$MgBr_2 \cdot OEt_2$-Promoted Coupling of Ketones and Activated Acyl Donors via Soft Enolization: A Practical Synthesis of 1,3-Diketones

Daniel Lim, Guoqiang Zhou, Alexandra E. Livanos, Fang Fang, Don M. Coltart*

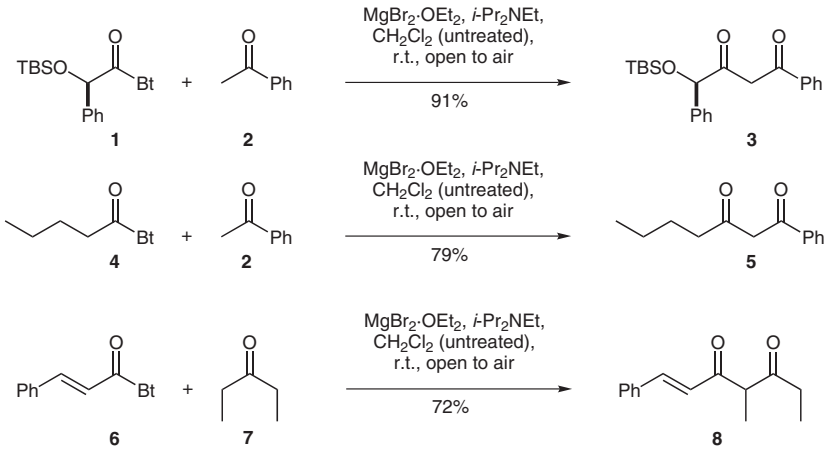
Department of Chemistry, Duke University, Durham, NC 27708, USA
Fax +1(919)6601605; E-mail: don.coltart@duke.edu

Received 2 November 2007; revised 10 December 2007

PSP No 126

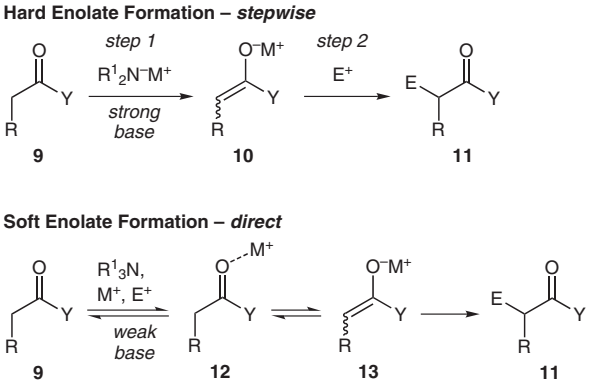
Abstract: Ketones undergo soft enolization and acylation on treatment with $MgBr_2 \cdot OEt_2$, *i*-Pr_2NEt, and various acylating agents to give 1,3-diketones. The process is particularly efficient for *N*-acylbenzotriazoles and *O*-pentafluorophenyl esters, and, in these cases, is conducted using untreated, reagent grade CH_2Cl_2 open to the air, thus providing an exceptionally simple approach to the synthesis of this important class of compounds.

Key words: soft enolization, acylation, carbanion, carbonyl compound, C–C coupling reaction



Scheme 1 1,3-Diketone synthesis via soft enolization

One of the most useful approaches to carbon–carbon bond formation is the reaction of a preformed enolate with a carbon-based electrophile.[1] The enolates are typically prepared via kinetic deprotonation of the parent carbonyl on treatment with a strong base, or the so-called hard enolization (Scheme 2). While effective, the stepwise procedures used to generate such enolates can be time consuming, particularly if enolate trapping is called for, and require that all manipulations be conducted under anhydrous conditions and at low temperature. An alternative to this is to use soft enolization (Scheme 2),[2] which offers a number of practical benefits. For instance, soft enolization does not employ a strong base and, consequently, is inherently milder and can be conducted under much less stringent conditions (e.g., open to the air, untreated solvent, r.t.) than are required of hard enolization procedures. In soft enolization, rather than forcing deprotonation irreversibly using a base many orders of magnitude stronger than the resulting enolate, a relatively weak base (e.g., tertiary amine) is used in combination with a Lewis-acid 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, such that it can be removed to an appreciable extent 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, which can further simplify the procedure.



