JOC Article

Superacid-Catalyzed Intramolecular Cyclization Reaction of Arylcyanopropionate: *Geminal* Substitution Effect on Superelectrophilicity

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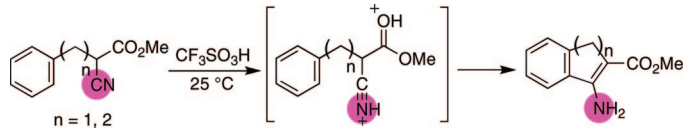

We present superacid-catalyzed intramolecular cyclization reactions of arylcyanopropionates to give cyclized five- and six-membered β-enamino esters in moderate to high yields. Known intramolecular ring-closing reactions of protonated nitrile to aromatic carbon atom are limited to the 6-membered case. Interestingly, a significant synergistic increase of reactivity of the cyano functionality was observed, and the cyano nitrogen atom was converted into an amino group, when an ester group was present in a *geminal* arrangement. Deuterium exchange experiments excluded the involvement of deprotonation of the α-proton in the cyclization process. The acidity dependence of the cyclization reactions and ^{13}C NMR studies of a model compound, methyl cyanoacetate, in various acidic media were consistent with the involvement of the *O*,*N*-diprotonated dication of methyl cyanoacetate, a *distonic* dication, in strong acid, and this is considered to be the de facto electrophile in the present cyclization reaction of arylcyanopropionates.

Introduction

Active methylene compounds are among the most versatile and widely used building blocks in organic synthesis because of both their flexibility as regards combination with electron-withdrawing groups and the ease of further transformation. The C−H bond at the α-position of multiple electron-withdrawing groups is acidic enough that the relevant proton can be easily removed under basic or acidic conditions to generate a π-conjugate system, which may exhibit various reactivities. In addition, it has been reported that *geminal* functional groups sometimes show very characteristic reactivities, which are rarely observed with compounds bearing a single functional group. A superacid-catalyzed intramolecular cyclization of methyl 3-aryl-2-nitropropionate to give new heterocyclic compounds, 4*H*-1,2-benzoxazines, was recently reported,[1] wherein the oxygen atom of the nitro group was introduced onto the aromatic ring. It turned out that the *geminal* ester group significantly facilitated the reaction. In that work, we showed that certain combinations of functional groups afforded novel reactivity, which cannot be observed with a single functional group. The nature of the reactivity and the effects of combinations of other functional groups, however, remained to be investigated.

In spite of its great versatility in organic synthesis, the cyano group has been used in only a limited number of acid-catalyzed aromatic functionalization reactions, such as the Gatterman reaction and Houben−Hoesch reaction, in which it is finally transformed into a carbonyl functionality through imine intermediates upon hydrolysis. While intramolecular ring-closing reactions of protonated nitriles to aromatic carbon atom are known, it has been recognized that cyclization to five-membered rings is difficult, and indeed the reported examples are limited only to six-membered cylizations.[2] In this paper, we present a novel intramolecular cyclization reaction of arylcyanopropionates to give both five- and six-membered β-enamino esters, utilizing the methodology we have developed. We observed a

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(1) (a) Nakamura, S.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2003**, *125*, 5282–5283. (b) Nakamura, S.; Sugimoto, H.; Ohwada, T. *J. Am. Chem. Soc.* **2007**, *129*, 1724–1732.

(2) (a) Moustafa, A. H.; Hitzler, M. G.; Lutz, M.; Jochims, J. C. *Tetrahedron* **1997**, *53*, 625–640. (b) Colquhoun, H. M.; Lewis, D. F.; Williams, D. J. *Org. Lett.* **2001**, *3*, 2337–2340. (c) Udwary, D. W.; Casillas, L. K.; Townsend, C. A. *J. Am. Chem. Soc.* **2002**, *124*, 5294–5303. (d) Henninger, J.; Polborn, K.; Mayr, H. *J. Org. Chem.* **2000**, *65*, 3569–3570. (e) Urgaonkar, S.; Shaw, J. T. *J. Org. Chem.* **2007**, *72*, 4582–4585.

