

Asymmetric Michael addition of formaldehyde *N,N*-dialkylhydrazones to alkylidene malonates

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Enantiopure formaldehyde *N,N*-dialkylhydrazones 1 smoothly react with prochiral alkylidene malonates 2 in the presence of MgI₂ to afford the corresponding Michael adducts 3 in excellent yields and good diastereoselectivities; direct racemization-free BF₃·OEt₂-catalyzed thiolysis of the hydrazone C=N bond affords the corresponding dithioketals 7 in optically pure or enantiomerically enriched form.

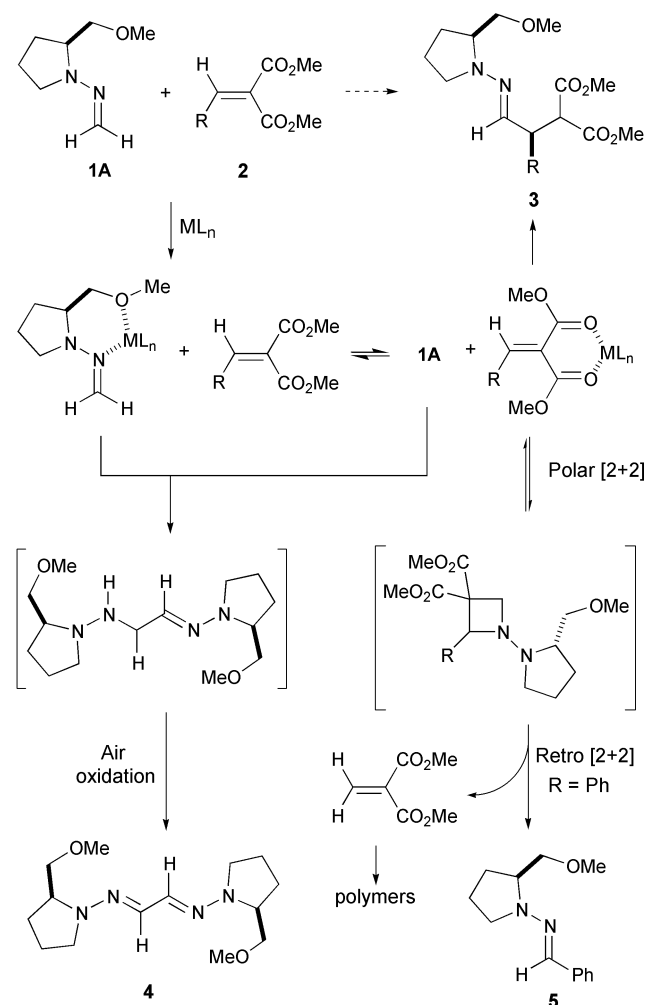
The asymmetric Michael addition of enolates,¹ silylketene acetals,² enamines³ and aza-enolates from hydrazones⁴ to alkylidene malonates has been successfully employed as the key reaction for the synthesis of various 1,5-dicarbonyl compounds. Use of an acyl (formyl) anion equivalent as the nucleophile in the same reaction opens access to 4-oxoesters in a similar manner. Though reports have been described for such a reaction leading to racemates,⁵ examples of *asymmetric* nucleophilic acylations of enolates are rare.⁶ On the other hand, SAMP-derived formaldehyde *N,N*-dialkylhydrazone **1A** had been successfully used as a neutral formyl anion equivalent⁷ for the asymmetric formylation of enones⁸ and α,β -unsaturated lactones,⁹ but the extension of this methodology to α,β -unsaturated esters was unsuccessful. The precedent of the addition of **1A** to nitroalkenes,¹⁰ which exhibit similar levels of reactivity to that of alkylidene malonates,[†] suggested that the addition of formaldehyde *N,N*-dialkylhydrazones to the latter should also be possible under non-catalysed conditions, or, at least, under mild conditions compatible with the hydrazone moiety. Results collected on the basis of this hypothesis are given herein.

Unexpectedly, the addition of formaldehyde SAMP-hydrazone **1A** to easily available dimethyl alkylidene malonates **2** was unsuccessfully essayed under a variety of uncatalysed conditions. On the other hand, the selection of a suitable promoter system for this reaction presented some difficulties. For instance, activation of **2** by common Lewis acids, such as ZnCl₂, AlCl₃, Ti(OⁱPr)₄ or trialkylsilyl triflates, afforded the expected hydrazone malonates **3**, but glyoxal bis-hydrazone **4** was also isolated as an undesired by-product.‡ In the case of the aromatic substrate **2d**, benzaldehyde SAMP-hydrazone **5** was also isolated as a by-product, even in dry media. Its formation can be explained by a [2 + 2] cycloaddition of **1A** to the activated malonate followed by a retrocycloaddition to the observed by-product and methylidene malonate, unstable against polymerization. Finally, it was concluded that use of stoichiometric amounts of freshly dried MgI₂§ allowed the establishment of the required equilibrium shown in Scheme 1, while minimizing the side reactions mentioned above.