Scheme 2 Hard and soft enolization

SYNTHESIS 2008, No. 13, pp 2148–2152
Advanced online publication: 18.03.2008
DOI: 10.1055/s-2008-1042947; Art ID: Z25207SS

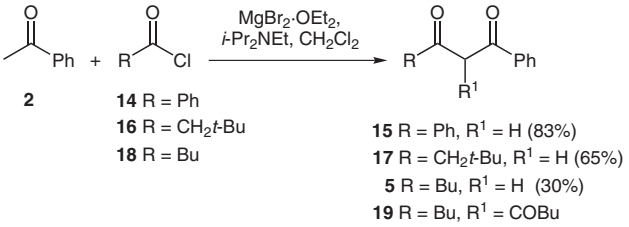
We recently reported on the initial stages of development of a MgBr$_2$·OEt$_2$-promoted direct aldol addition of simple thioesters based on soft enolization.[2c,d] Given the efficiency and operational simplicity of this reaction, we felt that it might provide the basis for workable solutions to the problems associated with the synthesis of 1,3-diketones (see below).

1,3-Diketones are extremely important compounds in synthetic organic chemistry.[3,4] They are widely represented in natural products, pharmaceuticals, and other biologically relevant compounds, or are key intermediates en route to the synthesis of such species.[3] Indeed, their interesting and at times unusual chemical properties are often used to facilitate other important synthetic methods, including the preparation of heterocycles and other aromatic compounds.[4] Many naturally occurring 1,3-diketones have been found to possess biological properties, including antioxidation, antitumor, antimicrobial, antiviral, and antifungal activity.[3]

Given the importance of 1,3-diketones, considerable effort has gone into the development of methods for their synthesis. The classic procedure, which is a modification of the well-known Claisen condensation,[5] involves acylation of a ketone by an ester in the presence of an alkoxide base.[3] Modest to good yields are obtained, although a large excess of the acylating agent must be used, and elevated temperatures and/or removal of the alcohol produced is often required. The coupling procedure is improved through the use of at least two equivalents of sodium or lithium hydride in the place of alkoxide, but this approach is limited in its applicability to substrates having even weakly acidic functionality elsewhere in the molecule. The procedure of choice for 1,3-diketone synthesis uses a strong, non-nucleophilic base such as LDA to preform the required enolate, which is followed by addition of the acylating agent, typically in the form of an acid chloride. Yields generally improve somewhat under these conditions, but consideration must still be paid to the presence of acidic functionality elsewhere in the reactants. Furthermore, competing O-acylation and bis-acylation are common.[5] The most notable drawback of this method, however, is that at least two equivalents of the enolate are required, making it inherently inefficient.[5] This stems from the fact that the 1,3-diketone product is significantly more acidic (pK_a ~9) than the parent ketone (pK_a ~20), and, so, as it forms it protonates the unreacted ketone enolate preventing acylation.

We reasoned that the inefficiency of conventional methods could be overcome if the required enolates were formed under soft rather than hard conditions. This could also be beneficial in that it might simplify the method in a practical sense, in comparison to the standard hard enolization approaches that require highly controlled conditions. Given the reversible nature of soft enolization, when applied in acylation reactions the β-dicarbonyl product (**11**, E = COR, Y = alkyl; Scheme 2) that forms would not be expected to interfere in a detrimental way, as in situations employing hard enolization. Deprotonation of this species by either the ketone enolate or amine would undoubtedly occur, but in a reversible sense, such that the intended ketone enolate could reform and ultimately undergo the desired acylation. Given the relatively weak nucleophilic nature of the dicarbonyl enolate, bis-acylation would not be expected to interfere appreciably with appropriate choice of acylating agent.

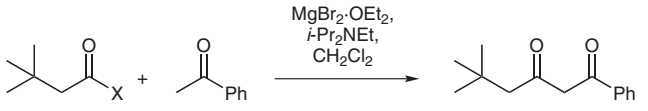
To explore this idea, acetophenone (**2**) was combined with benzoyl chloride (**14**), MgBr$_2$·OEt$_2$, and *i*-Pr$_2$NEt in CH$_2$Cl$_2$ (Scheme 3).[2b–d] The desired 1,3-diketone **15** was indeed isolated from this reaction in very good yield (83%) after only one hour. A control experiment was carried out in which acetophenone and benzoyl chloride were combined in CH$_2$Cl$_2$ in the presence of *i*-Pr$_2$NEt, but in the absence of MgBr$_2$·OEt$_2$, with no coupled product observed after 24 hours, thus confirming the essential nature of the Lewis acid in enolization. Encouraged by the result with MgBr$_2$·OEt$_2$, we conducted a similar reaction with the aliphatic system, 3,3-dimethylbutanoyl chloride (**16**). In this case the desired product **17** was also obtained, but in a somewhat lower yield (65%). Use of pentanoyl chloride (**18**) as the acylating agent also gave the desired β-diketone (**5**), albeit in a much lower yield (30%) due to formation of the α,α-bis-acylation byproduct **19**, as is typical when acid chlorides are used in enolate acylation.[5] None of the reactions showed any improvement in yield when left for longer than one hour.