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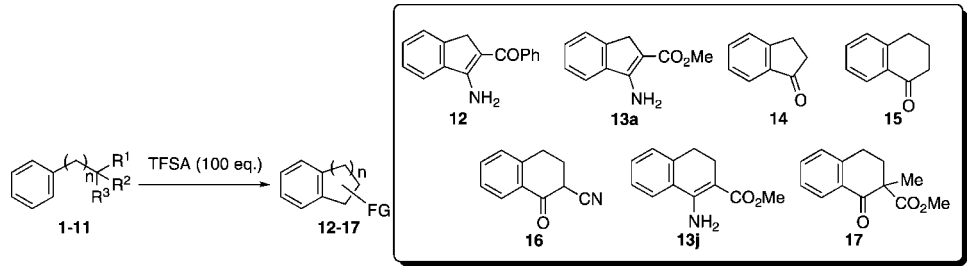
TABLE 1. Preliminary Investigation of Superacid-Catalyzed Intramolecular Cyclization



entry		*n*	R^1	R^2	R^3	temp (°C)	time (h)	product	yield (%)
1	**1**	1	$-CO_2Me$	$-CO_2Me$	−H	100	2		(82)[a]
2	**2**	1	$-SO_2Ph$	$-CO_2Me$	−H	70	0.5		(81)[a,b]
3	**3**	1	−CN	−COPh	−H	0	4	**12**	30
4	**4**	1	−CN	−CN	−H	25	3		(64)[a,b]
5	**5a**	1	−CN	$-CO_2Me$	−H	50	5	**13a**	52
6	**5a**	1	−CN	$-CO_2Me$	−H	25	48	**13a**	72
7	**6**	1	−CN	−H	−H	25	1		(56)[a,b]
8	**7**	1	−H	$-CO_2Me$	−H	25	48	**14**	100
9	**8**	2	−CN	−H	−H	25	1	**15**	81
10	**9**	2	−H	$-CO_2Me$	−H	25	1	**15**	97
11	**10**	2	−CN	−CN	−H	25	1	**16**	44
12	**5j**	2	−CN	$-CO_2Me$	−H	25	48	**13j**	84[c]
13	**11**	2	−CN	$-CO_2Me$	−Me	25	48	**17**	17
14	**5q**	3	−CN	$-CO_2Me$	−H	25	48		(90)[a]

[a] In parentheses, recovery was shown. [b] Long reaction time resulted in a complex mixture of products. [c] See also Table 2 (entry 8).

significant synergistic increase of reactivity of the cyano functionality, and the cyano nitrogen atom is converted to an amino group (i.e., an sp^3-nitrogen atom), when an ester group is present in the *geminal* arrangement.[3] We also compared the present reactions with those of the corresponding diester and dicyano counterparts. In the present reactions, *distonic* dications,[4] in which the two positive charge centers are separated by one carbon atom, rather than conjugate cations generated through loss of an α-proton, are proposed to be involved as activated electrophiles.

Results and Discussion

Superacid-Catalyzed Reactions of Arylcyanopropionates. First, we investigated the reactivities of several active methylene compounds in an arylalkane system bearing combinations of *geminal* functional groups in the presence of trifluoromethanesulfonic acid (TFSA) (Table 1). Unexpectedly, we found that methyl 2-cyano-3-arylpropionate **5a** gave the cyclized five-membered β-enamino ester analogue **13a** when it was treated with a large excess of TFSA (100 equiv). In this reaction, the cyano group was converted to an amino group. The yield of **13a** was increased to 72% when the solution was stirred at 25 °C for 48 h (entry 6). Reported examples are limited only to six-membered cylizations,[2] and we confirmed this, because the mononitrile case (**6**, 56% recovery, entry 7) and dinitrile case (**4**, 64% recovery, entry 4) did not provide the indane product under similar acidic conditions (25 °C, 1−3 h). It is noteworthy that the combination of a cyano and an ester group as *geminal* electron-withdrawing groups seems to be important for the present cyclization to give the β-enamino ester derivatives. In the case of a keto group, i.e., a benzoyl group (entry 3) in place of the ester group, the cyclization was also found to proceed at low temperature, though the yield was moderate (30%).[5] Interestingly, when the cyano group was replaced by an ester (i.e., a diester derivative, entry 1) or by a sulfone group (entry 2), efficient cyclization to give indene derivatives did not occur. Furthermore, the reaction of the monoester derivative **7** afforded 1-indanone **14** in quantitative yield (entry 8), and this is in sharp contrast to the reactivity in the mononitrile case (entry 7). These observations indicated that under the reaction conditions, the ester group seemed to have more electrophilicity by itself than a cyano group does, but when both ester and cyano groups are present in the *geminal* arrangement, the ester group enhances the electrophilic reactivity of the inert cyano group.

