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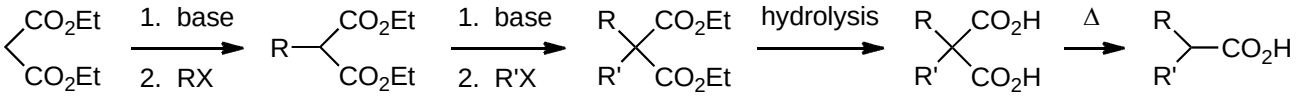
EFFICIENT AND MILD PROCEDURE FOR THE DECARBOXYLATIVE CYANOMETHYL ESTERIFICATION OF ARYLMALONIC ACIDS USING ClCH$_2$CN/1,8-DIAZABICYCLO[5.4.0]UNDEC-7-ENE

Niiha Sasakura, Tomoyuki Yamauchi, Keiji Nakano, Yoshiyasu Ichikawa, and Hiyoshizo Kotsuki*

Laboratory of Natural Products Chemistry, Faculty of Science, Kochi University, Akebono-cho, Kochi 780-8520, Japan
e-mail: kotsuki@kochi-u.ac.jp

Abstract – An efficient and mild procedure for the decarboxylative cyanomethyl esterification of arylmalonic acids has been developed. The reaction can be performed at room temperature by using chloroacetonitrile and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene, and the desired arylacetic acid cyanomethyl esters are obtained in high yields within a short period of time.

Malonic ester synthesis is one of the most fundamental techniques for the chain elongation of carboxylic acids based on a carbon-carbon bond-forming strategy.[1] This procedure can usually be performed through a three-step process, *i.e.*, alkylation of malonic esters, hydrolysis to free dicarboxylic acids, and decarboxylation by heating (Scheme 1). In this synthetic sequence, the final step of decarboxylation requires rather high temperatures, although alternative methods have been reported to avoid this difficulty.[2]



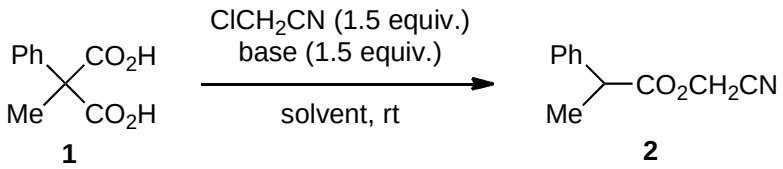
Scheme 1. Malonic ester synthesis

In our separate work on organocatalytic asymmetric synthesis,[3] we needed to prepare a variety of arylacetic acid derivatives using malonic ester synthesis in a quite simple methodology. Unexpectedly,

however, we found that the treatment of arylmalonic acid intermediate **1** with chloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a strong amidine base in THF gave the corresponding monoester **2** accompanied by unusual decarboxylation.[4] Very recently, Lafrance et al. reported a closely related work on the *N,N*'-carbonyldiimidazole-directed decarboxylation of malonic acids.[5] This result prompted us to report our independent findings in this field.

First, several organic bases were examined to optimize the conditions (Table 1). Pyridine showed no activity, and Et_3N rather weakly promoted the desired reaction compared with DBU, while no reaction was observed in the absence of a base (Table 1, Entries 1-4). At least 1.5 equiv. of both chloroacetonitrile and DBU were necessary to achieve high yield, and a reduction to stoichiometric amounts compromised the reactivity (Table 1, compare Entries 4 and 5). Next, we found that there was a significant solvent effect: THF, CH_2Cl_2, DMF, MeCN, and $MeNO_2$ were tested, but they were less effective than toluene (Table 1, Entries 5-10). The solvent-free system was somewhat complicated and **2** was recovered in 65% yield (Table 1, Entry 11). Thus, the best conditions were as follows: $ClCH_2CN$ (1.5 equiv.), DBU (1.5 equiv.), in toluene.