Scheme 3 MgBr$_2$·OEt$_2$-promoted direct acylation of acetophenone and representative acid chlorides

To increase the yield for the aliphatic systems, we investigated the effect of the acylating component. To do this, a variety of known acylating agents were screened, both with and without added DMAP[6] as a nucleophilic acylation catalyst. The results are summarized in Table 1. Addition of DMAP 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 **20** failed to react altogether, and, while thioester **21** did produce the desired product, yields were lower than for the corresponding acid chloride **16**. *O*-Pfp (*O*-pentafluoryl) ester **22** proved to be a suitable acylating agent, giving 79% yield of the β-diketone within 12 hours and 92% within 24 hours. Even better yields and shorter reactions times resulted from the use of *N*-acylbenzotriazole **23**.[7]

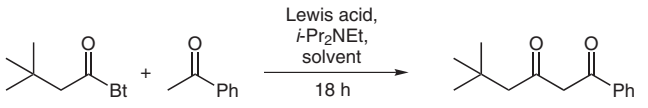
Table 1 $MgBr_2 \cdot OEt_2$-Promoted Direct Acylation of Acetophenone with Different Acylating Agents



Entry	Acylating agent	Nucleophilic catalyst	Time (h)	Isolated yield (%)
1	**16** X = Cl	–	1	63
2	**16** X = Cl	DMAP	1	65
3	**20** X = *O*-succinimide	–	–	n.r.
4	**21** X = SC_6H_4-4-NO_2	–	24	40
5	**21** X = SC_6H_4-4-NO_2	DMAP	24	39
6	**22** X = OC_6F_5	–	12	79
7	**22** X = OC_6F_5	DMAP	12	80
8	**22** X = OC_6F_5	–	24	92
9	**23** X = benzotriazole	–	3	96
10	**23** X = benzotriazole	DMAP	3	94

We next surveyed a variety of different Lewis acid and solvent combinations to determine their effect on the course of the reaction with *N*-acylbenzotriazole **23** (Table 2). Of those combinations examined, $MgBr_2 \cdot OEt_2$ in CH_2Cl_2 was clearly superior, which was consistent with earlier observations on soft enolization,[2b–d] although $ZnCl_2$ in CH_2Cl_2 also produced good results.

Table 2 Effect of Reaction Conditions on Coupling

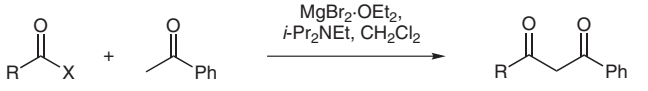


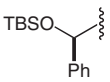
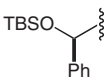
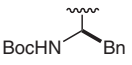
Entry	Lewis acid	Solvent	Conversion (%)
1	$MgBr \cdot OEt_2$	CH_2Cl_2	96
2	$MgBr \cdot OEt_2$	THF	94
3	$MgBr \cdot OEt_2$	toluene	82
4	$ZnCl_2$	CH_2Cl_2	61
5	$ZnCl_2$	THF	trace
6	$ZnCl_2$	toluene	9
7	$CuOTf_2$	CH_2Cl_2	trace
8	$CuOTf_2$	THF	trace
9	$CuOTf_2$	toluene	trace
10	NiI_2	CH_2Cl_2	n.r.
11	NiI_2	THF	n.r.
12	NiI_2	toluene	n.r.

In addition to their effectiveness in this reaction, another compelling reason for the use of $MgBr_2 \cdot OEt_2$ and *N*-acylbenzotriazoles or *O*-Pfp esters is that they are relatively insensitive to air and moisture. This would potentially allow us to conduct the coupling reactions open to the air using untreated, reagent grade CH_2Cl_2, resulting in even greater practical simplification of the procedure. To test this, *N*-acylbenzotriazole **23** and *O*-Pfp ester **22** were each combined with acetophenone, $MgBr_2 \cdot OEt_2$ and *i*-Pr_2NEt using untreated, reagent grade CH_2Cl_2, open to the air. The desired 1,3-dicarbonyl product **17** was obtained with no change in either the isolated yield or reaction time, in comparison to the use of anhydrous CH_2Cl_2 and an argon atmosphere (see Table 3, entry 1). In addition to these practical benefits, $MgBr_2 \cdot OEt_2$ and benzotriazole are extremely inexpensive, adding an economic advantage to the procedure. In contrast, however, pentafluorophenol is more costly and does not, outright, offer a substantial advantage in this regard. However, we found that it is readily recovered from the crude reaction mixture by simple extraction into saturated $NaHCO_3$, followed by acidification (10% HCl) and back-extraction.