While it was difficult to obtain a five-membered-ring product from 3-phenylpropionitrile **6** (entry 7), a six-membered-ring cyclization was possible even in the case of the monocyano substituent: 4-phenylbutyronitrile **8** gave 1-tetralone **15** in 81% yield (entry 9) in TFSA (25 °C, 1 h), after aqueous workup. Methyl 4-phenylbutyrate **9** also afforded the same cyclized product **15**, in 97% yield under similar conditions (entry 10). The cyclization reaction of methyl 2-cyano-4-phenylbutyrate (**5j**) gave a six-membered β-enamino ester (**13j**) in 84% yield (25 °C, 48 h, entry 12, see also Table 2 (entry 10)). On the other hand, a seven- or larger-membered ring could not be obtained (entry 14).

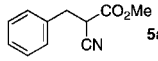
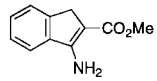
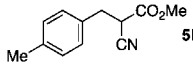
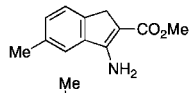
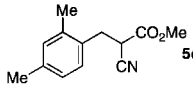
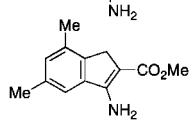
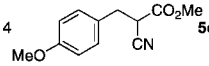
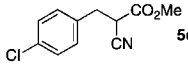
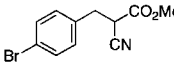
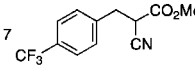
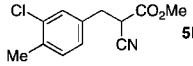
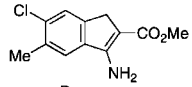
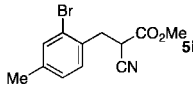
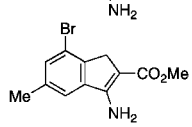
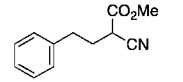
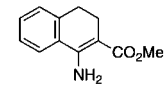
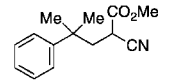
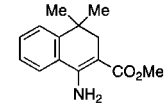
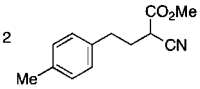
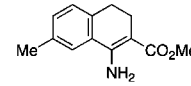
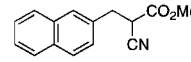
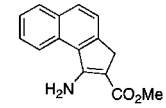
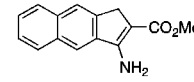
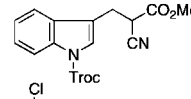
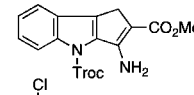
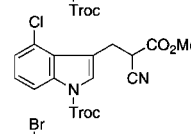
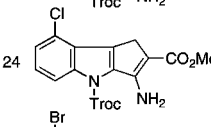
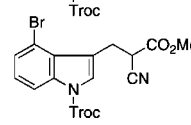
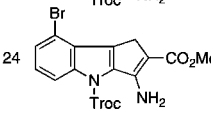
Generality of Cyclization of Arylcyanopropionates. Cyclic β-enamino esters are versatile building blocks in organic synthesis, and efficient methodologies for the synthesis of this

(3) Conversion of a cyano group to an amine functional group occurs in a few synthetic reactions of heterocyclic compounds, such as the Gewald aminothiophen synthesis (Li, J. J. *Name Reactions in Heterocyclic Chemistry*: John Wiley & Sons: Hoboken, NJ, 2005; Chapter 5). The reactions involve aromatization of heterocycles, i.e., enamine formation due to the presence of acidic protons at the α-position of the cyano group.

(4) (a) Olah, G. A.; Klumpp, D. A. *Acc. Chem. Res.* **2004**, *37*, 211–220. (b) Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 767–788. (c) Olah, G. A. ; Klumpp, D. A. *Superelectrophiles and Their Chemistry*; John Wiley & Sons: Hoboken, NJ, 2008.

(5) An extended reaction time (48 h) afforded a complex mixture of products.

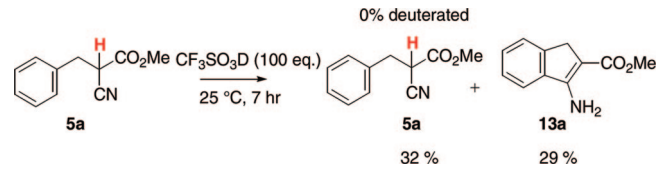
TABLE 2. Superacid-Catalyzed Cyclization of Methyl 3-Aryl-2-cyanocarboxylates[a]

entry	substrate	time (hr)	product	yield (%)
1	 **5a**	48	 **13a**	72
2	 **5b**	4	 **13b**	43
3	 **5c**	48	 **13c**	48
4	 **5d**	0.5	–	0[b]
5	 **5e**	48	–	0[c]
6	 **5f**	24	–	0[c]
7	 **5g**	24	–	0[c]
8	 **5h**	48	 **13h**	42
9	 **5i**	48	 **13i**	27
10	 **5j**	48	 **13j**	84[d]
11	 **5k**	48	 **13k**	84
12	 **5l**	3	 **13l**	67
13	 **5m**	48	 **13m**	86
				trace
14	 **5n**	6	 **13n**	55
15	 **5o**	24	 **13o**	50
16	 **5p**	24	 **13p**	38

