Pergamon

Tetrahedron Letters 41 (2000) 9847–9851

TETRAHEDRON LETTERS

Stereoselective formation of activated cyclopropanes with pyridinium ylides bearing a (–)-8-phenylmenthyl group as the chiral auxiliary

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Received 16 August 2000; revised 28 September 2000; accepted 29 September 2000

Abstract

The reaction of various mono-substituted methylidenemalononitriles with (–)-8-phenylmenthyl α-pyridiniumacetate in the presence of base afforded the corresponding dicyanocyclopropane compounds with exclusive *trans*-selectivity and good diastereoselectivity (up to 86:14). The stereochemistry of the major products were determined to be of 1*R* configuration by X-ray structural analysis of the crystalline *trans*-2,2-dicyano-3-(4-pyridyl)cyclopropanecarboxylate. The geometric and diastereofacial selectivities were rationalized assuming *anti*-periplanar approach in the open-chain model, followed by epimerization and then cyclization to give the cyclopropane compounds.

Keywords: pyridinium ylide; activated cyclopropane; 8-phenylmenthyl; diastereoselective.

Cyclopropane derivatives constitute an interesting group of compounds since they are highly reactive due to their intrinsic ring strain, and have thus been utilized as synthetic intermediates.[1] Among the common methods of cyclopropane synthesis, high levels of asymmetric induction have been reported for catalytic metal–carbenoid reactions.[2] However, this approach has not been extended to reactions with electron-deficient olefins, and for this type of olefin, Michael addition type reactions have proven to be more appropriate, with rather high selectivities observed for substrate controlled reactions.[3] Highly electron-deficient cyclopropanes, in particular, have attracted our interest because of their unique reactivity.[4] However, asymmetric synthesis of such compounds by the use of Michael acceptors with two electron withdrawing groups has essentially been an unexplored area. Pyridine has been utilized as a leaving group in

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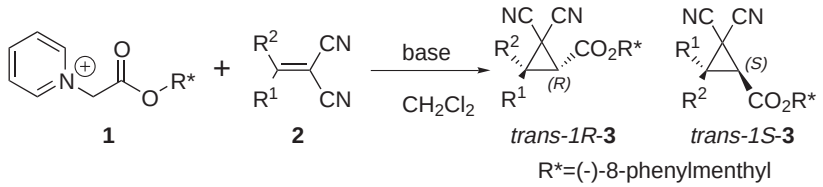
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01743-3

intermolecular reactions,[5] and has also been demonstrated to be useful for intramolecular reactions to furnish cyclopropanes with exclusive *trans* geometry.[6,7] In conjunction with our recent observations that the (−)-8-phenylmenthyl group is effective in inducing high diastereoselectivity in the formation of glycidic esters via the Darzens reaction,[8] we have examined the use of pyridinium ylides bearing this chiral auxiliary for cyclopropane synthesis. Herein we describe our results (Scheme 1).



1 **2** *trans-1R*-**3** *trans-1S*-**3**

Scheme 1.

The pyridinium salt utilized in the reactions was prepared by the reaction of (−)-8-phenylmenthyl chloroacetate with pyridine. Optimization of reaction conditions for cyclopropanation was carried out by using phenylmethylidenemalononitrile as substrate. Throughout the whole investigation, only the *trans* cyclopropane products could be observed.[6,9] A comparison of a range of solvents (*i*-PrOH, DMF, DMSO, MeCN, THF, Et_2O, toluene, CH_2Cl_2) with NaH as the base revealed that the effect of solvent upon selectivity was minimal (68:32 to 83:17) and that CH_2Cl_2 was most suitable in terms of both yield (76%) and selectivity (83:17). Along with Et_3N which was used in the originally reported reactions,[6,7] NaH, *t*-BuOK, and KHMDS were examined as base. Provided that the reaction was carried out in the same solvent (THF, Et_2O, or CH_2Cl_2), the diastereomeric ratios were essentially the same regardless of which base was used. It is interesting to note that although the nature of Et_3N and metal-containing bases are different, the selectivity was the same. In the case of Et_3N, the ratio was the same whether the reaction was carried out at 0 or 50°C.

