In conclusion, we have developed an efficient direct coupling reaction between ketones and N-acylbenzotriazoles or O-Pfp esters, based on soft enolization, that proceeds under mild conditions to generate 1,3-diketones. The reaction is conducted with inexpensive MgBr2·OEt2 in untreated, reagentgrade solvent open to the air, and produces innocuous byproducts on workup, making it operationally simple. Furthermore, it is compatible with a range of substrates, including those having base-epimerizable centers adjacent to carbonyl groups, as well as those possessing other basesensitive functionality. Thus, syntheses employing this carbon-carbon bond-forming method may well benefit in the avoidance of protecting groups. Given the importance of 1,3-dicarbonyl compounds in general, along with the operational simplicity and mild nature of this reaction, we expect that it will meet with wide application in synthetic chemistry.

Acknowledgment. D.L. and G.Z. are grateful for Burroughs Wellcome Fellowships from the Duke University Department of Chemistry. This work was supported, in part, by the ACS Petrolum Research Fund.

Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701599V