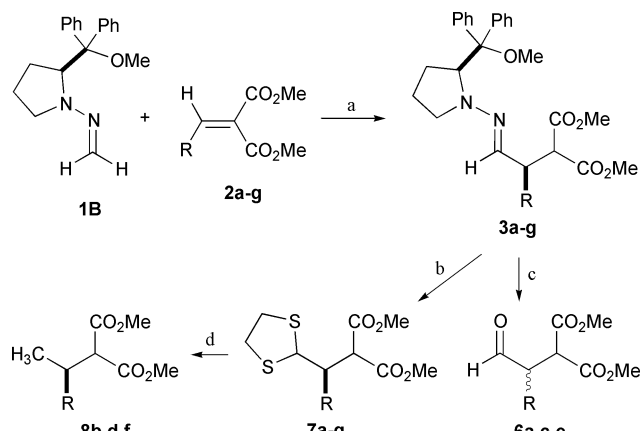
As use of the SAMP-hydrazone **1A** afforded disappointing diastereoselectivities, a second optimization study was required in order to improve the stereochemical result. Therefore, several formaldehyde hydrazones, carrying pyrrolidine-based auxiliaries as a common characteristic,¶ were prepared and reacted with ethylidene derivative **2a** as a model substrate in the presence of MgI₂ as the promoter (Scheme 2, R = Me). From this study, (*S*)-1-methyleneamino-2-(1-methoxydiphenylmethyl)pyrrolidine (**1B**) emerged as the most convenient reagent, affording the corresponding adduct **3a** in 91% yield as a 89:11

mixture of diastereomers. The optimized conditions were then used for the addition of reagent **1B** to several aliphatic and aromatic alkylidene malonates **2b–g** (Scheme 2, Table 1).||

Regeneration of the formyl group to obtain aldehydes **6** was accomplished by ozonolytic cleavage of the hydrazone C=N double bond in moderate-to-good yields (60–87%), but the products were found to racemize partially during the chromatographic separation.** Even though the crude aldehydes were obtained with a reasonable purity and could be eventually used without purification at this step, alternative removals of the auxiliary were also investigated. Fortunately, it was found that the direct dithioketalization of the hydrazone moiety¹¹ was a suitable reaction to this aim. Thus, treatment of adducts **3** with ethanedithiol in the presence of an excess of BF₃·OEt₂ (2.5–5 eq.) afforded the desired dithioketals **7** (Scheme 2, Table 2). The enantiomeric purities of these adducts were independently



Scheme 1



Scheme 2 Reagents and conditions: a: MgI_2 , CH_2Cl_2 . b: $\text{HS}(\text{CH}_2)_2\text{SH}$ (1.5 eq.), $\text{BF}_3 \cdot \text{OEt}_2$ (2.5–5 eq.). c: O_3 , Me_2S , $-78^\circ\text{C} \rightarrow \text{rt}$. d: Ra-Ni , MeOH .

measured by HPLC or ^1H NMR LIS experiments carried out with $\text{Eu}(\text{hfc})_3$, thereby confirming the absence of racemization in this reaction, even for the more sensitive aromatic substrates.

As illustrative examples of another potentially useful transformation, Ra-Ni mediated desulfuration of **7b,d,f** was also effected to afford malonates **8b** (75%), **8d** (70%), and **8f** (71%), respectively. Comparison of the optical rotation of (*S*)-**8f** with literature data was used for the assignment of its absolute configuration.^{††} As the transformations **3**→**7** and **7**→**8** are assumed to proceed without inversion of neighbor stereogenic centers, the (*3S*) configuration of **3f** and **7f** was deduced thereof. The absolute configuration of all other products was assigned by analogy.

In summary, the MgI_2 -promoted Michael addition of enantiopure formaldehyde hydrazone **1B** to alkylidene malonates **2** appear as a convenient method for the synthesis of enantiomer-

Table 1 Synthesis of hydrazono malonates **3a–g**

3	R	T (°C)	t (h)	Yield ^a (%)	de ^b	Conf.
a	Me	-78	24	91	78 ^c	(<i>S,R</i>)
b	Et	-78	24	95	68 ^c	(<i>S,R</i>)
c	$\text{CH}_2\text{CH}_2\text{Ph}$	-78	48	70	70 ^c	(<i>S,R</i>)
d	Ph	0	7	88	76 (>98)	(<i>S,S</i>)
e	<i>p</i> - $\text{NO}_2\text{C}_6\text{H}_4$	0	3	98	80 (>98)	(<i>S,S</i>)
f	2-Naphthyl	0	6	98	90 (>98)	(<i>S,S</i>)
g		0	6	97	79 (>98)	(<i>S,S</i>)

^a Yield of isolated product. ^b Determined by ^1H NMR analysis of the crude reaction mixtures; in parenthesis: de of purified major diastereomer. ^c Inseparable mixture of diastereomers.