[a] Typical procedure (**13a**): **5a** (1 mmol) was dissolved in 7.8 mL of TFSA (100 mmol, 100 equiv) in an ice−water bath, and the solution was allowed to warm to 25 °C. After 48 h, the solution was poured into ice−water, and the mixture was extracted with $CHCl_3$. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated to give a residue, which was column-chromatographed on silica gel (eluent: *n*-hexane:ethyl acetate = 10:1). Removal of the solvent afforded **13a** in 72% yield. [b] Decomposition. [c] Recovery of the substrate (**5e**: quantitative yield; **5f**: 77%; **5g**: 62%). [d] See also Table 1 (entry 12).

skelton are in high demand.[6] For example, Murakami et al. recently reported a synthetic method for five- and six-membered β-enamino esters by means of rhodium-catalyzed nucleophilic conjugate addition of organoboron species to unsaturated esters.[7] A series of β-enamino esters can also be synthesized with our protocol and these products are accessible only by the present reaction (Table 2).[8] In the case of aromatic methyl substitution, the corresponding cyclic products **13b** and **13c** were obtained in moderate yields (43% and 48% yield, respectively) (entries 2 and 3), while decomposition of the substrate occurred in the case of methoxy substitution (entry 4). An aromatic halogen atom (entries 5 and 6) and an electron-withdrawing group (CF_3, entry 7) inhibited the reaction, while the reaction proceeded when a combination of halogen atom and methyl groups was involved (entries 8 and 9). Some six-membered β-enamino esters were also obtained in good yields (entries 10−12). It was also found that tricyclic β-enamino esters could be obtained when a naphthalene or indole moiety was used instead of the benzene (entries 13−16). These substituent effects, i.e., preference for electron-rich aromatic rings, suggested that the reactions proceeded through a Friedel−Crafts-type mechanism at the cyano group.

SCHEME 1



Reaction Mechanisms Involving Distonic Dications. (a) Contribution of Deprotonation Process. To investigate the reaction mechanism, deuterium exchange experiments were carried out with **5a** and related compounds. A solution of **5a** in CF_3SO_3D (TFSA-*d*, 100 equiv) was kept at 25 °C for 7 h, and workup with D_2O afforded **13a** in 29% yield, together with recovery of **5a** in 32% yield (Scheme 1). In this case, no deuterium exchange was observed at the α-proton of the recovered **5a**, suggesting that acid-catalyzed deprotonation of the α-proton of **5a** would not be in equilibrium even under strongly acidic conditions. Similarly, no deuterium exchange of the α-protons was observed in the cases of the diester **1** and

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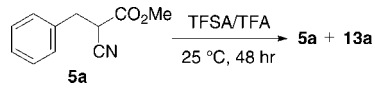
(8) The substrates for the cyclization reaction, methyl 3-aryl-2-cyanopropionates, were easily synthesized from the corresponding arylaldehyde and methyl cyanoacetate, via Knøvenagel condensation and subsequent reduction with hydrogenation or the triethylamine−formic acid azeotrope. See the Supporting Information.

TABLE 3. Acidity Dependence of the Cyclization Reaction



entry	ratio of the acids (TFSA:TFA)	H_0	yield (%) 5a	13a
1	100:0	−14.1	0	72
2	99:1	−13.6	2	64
3	9:1	−13.0	3	53
4	1:1	−11.2	62	0
5	0:100	−2.7	100	0

TABLE 4. ^{13}C NMR Analysis of Methyl Cyanoacetate in Solutions of Varying Acidity

solvent/acid	H_0	^{13}C NMR signals
$CHCl_3$	n/a	24.7, 53.7, 113.7, 164.0
TFA	−2.7	23.4, 53.9, 111.4, 166.7
TFA:TFSA (1:1)	−11	23.9, 55.2, 110.1, 168.5
TFA:TFSA (1:9)	−13	24.3, 57.1, 109.0, 171.4
TFSA	−14	24.6, 59.7, 107.6, 175.2
TFSA (1% SbF_5)	−17	24.6, 60.4, 107.2, 176.2

dicyanide **4** in TFSA-*d* under similar reaction conditions (see ref 9). This observation is in sharp contrast to the case of 3-aryl-2-nitropropionate, in which deprotonation of the α-proton occurred in TFSA, and this deprotonation process was rate-determining.[1] Furthermore, methyl 2-methyl-2-cyano-4-phenylbutyrate, in which the α-proton was replaced with a methyl group, afforded a cyclized keto ester in a low yield of 17% when it was treated with TFSA (25 °C, 48 h), followed by aqueous workup (Table 1, entry 13). This result excluded involvement of loss of the α-proton in the cyclization process.