Having secured a mild and straightforward method for the synthesis of β-diketone **17**, we explored the scope of the method with respect to other *N*-acylbenzotriazoles and *O*-

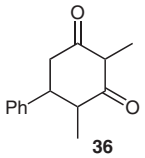
Table 3 $MgBr_2 \cdot OEt_2$-Promoted Coupling Using Untreated Solvent Open to the Air



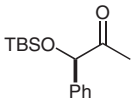
Entry	X	R	1,3-Diketone	Time (h)	Yield (%)
1	Bt	CH_2t-Bu	**17**	2.5	96
2	*O*-Pfp	CH_2t-Bu	**17**	24	92
3	Bt	*t*-Bu	**24**	4	99
4	*O*-Pfp	*t*-Bu	**24**	24	81
5	Bt	Ph	**15**	2.5	95
6	*O*-Pfp	Ph	**15**	24	87
7	Bt		**3**	4	91
8	*O*-Pfp		**3**	24	86
9	Bt	Bu	**5**	2.5	79
10	*O*-Pfp	Bu	**5**	24	61
11	*O*-Pfp		**25**	3	73
12	Bt	$CH_2CH_2CH{=}CH_2$	**26**	24	70
13	*O*-Pfp	$CH_2CH_2CH{=}CH_2$	**26**	24	53
14	Bt	(*E*)-CH=CHPh	**27**	2.5	81

Pfp esters (see Table 3). 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 investigated the scope of the coupling reaction using a variety of ketones with various *N*-acylbenzotriazoles and *O*-Pfp esters (see Table 4). Once again, in all cases the desired 1,3-diketone was obtained in good to excellent yield. Notably, the coupling could be conducted using cyclohexanone as the nucleophile to give the corresponding monosubstituted 1,3-diketone **36** (Figure 1) 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]-1*H*-benzotriazole and pentan-3-one were coupled to give the desired 1,3-dicarbonyl compound **8** without subsequent cyclization to the corresponding 1,3-cyclohexanedione **36**, as is typical of such systems.[3]



36

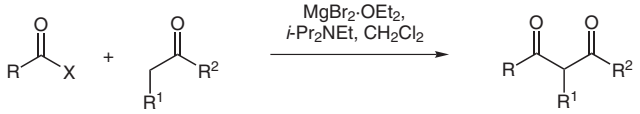


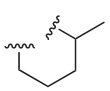
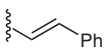
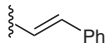
37

Figure 1 Compounds **36** and **37**

To further explore the versatility of our method, we synthesized **3** in an inverse sense by switching the respective ketone and *N*-acylbenzotriazole. Thus, methyl ketone **37** (Figure 1) was prepared according to known procedures[8] and was subjected to the coupling with 1-benzoylbenzotriazole. β-Diketone **3** was indeed produced from this reaction, and in a yield (88%) comparable to that obtained when prepared from acetophenone and **1** (92%) (Table 3, entry 7).

Table 4 MgBr$_2$·OEt$_2$-Promoted Coupling Using Untreated Solvent Open to the Air



Entry	R	X	R^1	R^2	Diketone	Time (h)	Yield (%)
1	CH_2t-Bu	Bt	H	2-$MeOC_6H_4$	**28**	2.5	92
2	CH_2t-Bu	*O*-Pfp	H	2-$MeOC_6H_4$	**28**	24	68
3	CH_2t-Bu	Bt	H	4-$MeOC_6H_4$	**29**	4	99
4	CH_2t-Bu	*O*-Pfp	H	4-$MeOC_6H_4$	**29**	24	99
5	CH_2t-Bu	Bt	H	2-furyl	**30**	2.5	91
6	CH_2t-Bu	*O*-Pfp	H	2-furyl	**30**	24	72
7	CH_2t-Bu	Bt	Me	Ph	**31**	4	92
8	CH_2t-Bu	*O*-Pfp	Me	Ph	**31**	24	65
9	CH_2t-Bu	Bt	OTBS	Ph	**32**	2.5	65
10	CH_2t-Bu	*O*-Pfp	OTBS	Ph	**32**	24	68
11	CH_2t-Bu	Bt	H	2-HOC_6H_4	**33**	24	50
12	CH_2t-Bu	*O*-Pfp	H	2-HOC_6H_4	**33**	24	65
13	CH_2t-Bu	Bt			**34**	3	99
14	CH_2t-Bu	*O*-Pfp			**34**	24	58
15	CH_2t-Bu	Bt			**35**	3	66
16	CH_2t-Bu	*O*-Pfp			**35**	24	62
17	Ph	Bt	H		**27**	3	81
18		Bt	Me	Et	**8**	16	72