Table 1. Optimization of the decarboxylative transformation of malonic acid **1** to **2** with $ClCH_2CN$/organic base[a]

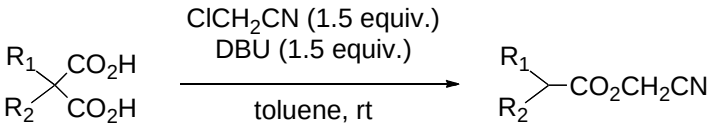


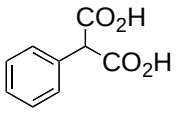
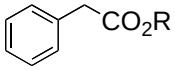
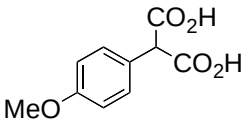
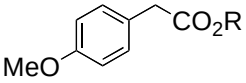
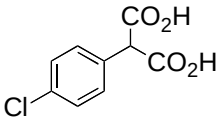
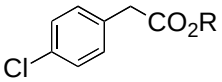
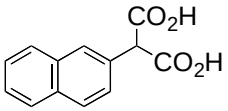
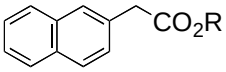
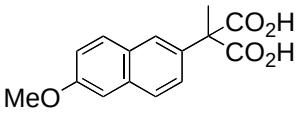
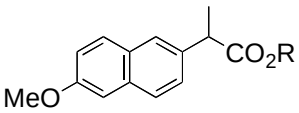
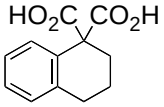
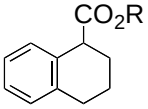
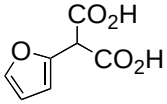
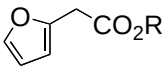
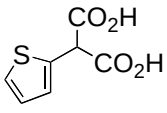
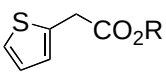
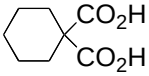
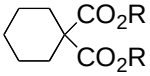
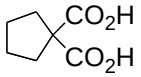
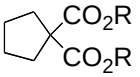
Entry	Base	Solvent	Time (h)	Yield (%)[b]
1	none	THF	36	no rxn
2	pyridine	THF	36	no rxn
3	Et_3N	THF	36	40
4[c]	DBU	THF	36	69
5	DBU	THF	6	92
6	DBU	CH_2Cl_2	8	82
7	DBU	toluene	4	96
8	DBU	DMF	5	82
9	DBU	MeCN	3	89
10	DBU	$MeNO_2$	36	57
11	DBU	none	6	65

[a] Reaction conditions: **1** (1.0 mmol), $ClCH_2CN$ (1.5 mmol), and organic base (1.5 mmol), in the solvent (2.0 mL).
[b] Isolated yield.
[c] $ClCH_2CN$ (1.05 mmol) and DBU (1.05 mmol) were used.

With the optimized reaction conditions in hand, we then investigated the general scope of this chemistry by using various substituted malonic acids as substrates (Table 2).

Table 2. Decarboxylative esterification of substituted malonic acids with $ClCH_2CN$/DBU[a]



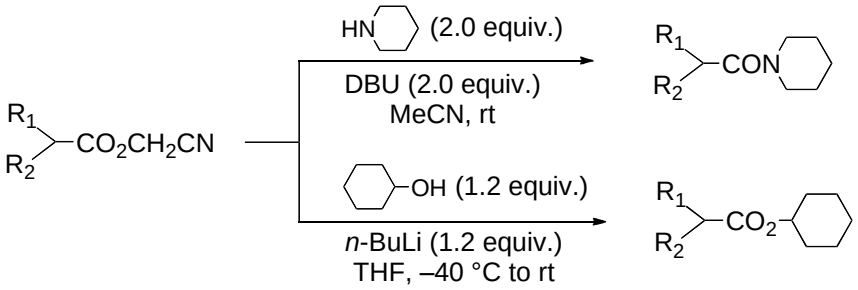
Entry	Substrate	Time (h)	Product (R = CH_2CN)		Yield (%)[b]
1		0.5		**3**	99
2		0.25		**4**	86
3		0.25		**5**	92
4		0.5		**6**	84
5		3		**7**	72
6		0.5		**8**	93
7		1.5		**9**	61
8		1.5		**10**	80
9[c]		1		**11**	95
10[c]		1		**12**	89