(b) Acidity Dependence of Reactions. Reaction of **5a** showed acidity dependence: the reaction rate (in terms of the product yield after 48 h) increased as the acidity of the reaction medium was increased by mixing TFSA into TFA (Tables 3 and 4).[10–12] The reaction proceeded in a 99:1 (w/w) or 9:1 (w/w) mixture of TFSA/TFA to afford **13a** in slightly lower yield (64% or 53%, respectively) than in TFSA (72% yield) (entries 1−3), while no cyclized product **13a** was obtained and **5a** was recovered in part when TFSA/TFA = 1:1 (w/w) (entry 4) or TFA alone (entry 5) was used. The basicity values of ester carbonyl oxygen atoms and nitrile nitrogen atoms are typically approximately −6.5 and −11, respectively.[13] In the case of cyanopropionates, the electron-withdrawing nature of the substituents (ester and nitrile) will reduce the basicity of each individual functionality. When TFSA/TFA = 1:1, a mixture in which the acidity (H_0) is estimated to be −11.2, was used as the reaction medium, either the ester carbonyl oxygen atom or the cyano nitrogen atom of the cyanopropionates should be protonated, with the former being favored.[13] Under these conditions, however, the cyclization product **13a** was not obtained at all, as described above. Therefore, these results indicated that cations bearing either the *O*-protonated ester carbonyl group or *N*-protonated cyano group have an insufficient entraining effect to increase the reactivity of the inert cyano group in the *geminal* arrangement.

Direct Observation of Distonic Dications. We also carried out direct spectroscopic observation of cationic species formed from a model compound, methyl cyanoacetate, in various acidic media (Table 4). As the acidity of the medium was increased, the ester carbonyl carbon atom was deshielded, whereas the cyano carbon atom was shielded in the ^{13}C NMR spectra. After consideration of the perturbations of the ^{13}C chemical shifts arising from the solvent effect,[14] the observed acidity-dependent changes of the chemical shifts were consistent with those arising from protonation of the ester carbonyl oxygen atom and that of the nitrile nitrogen atom, respectively, as reported previously.[11b,12f,15] There are small differences in the ^{13}C chemical shifts of the species formed in TFSA and in a more acidic medium, i.e., TFSA containing 1% (w/w) SbF_5 ($H_0 \approx -17$). All these data are consistent with the postulate that the *O*,*N*-diprotonated dication (**18**) of methyl cyanoacetate, a *distonic* dication, is formed in the strong acid, and is a de facto electrophile in the present cyclization reaction of arylcyanopropionates. The experimentally observed changes of the ^{13}C chemical shifts of the species formed in TFSA, as compared with the neutral state, were in good agreement with those of GIAO calculation for the *O*,*N*-diprotonated dication, i.e., low-field shift of the carbonyl carbon atom upon protonation of the carbonyl group and high-field shift of the nitrile carbon atom upon protonation of nitrile nitrogen atom in the ^{13}C NMR spectra (Table 5).[16,17] This also supports the present conclusion concerning the formation of the *O*,*N*-diprotonated dication (**18**). When toluene was added to a

(9) To 100 equiv of TFSA-*d* was added 300 μmol of the substrate at 0 °C. The reaction mixture was stirred for 7 h at 25 °C, then poured into 20 mL of D_2O, and extracted with $CHCl_3$. The organic phase was washed with saturated NaCl, dried over Na_2SO_4, and evaporated under reduced pressure to give a residue. The residue was column-chromatographed on silica gel. Removal of the solvent afforded the substrate **1a** in 32% yield and the product **2a** in 29% yield. ^{1}H NMR spectra of the crude product and of the separated recovered substrate indicated that no proton or deuterium at the methylene position was exchanged under the reaction conditions.

(10) (a) Hammett, L. P.; Deyrup, A. J. *J. Am. Chem. Soc.* **1932**, *54*, 2721–2739. (b) Paul, M. A.; Long, F. A. *Chem. Rev.* **1957**, *57*, 1–45. (c) Jorgenson, J. J.; Hartter, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 878–883. (d) Ryabova, R. S. *Zh. Fiz. Khim.* **1966**, *40*, 339–345.