The scope of this asymmetric reaction was examined by carrying it out with several substrates in CH_2Cl_2 with either NaH or Et_3N, as partially shown in Table 1. Both bases were examined

Table 1
Reaction with various alkylidenemalononitriles in CH_2Cl_2 with Et_3N as base at 0°C[a]

Entry	R^1	R^2	Yield (%)	Diastereomeric ratio[b]
1	C_6H_5	H	78	83:17
2	*p*-$CH_3OCOC_6H_4$	H	91	83:17
3	*p*-$O_2NC_6H_4$	H	91	84:16
4	4-Pyridyl	H	82	84:16
5	*n*-Butyl	H	97	70:30
6	*i*-Butyl	H	96	73:27
7	*i*-Propyl	H	93	66:34
8	*t*-Butyl	H	99	86:14
9	–$(CH_2)_5$–		82	55:45

[a] Typical reaction conditions: a mixture of the pyridinium salt (0.12 mmol), Et_3N (0.18 mmol), substrate (0.10 mmol) in CH_2Cl_2 (2 mL) was stirred for 12 h at 0°C.

[b] The ratio was determined by ^1H NMR of the isolated diastereomeric mixture.

for all the substrates, due to concern that the same selectivity observed for differing bases in the case of phenylmethylidenemalononitrile could have been coincidental. However, here again the diastereoselectivity was not affected by the base, regardless of the substrate. While the benzene ring substituent did not influence the selectivity (entries 1–4), for alkyl substituted substrates, the bulky *t*-butylmethylidenemalononitrile gave the best diastereoselectivity (entries 5–8). Whereas cyclohexanone was a good substrate for diastereoselective glycidic ester synthesis,[8] the reaction of its malononitrile derivative was found to be essentially unselective (entry 9).

The major diastereomer of the cyclopropane derivative bearing a 4-pyridyl group, *trans*-2,2-dicyano-3-(4-pyridyl)cyclopropanecarboxylate, turned out to be crystalline and was thus subjected to X-ray structural analysis.[10] The absolute stereochemistry upon the cyclopropane ring was determined to be 1*R*,3*S* as shown in Fig. 1. The major diastereomers of the other products are expected to have analogous stereochemistry. This stereochemistry can be rationalized as follows, if we assume that the Michael addition of the pyridinium ylide occurs in an *anti*-periplanar fashion, in regards with the alignment of the interacting π bonds, as depicted in Scheme 2. Considering the reaction conditions, the ylide geometry in which the large pyridyl and 8-phenylmenthyloxy ester groups are in a *trans* relationship is expected to be predominant. Michael addition should occur from the front-side of this ylide which is not blocked by the phenyl group, and in a way to minimize *gauche* interactions to give intermediate *cis*-A rather than *trans*-A. Upon ring closure to give the cyclopropane product, however, this intermediate *cis*-A experiences severe steric repulsion between the carboxylate group and the R group, and thus product formation is an unfavored process. Due to the presence of two carbanion stabilizing groups, this intermediate should have a relatively long lifetime,[4a,d] and therefore could undergo epimerization at the carbon in between the pyridinium and carboxylate groups. This gives rise to intermediate *trans*-B, in which steric strain in the cyclization process is alleviated, and which should thus readily give the observed major diastereomer, *trans*-1*R*-**3**. The loss in selectivity can be attributed to the long lifetime of the intermediates, which allows for the competition of retro-Michael reactions that may lead to *trans*-1*S*-**3** via *trans*-A. Since ring closure is expected to be very slow for the reaction of cyclohexylidenemalononitrile, the fact that diastereoselectivity was low is in good agreement with a fast epimerization process succeeding a possibly selective Michael addition.