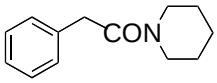
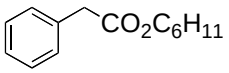
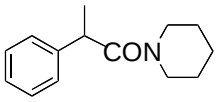
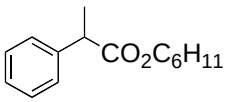
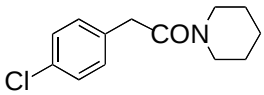
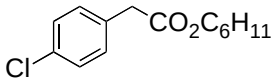
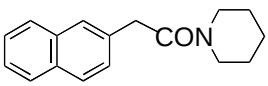
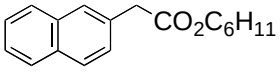
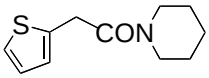
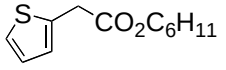
[a] Reaction conditions: dicarboxylic acid (1.0 mmol), $ClCH_2CN$ (1.5 mmol), DBU (1.5 mmol), in toluene (2.0 mL).
[b] Isolated yield.
[c] $ClCH_2CN$ (3.0 mmol) and DBU (3.0 mmol) were used.

As expected, a variety of aromatic and heteroaromatic malonic acids underwent decarboxylative esterification in good to high yields (Table 2, Entries 1-8). The reaction was also successful with the rigid tetralin system (Table 2, Entry 6). One notable limitation of this method is that alkyl-group-substituted malonic acids were less reactive, and the corresponding diesters were formed exclusively (Table 2, Entries 9 and 10).[6]

It is well known that cyanomethyl esters are stable but useful as mildly activated functionalities.[7] Accordingly, we examined their utility in amidation and transesterification by the action of piperidine and cyclohexanol as typical *N*- and *O*-nucleophiles. The results are summarized in Table 3.

Table 3. Amidation and transesterification of cyanomethyl esters[a]



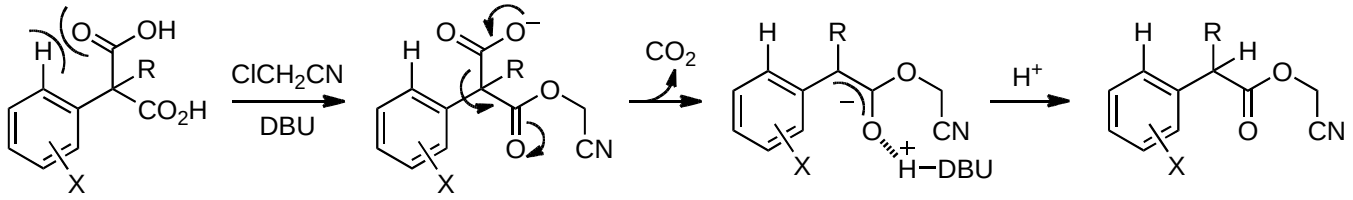
Entry	Time (h)	Product	Yield (%)[b]	Entry	Time (h)	Product	Yield (%)[b]
1	0.25		97	6	0.1		80
2	2.0		73	7	0.4		86
3[c]	0.5		74	8	0.4		87
4	0.5		83	9	0.75		84
5	1.0		78	10	0.25		52[d]

[a] Reaction conditions (*amidation*): cyanomethyl ester (1.0 mmol), piperidine (2.0 mmol), DBU (2.0 mmol), in MeCN (2.0 mL); (*tranesterification*): cyanomethyl ester (1.0 mmol), cyclohexanol (1.2 mmol), *n*-BuLi (1.2 mmol), in THF(2.0 mL).
[b] Isolated yield.
[c] In the presence of powdered molecular sieves 4A (300 mg).
[d] Unidentified by-products were formed.

In all cases, the desired reactions proceeded cleanly to afford the corresponding piperidinyl amides and

cyclohexyl esters in good to high yields. Thus, the overall process starting from malonic acid precursors provides a new entry to derive pharmaceutically important arylacetic acid derivatives.[8]

In our decarboxylative esterification, the best solvent was determined to be toluene, where the reaction took place in a two-phase system. In this case, arylacetates formed by decarboxylation should be smoothly transferred to the less polar toluene phase prior to contamination with venomous side-reactions. In contrast, the same components in an aprotic polar solvent such as THF or DMF became a clear homogeneous solution, which led to inevitable interference from excess reagents or by-products formed in situ. A plausible mechanism to account for the present decarboxylation is shown in Scheme 2. Mono-esterification followed by decarboxylation produced the anionic intermediate that is stabilized by virtue of the electron-withdrawing nature of a cyanomethyl group.