(11) (a) Saito, S.; Saito, S.; Ohwada, T.; Shudo, K. *Chem. Pharm. Bull.* **1991**, *39*, 2718–2720. (b) Saito, S.; Sato, Y.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1994**, *116*, 2312–2317.

(12) For recent representative studies on the acidity dependence of superacid-catalyzed organic reactions, see: (a) Olah, G. A.; Mathew, T.; Marinez, E. R.; Esteves, P. M.; Etzkorn, M.; Rasul, G.; Prakash, G. K. S. *J. Am. Chem. Soc.* **2001**, *123*, 11556–11561. (b) Klumpp, D. A.; Baek, D. N.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1997**, *62*, 6666–6671. (c) Yokoyama, A.; Ohwada, T.; Shudo, K. *J. Org. Chem.* **1999**, *64*, 611–617. (d) Ohwada, T.; Suzuki, T.; Shudo, K. *J. Am. Chem. Soc.* **1998**, *120*, 4629–4637. (e) Ohwada, T.; Yamazaki, T.; Suzuki, T.; Saito, S.; Shudo, K. *J. Am. Chem. Soc.* **1996**, *118*, 6220–6224. (f) Sato, Y.; Yato, M.; Ohwada, T.; Saito, S.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 3037–3043.

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(14) These changes of the chemical shifts should be partially due to solvent effects, i.e., differences in polarity and hydrogen-bonding ability of $CDCl_3$ and TFA. In these solvents, no protonation of the carbonyl oxygen atom or the cyano nitrogen atom occurred, judging from the pK_{BH^+} values. In TFA, the ^{13}C carbon of the ester carbonyl atom was deshielded (2.7 ppm) and that of the nitrile carbon atom was shielded (2.3 ppm), as compared with those in $CDCl_3$. On the other hand, the magnitude of the chemical shift changes observed in going from TFA to TFSA-SbF_5 was larger than in the case of going from $CDCl_3$ to TFA.

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(16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montogomery, J. A., Jr.; Kudin, K. N.; Burant, J. C.; Millam, J. M. Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Peterson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C. ; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, G.; Dapprich, S.; Daniels, A. K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Gaussian, Inc.: Pittsburgh, PA, 2003.

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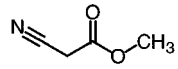
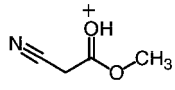
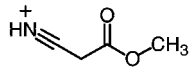
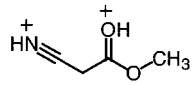
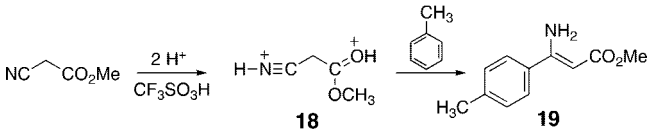
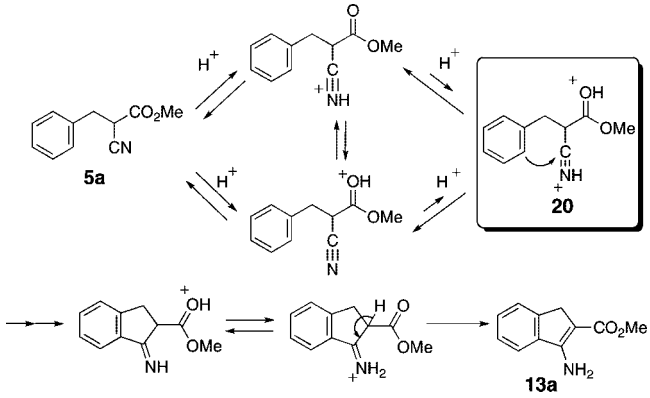
TABLE 5. ^{13}C NMR GIAO Data Obtained at Several Calculation Levels