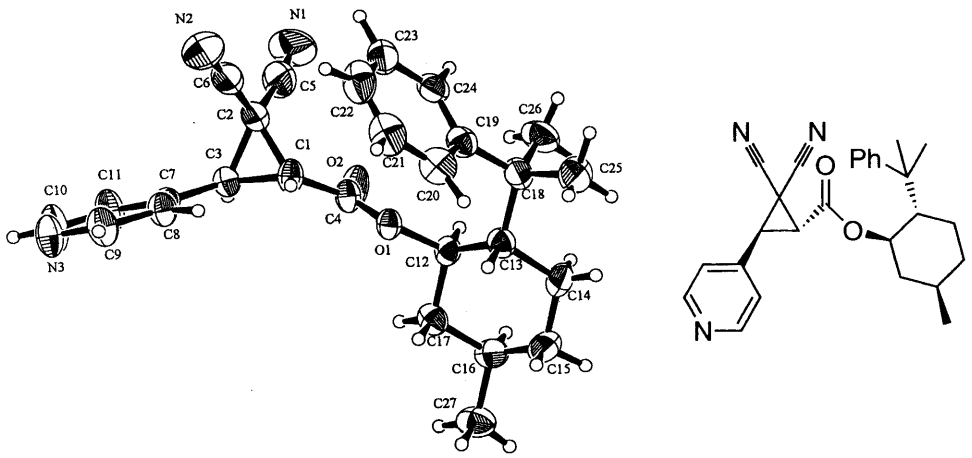
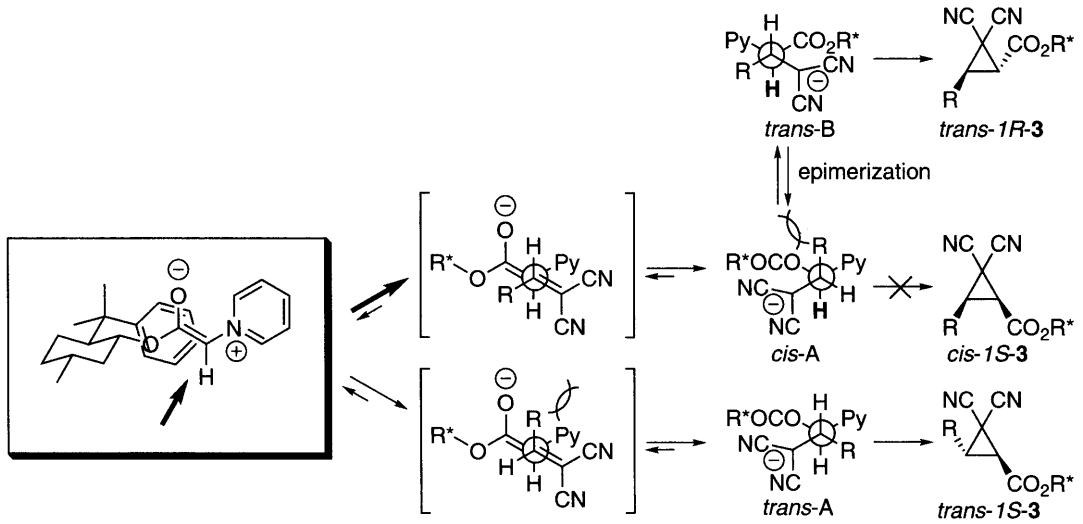


Figure 1. ORTEP drawing of the major 4-pyridyl diastereomer



Scheme 2.

In summary, we have developed a method of preparing optically active highly electron-deficient cyclopropanes by utilizing the facial discriminating ability of the (−)-8-phenylmenthyl chiral auxiliary. Effects of substituents upon the pyridine ring are currently under investigation.

Acknowledgements

This work was partially supported by a grant-in-aid (no.11740354) from the Ministry of Education, Science, Sports, and Culture, Japan. NMR and HRMS spectra data were measured at the Instrument Center for Chemical Analysis of Hiroshima University.

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9. As an example of characteristic spectroscopic differences between diastereomers, selected ^{1}H NMR signals of 4-pyridylmethylidenemalononitrile are: major diastereomer, 2.04 (d, $J=8.0$ Hz, 1H, ring), 3.02 (d, $J=8.0$ Hz, 1H, ring), 5.00 (dt, $J=4.5$, 11.0 Hz, 1H, CO_2CHRR'); minor diastereomer, 1.93 (d, $J=8.0$ Hz, 1H, ring), 3.36 (d, $J=8.0$ Hz, 1H, ring), 4.98 (dt, $J=4.5$, 11.0 Hz, 1H, CO_2CHRR').
10. Details of the X-ray analysis will be given in a full report.