Scheme 2. Plausible mechanism for the decarboxylative esterification of arylmalonic acid

In conclusion, we have developed an efficient and mild procedure for the decarboxylative esterification of arylmalonic acids using $ClCH_2CN$ and DBU. This method is useful for preparing a variety of arylacetic acid cyanomethyl esters with a very simple strategy. Interestingly, the overall process resembles arylmalonate decarboxylase (AMDase) catalysis.[9] This suggests that we may be able to extend this approach to asymmetric organocatalysis, and further studies along these lines are now in progress in our laboratory.

Experimental Section

General procedure: To a suspension of dicarboxylic acids (1.0 mmol) in toluene (2.0 mL) were added at rt DBU (1.5 mmol) and $ClCH_2CN$ (1.5 mmol), and the mixture was stirred until the reaction was complete. The mixture was then diluted by the addition of AcOEt, washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The crude product was purified by silica gel column chromatography (elution with CH_2Cl_2) to afford the pure ester.

Amidation of cyanomethyl ester: To a solution of cyanomethyl ester (1.0 mmol) in dry MeCN (2.0 mL) were added piperidine (2.0 mmol) and DBU (2.0 mmol) at rt. After completion, the mixture was diluted by the addition of AcOEt, washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by silica gel column chromatography (elution with hexane/ AcOEt) to afford the pure amide.

Transesterification of cyanomethyl ester: To a solution of cyclohexanol (1.0 mmol) in THF (2.0 mL) was added *n*-BuLi (1.2 mmol) at –40 °C under Ar. After stirring for 10 min, the solution was introduced to a solution of cyanomethyl ester in THF (2.0 mL) via cannula at 0 °C. After completion, the mixture was quenched by the addition of sat. aq. NH_4Cl and extracted with AcOEt. The combined extracts were washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by silica gel column chromatography (elution with hexane/AcOEt) to afford the pure ester.

ACKNOWLEDGEMENTS

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3. Y. Inokoishi, N. Sasakura, K. Nakano, Y. Ichikawa, and H. Kotsuki, *Org. Lett.*, 2010, **12**, 1616.
4. The evolution of CO_2 was confirmed by a positive $CaCO_3$ test.
5. D. Lafrance, P. Bowles, K. Leeman, and R. Rafka, *Org. Lett.*, 2011, **13**, 2322.
6. Under the standard conditions (1.5 equiv. of $ClCH_2CN$, 1.5 equiv. of DBU, in toluene, rt), the reactants were recovered almost completely and the diester was obtained in only 15% yield after 12 h: compare with Table 2, Entry 10.
7. For example, see: (a) S. A. Robertson, J. A. Ellman, and P. G. Schultz, *J. Am. Chem. Soc.*, 1991, **113**, 2722; (b) H. M. Hugel, K. V. Bhaskar, and R. W. Longmore, *Synth. Commun.*, 1992, **22**, 693; (c) W. Fitz and C.-H. Wong, *J. Org. Chem.*, 1994, **59**, 8279; (d) S. Findlow, P. Gaskin, P. A. Harrison, J. R. Lenton, M. Penny, and C. L. Willis, *J. Chem. Soc., Perkin Trans. 1*, 1997, 751; (e) R. Shen, C. T. Lin, and J. A. Porco, Jr., *J. Am. Chem. Soc.*, 2002, **124**, 5650; (f) R. Shen, C. T. Lin, E. J. Bowman, B. J. Bowman, and J. A. Porco, Jr., *J. Am. Chem. Soc.*, 2003, **125**, 7889; (g) Q. Su and J. S. Panek, *J. Am. Chem. Soc.*, 2004, **126**, 2425; (h) C. Bouillon, G. Quéléver, and L. Peng, *Tetrahedron Lett.*, 2009, **50**, 4346; (i) C. Bouillon, A. Tintaru, V. Monnier, L. Charles, G. Quéléver, and L. Peng, *J. Org. Chem.*, 2010, **75**, 8685.
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