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, racemic **3** was prepared from racemic **1** and acetophenone. This was analyzed via HPLC using a chiral, nonracemic stationary phase under conditions that gave baseline separation of the enantiomers. Subsequent analysis of compound **3** derived from optically pure **1** and acetophenone, and from optically pure **37** and 1-benzoylbenzotriazole under the same conditions established that no racemization had occurred during either of the synthetic procedures. This demonstrates that our soft enolization method for 1,3-dicarbonyl synthesis is also compatible with substrates prone to base induced 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 extremely mild conditions to generate 1,3-diketones (Scheme 1). The reaction is conducted using inexpensive $MgBr_2{\cdot}OEt_2$ in untreated, reagent grade solvent open to the air, and produces innocuous by-products on workup. 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 base sensitive functionality. Thus, syntheses employing this carbon–carbon bond-forming method are likely to 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.

Unless stated to the contrary, where applicable, the following conditions apply: Reactions were stirred magnetically using Teflon-coated magnetic stirring bars. Stirring bars, syringe needles and glassware were dried in an oven at 120 °C for at least 12 h prior to use and allowed to cool open to the air prior to use. Commercially available Norm-Ject disposable syringes were used. Commercial grade solvents were used for routine purposes without further purification. Flash column chromatography was performed on silica gel 60 (230–400 mesh).

5,5-Dimethyl-1-phenylhexane-1,3-dione (17); Typical Procedure (Table 3, Entry 1)

This reaction was conducted using untreated CH_2Cl_2, open to the air.

Acetophenone (**2**; 0.065 mL, 0.63 mmol) was added dropwise via a syringe to a stirred suspension of 3,3-dimethyl-1-oxobutylbenzotriazole (0.1648 g, 0.76 mmol) and $MgBr_2{\cdot}OEt_2$ (0.4144 g, 1.58 mmol) in CH_2Cl_2 (10 mL), followed by *i*-Pr_2NEt (0.33 mL, 1.90 mmol). The reaction flask was capped to prevent evaporation. The stirring was continued for 2.5 h, by which time a solution had formed, and 10% aq HCl (10 mL) was added. The stirring was continued for 5 min and the aqueous layer was extracted with CH_2Cl_2 (3 ´ 5 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to give a yellow oil. Flash chromatography over silica gel using 10:90 EtOAc–hexanes gave **17** (0.4168 g, 96%) as a pure, yellow oil. Spectroscopic data were identical to those reported previously.[9]

Acknowledgment

D.L. and G.Z. are grateful for Burroughs Wellcome Fellowships from the Duke University Department of Chemistry. A.E.L. thanks GlaxoSmithKline for an Undergraduate Summer Research Fellowship. This work was supported, in part, by the ACS Petroleum Research Fund.

References

(1) For various examples, see: *Comprehensive Organic Synthesis*, Vol. 2; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: London, **1991**.
(2) (a) Rathke, M. W.; Cowan, P. J. *J. Org. Chem.* **1985**, *50*, 2622. (b) Lim, D.; Fang, F.; Zhou, G.; Coltart, D. M. *Org. Lett.* **2007**, *9*, 4139. (c) Zhou, G.; Yost, J. M.; Coltart, D. M. *Synthesis* **2007**, 478. (d) Yost, J. M.; Zhou, G.; Coltart, D. M. *Org. Lett.* **2006**, *8*, 1503.
(3) Kel'in, A. V. *Curr. Org. Chem.* **2003**, *7*, 1691.
(4) Kel'in, A. V.; Maioli, A. *Curr. Org. Chem.* **2003**, *7*, 1855.
(5) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed.; Wiley: Hoboken, **2007**, Chap. 16.
(6) (a) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129. (b) Spivey, A. C.; Arseniyadis, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 5436.
(7) For lead references on C-acylation via *N*-acylbenzotriazoles, see: (a) Katritzky, A. R.; Wang, Z.; Wang, M.; Wilkerson, C. R.; Hall, C. D.; Akhmedov, N. G. *J. Org. Chem.* **2004**, *69*, 6617. (b) Katritzky, A. R.; Suzuki, K.; Wang, Z. *Synlett* **2005**, 1656.
(8) Vries, E. F. S.; Steenwinkel, P. *J. Org. Chem.* **1993**, *58*, 4315.
(9) Nilsson, L. *Acta Chem. Scand.* **1979**, *33*, 203.