species	calculation method	^{13}C NMR signals
	B3LYP/6-311g(d,p)//B3LYP/6-311g(d,p)	23.2, 53.8, 112.6, 167.8
	B3PW91/6-311++g(d,p)//B3PW91/6-311++g(d,p)	20.6, 50.1, 112.6, 164.5
	HF/6-311++g(d,p)//MP2/6-311++g(d,p)	12.3, 40.0, 117.0, 163.8
	B3LYP/6-311g(d,p)//B3LYP/6-311g(d,p)	26.8, 73.3, 107.1, 191.4
	B3PW91/6-311++g(d,p)//B3PW91/6-311++g(d,p)	23.4, 67.6, 107.2, 186.9
	HF/6-311++g(d,p)//MP2/6-311++g(d,p)	14.4, 56.6, 111.2, 187.3
	B3LYP/6-311g(d,p)//B3LYP/6-311g(d,p)	25.0, 62.1, 112.8, 158.1
	B3PW91/6-311++g(d,p)//B3PW91/6-311++g(d,p)	21.8, 57.8, 111.2, 155.1
	HF/6-311++g(d,p)//MP2/6-311++g(d,p)	13.9, 46.1, 111.0, 157.2
	B3LYP/6-311g(d,p)//B3LYP/6-311g(d,p)	25.9, 80.6, 102.3, 179.9
	B3PW91/6-311++g(d,p)//B3PW91/6-311++g(d,p)	22.4, 73.3, 100.5, 175.8
	HF/6-311++g(d,p)//MP2/6-311++g(d,p)	14.4, 61.4, 99.7, 177.8

SCHEME 2



SCHEME 3. Plausible Cyclization Mechanism



solution of methyl cyanoacetate in TFSA, methyl 3-amino-3-*p*-tolyl-acrylate **19** was obtained in 30% yield after aqueous workup. This is also consistent with our proposed reaction mechanism involving the *distonic* dication (Scheme 2).

Proposed Reaction Mechanisms. A plausible reaction mechanism of the intramolecular cyclization is shown in Scheme 3. Generation of the *distonic O,N*-diprotonated dicationic species (**20**) can be attributed to activation of the electrophilic center of the nitrile carbon atom. The intramolecular cyclization proceeds to give indane intermediates, followed by deprotonation of the α-proton of the ester to generate the *β*-enamino ester. In the case of the Houben−Hoesch-type reaction, *N,N*-diprotonated nitriles have been proposed as true electrophiles.[11] In Scheme 3, however, the protonated ester group activates the electrophilicity of the monoprotonated nitrile group.

In summary, we have developed a new superacid-catalyzed cyclization reaction that allows us to synthesize both five- and six-membered cyclic *β*-enamino esters from aromatic ring-containing cyanoacetates. The present reactions provide the first access to some *β*-enamino esters through ring closure of protonated nitriles by carbon attachment to the aryl ring. We observed a significant synergistic increase of reactivity of the cyano functionality, and found that the cyano nitrogen atom was converted into an amino group when an ester group was present in a *geminal* arrangement. We also studied the effect of ring size and acidity on this reaction. On the basis of deuterium exchange and spectroscopic studies, we propose the involvement of *distonic O,N*-diprotonated dicationic species (**20**). Interestingly, we found that changing one of the *geminal* groups from nitro to cyano significantly changes the mechanistic path of the reaction (see Scheme 1).

Experimental Section

Synthesis of Methyl 2-Cyano-3-arylpropionates 5 and the Other Relative Compounds. Method A: Hydrogenation with Wilkinson's Catalyst. Typical Procedure: Methyl 2-Cyano-3-phenylpropionate (5a). To the mixture of benzaldehyde (2.78 g, 26.2 mmol) and methyl cyanoacetate (2.60 g, 26.2 mmol) was added aluminum oxide 90 (10.9 g), and the mixture was kept for 1 h at rt, followed by extraction with $CHCl_3$. Evaporation of the solvent gives the crude condensation product (4.43 g, 23.7 mmol), which was used in the next reaction without further purification.

The crude product was then dissolved into a mixture of THF (20 mL) and EtOH (200 mL), and to the solution was added $Rh(PPh_3)Cl$ (1.21 g, 1.31 mmol, 5 mol %). The solution was stirred for 3 days at rt under H_2 atmosphere. Water (300 mL) was added and the whole was extracted with ether. The organic phase was washed with brine and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to give a residue that was column chromatographed on silica gel (eluent *n*-hexane:AcOEt = 6:1). Removal of the solvent afforded **5a** as a colorless oil (3.39 g, 17.9 mmol). Total yield 68%. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36−7.25 (m, total 5H), 3.78 (s, 3H), 3.72 (dd, J = 5.7, 8.5 Hz, 1H), 3.27 (dd, J = 5.7, 13.8 Hz, 1H), 3.18 (dd, J = 8.5, 13.8 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 166.0, 135.2, 129.0, 128.9, 127.9, 116.0, 53.6, 39.6, 35.8. ESI-HRMS calcd for $C_{11}H_{11}NNaO_2$ ($[M + Na]^+$) 212.0687, found 212.0701.