Table 2 Synthesis of dithioketals **7a–g**

7	R	t (h)	Yield ^a (%)	ee	Conf.	$[\alpha]^{24}_\text{D}$ (c, CH_2Cl_2)
a	Me	96	87	79 ^b	(<i>R</i>)	+5.1 (1.1)
b	Et	48	70	70 ^c	(<i>R</i>)	+11.8 (0.9)
c	$\text{CH}_2\text{CH}_2\text{Ph}$	96	60	68 ^b	(<i>R</i>)	+0.8 (1.0)
d	Ph	48	61	>98 ^c	(<i>S</i>)	+6.6 (1.1)
e	<i>p</i> - $\text{NO}_2\text{C}_6\text{H}_4$	24	65	>98 ^b	(<i>S</i>)	-2.1 (1.0)
f	2-Naphthyl	48	63	97 ^b	(<i>S</i>)	+9.6 (1.2)
g		16	70	>98 ^b	(<i>S</i>)	+28.1 (1.3)

^a Yield of isolated product. ^b Determined by HPLC using a chiral stationary phase column (Daicel Chiralpak AD). ^c Determined by ^1H NMR shift experiments using $\text{Eu}(\text{hfc})_3$.

ically enriched, 1,4-dicarbonyl derivatives. Extension of this methodology to related substrates bearing two different electron-withdrawing groups on the same olefinic carbon is a current object of study in our laboratories.

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Notes and references

[†] As discussed in ref. 3, the electrophilic reactivity of nitroalkenes and alkylidenemalonates can be *a priori* correlated with the pK values in nonaqueous solvents of the anions generated upon addition. See also: W. N. Olmstead and F. G. Bordwell, *J. Org. Chem.*, 1980, **45**, 3299.

[‡] The formation of this product is consistent with activation of the reagent **1A** by the Lewis acid, followed by nucleophilic attack of a second molecule of free reagent. Air oxidation of the resulting α -hydrazinohydrazone finally affords the undesired product **4**.

[§] Sub-stoichiometric amounts of MgI_2 were also effective as catalyst, but yields and selectivities were lower in this case. For instance, **3a** was obtained with 51% de and 77% yield by using 0.1 eq of MgI_2 under the conditions given Table 1. Drying of the catalyst (0.05 mbar, 40°C , 5 h) is essential in order to obtain reproducible results.

[¶] As in related enamines, the pyrrolidine ring confers high nucleophilicity to the aza-enamine system: G. Häfelinger and H.-G. Mack, in *The Chemistry of Enamines*, ed. S. Patai and Z. Rappoport, John Wiley & Sons, New York, 1994, pp. 1–85.

^{||} *Synthesis of compounds 3*. Method A. To a stirred, cooled solution of **2a–c** (1 mmol) and MgI_2 (1 mmol) in dry CH_2Cl_2 (1 mL) was added a solution of hydrazone **1B** (1.5 mmol) in CH_2Cl_2 (1 mL) under an argon atmosphere. The mixture was stirred until completion (TLC), diluted with more CH_2Cl_2 (10 mL), washed with H_2O , dried (MgSO_4), and purified by flash chromatography. Method B. To a stirred, cooled solution of **2d–g** (1 mmol) and hydrazone **1B** (2 mmol) in dry CH_2Cl_2 (1 mL) was added MgI_2 (1 mmol) under an argon atmosphere. The mixture was then treated as described above.

^{**} Extensive racemization was observed starting from the sensitive aromatic compound **3d** in optically pure form, as determined by shift experiments using $\text{Eu}(\text{hfc})_3$. A much higher stability was expected in the aliphatic series, but, starting from optically pure **3a**, a 5–20% racemization was also observed after chromatographic purification.

^{††} (*S*)-**8f**: had $[\alpha]^{21}_\text{D} +44.3$ (c 0.7, MeOH). Lit: $[\alpha]^{24}_\text{D} +45.0$ (c 1, MeOH): J.-Y. Legros, M. Toffano and J.-C. Fiaud, *Tetrahedron*, 1995, **51**, 3235.

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