Method B: Reduction with Triethylamine−Formic Acid Azeotrope. Typical Procedure: Methyl 2-Cyano-3-phenylpropionate (5a). To a solution of benzaldehyde (2.00 mL, 19.7 mmol) and methyl cyanoacetate (1.74 mL, 19.7 mmol, 1 equiv) in $CHCl_3$ (5 mL) was added aluminum oxide 90 (1 g) at 18 °C. Then, the solution was stirred for 10 min, and the whole was filtered to remove aluminum oxide. The solution was evaporated under reduced pressure to give a residue. The crude was recrystallized

from *n*-hexane/$CHCl_3$ to afford the condensation product as colorless needles (3.34 g, 12.2 mmol, 91%).

To a solution of the condensation product (1.00 g, 5.34 mmol) in DMF (100 mL) were added formic acid (2.01 mL, 53.4 mmol, 10 equiv) and triethylamine (2.98 mL, 21.4 mmol, 4 equiv) and the reaction mixture was stirred at 18 °C for 1 week. Then, water (100 mL) was added, and the whole was extracted with AcOEt. The organic phase was washed with brine and dried over Na_2SO_4, then the solvent was evaporated under reduced pressure to give a residue, which was column chromatographed on silica gel (eluent: *n*-hexane:ethyl acetate = 10:1) to afford **5a** as a colorless oil (515 mg, 2.72 mmol, 51%).

Superacid-Catalyzed Intramolecular Cyclization Reaction of Methyl 3-Aryl-2-Cyanopropionates and the Related Compounds. Typical Procedure: Methyl 3-amino-1*H*-indene-2-carboxylate (13a). To ice-cooled TFSA (8.9 mL, 100 mmol, 100 equiv) was slowly added **5a** (188 mg, 0.99 mmol), and the solution was stirred at 25 °C for 48 h. To the solution was added $CHCl_3$ (10 mL) and the mixture was poured into ice−water (50 mL), which was extracted with $CHCl_3$. The organic phase was washed with brine and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to give a residue, which was column chromatographed on silica gel (eluent *n*-hexane:AcOEt = 6:1). Removal of the solvent afforded **13a** as a pale yellow solid (136 mg, 0.72 mmol). Yield 72%. Mp 104.0−105.0 °C (recrystallized from ether, white needles). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.49−7.34 (m, total 4H), 5.96 (br s, 2H), 3.80 (s, 3H), 3.57 (s, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 168.2, 156.1, 144.2, 138.0, 128.7, 126.3, 124.8, 118.7, 98.1, 50.5, 34.6. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.58; H, 6.02; N, 7.31.

Deuterium Exchange Experiment. To 100 equiv of TFSA-*d* was added 300 mmol of the substrate at 0 °C. The reaction mixture was stirred for 7 h at 25 °C, then poured into 20 mL of D_2O, and extracted with $CHCl_3$. The organic phase was washed with saturated NaCl, dried over Na_2SO_4, and evaporated under reduced pressure to give a residue. The residue was column chromatographed on silica gel. Removal of the solvent afforded the substrate **5a** in 32% yield and the product **13a** in 29% yield. ^{1}H NMR spectra of the crude product and of the separated recovered substrate indicated that no proton or deuterium at the methylene position was exchanged under the reaction conditions.

Experiments of Acidity Dependence of Reactions. TFSA and TFA were mixed in various weight ratios under an Ar atmosphere. To 5 mL of the combined acid was added 0.5 mmol of **5a** at 0 °C. The whole was stirred at 25 °C for 48 h. Then the mixture was poured into 50 mL of ice−water and the whole was extracted with $CHCl_3$. The organic phase was washed with saturated NaCl and dried over Na_2SO_4, then the solvent was evaporated under reduced pressure to give a residue. The residue was column chromatographed on silica gel. Removal of the solvent afforded **5a** and **13a**.

Low-Temperature ^{13}C NMR Analysis of Methyl Cyanoacetate. TFSA (0.5 mL) was added to a dried, Ar-filled test tube (or flask) and cooled to −78 °C. To the solution was added methyl cyanoacetate (20 mg). With vigorous stirring, the resulting solution is transferred to a dried, cold NMR tube (precooled to −78 °C). A coaxial insert containing acetone-d_6 is then inserted into the NMR tube and the NMR spectra were obtained at −15 to −10 °C.

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Supporting Information Available: Spectroscopic and analytical data, experimental procedures, Cartesian coordinates, and energetic values of calculated species. This material is available free of charge via the Internet at http://pubs.acs.org.

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