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Synthesis of *β*-Cyanopropan-1-one Derivates by Domino Reaction

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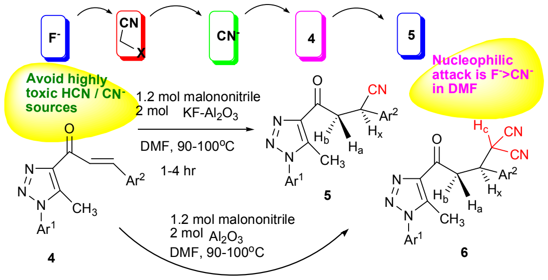

Polysubstituted *β*-cyanopropan-1-one was synthesized by the Domino nucleophilic addition reaction of four-component Al_2O_3-catalyzed and low-toxicity reagents. (16 words)

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Domino nucleophilic addition was used for four-component Al_2O_3-catalyzed environmentally friendly synthesis of polysubstituted β-cyanopropan-1-one. Domino nucleophilic addition involves removal of the cyano group linked to active methylene by the action of KF, and direct addition to enones. The reaction capability for nucleophilic attack is F^- >CN^- in DMF. The use of low-toxicity reagents hints that the reaction is more environmentally friendly than traditional approaches.

Cascade reactions and multicomponent domino reactions are being increasingly applied to the construction of natural and designed molecules. Such processes, in which ideally a single event triggers the conversion of a starting material to a product which then becomes a substrate for the next reaction until termination leads to a stable final product, are highly desirable not only due to their elegance, but also because of their efficiency and economy in terms of reagent consumption and purification. Often, these multistep, one-pot procedures are accompanied by dramatic increases in molecular complexity and impressive selectivity. The discovery of new molecular diversity from Nature and the demand for more efficient and environmentally benign chemical processes dictates and invites the further development of such synthetic strategies and tactics as we move into a new age of chemical synthesis.[1]

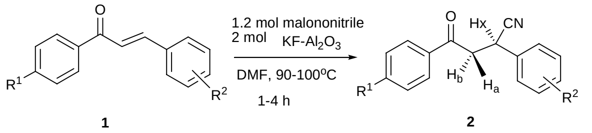
Conjugate hydrocyanation of α,β-unsaturated carbonyl compounds is of great interest because the resulting β-cyanoadducts are easily converted to other products under various conditions. A powerful method for cyano introduction in the β-position is the hydrocyanation reaction of conjugated α,β-unsaturated ketones with HCN(HCN, potassium and acetic acid, acetone cyanohydrin as the cyanide source)[2] or a transition metal cyanide in the presence of Lewis acid catalysts such as Gd,[3] Al complexes[4] and $SnCl_2$.[5] Recently, efficient conjugate hydrocyanation of chalcones and related enones with a TMSCN (TMSCN, costly price, easily decompose) under solvent- and additive-free microwave conditions was reported by Iida, et al.[6] There are other efficient methods for the synthesis of β-cyanoketones. For example, β-cyanoadducts can be prepared by reacting α,β-unsaturated ketones with acetone cyanohydrin in the presence of TBAF or Na_2CO_3.[7] Reaction of α,β-enones with KCN also yields Michael adducts.[8]

Here we report a new method for the synthesis of β-cyanoketones. A series of 1,4-adducts was obtained by the reactions of chalcones (*E*)-3-aryl-1-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)-prop-2-en-1-ones with malononitrile in the presence of KF-Al_2O_3 and *N*,*N*-dimethylformamide (DMF). Fluoride salts are useful as potential bases in a variety of synthetic reactions,[9] but their low solubility in ordinary solvents limits their application in organic synthesis. Inorganic solid supports are increasingly used as catalysts for many years because of higher selectivity, milder reaction conditions and easier work-up.[10] In particular, KF-coated alumina is a versatile solid-supported reagent for Knoevenagel,[11] Henry,[12] Darzens,[13] Witting,[14] alkylation,[15] elimination,[16] and many other reactions.[17] We found that KF-Al_2O_3 was an efficient catalyst for reactions between α,β-unsaturated ketones and malononitrile for β-cyanoketone synthesis.

When (*E*)-1,3-diarylprop-2-en-1-ones **1** (1 equiv), malononitrile (1.2 equiv), and KF-Al_2O_3 (2 equiv) were heated at 90–100°C for 1–4 h in DMF (**Table 1**), the desired 2,4-diarylbutyronitriles **2** were obtained in good yield. The 1*H*-1,2,3-triazole derivative is a heterocyclic compound with wide biological activity and applications in many fields.[17] Our interest in the 1*H*-1,2,3-triazole heterocyclic ring[18] prompted us to synthesize some new 2-[1-aryl-3-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)-3-oxopropyl]malononitriles,
but we obtained a new series of 2-aryl-4- (1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl) butyro nitriles **5** by the reactions of compounds **4** (1 equiv) and malononitrile (1.2 equiv) in the presence of KF-Al_2O_3 (2 equiv) at 90–100°C for 6–8 h(**Table**

2). The 1*H*-1,2,3-triazole heterocyclic ring as the target for the hydrocyanations is in order to research effiction of diversified structure on the reaction, as most system of ring organic compounds is consist of carbon ring and nitrogen heterocyclic ring(Pyridine N, pyrrole N, imidazole or triazole N etc., 1,2,3-triazole heterocyclic ring could replace all of them).

Table 1. Cyano Michael Addition Catalyzed by Al_2O_3

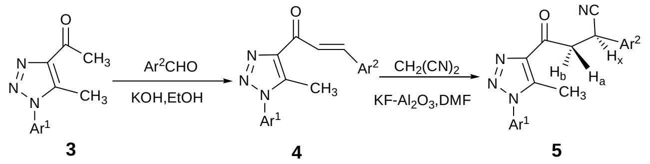


R^1	R^2	Product	Time (h)	Yield (%)[a]
H	H	**2a**	2	63
H	CH_3	**2b**	2	72
H	3,4-diCH_3	**2c**	3	75
H	4-Cl	**2d**	1	55
H	3-Cl	**2e**	1.5	72
H	4-CH_3O	**2f**	1	69
CH_3	4-Cl	**2g**	2	66
CH_3	4-CH_3O	**2h**	1	62
CH_3	4-$(CH_3)_2N$	**2i**	4	57

[a] Isolated yield.

The targets were synthesized according to the procedure in **Table 2**. From the results we hypothesized that KF might be crucial for removal of the cyano group from malononitrile. To confirm our hypothesis, we reacted **4f** (1 equiv), malononitrile (1.2 equiv) and KF (2 equiv) in DMF at 100°C for 8 h and obtained **5f** in 35% yield without alumina. Based on our results, we propose a possible reaction mechanism in **Scheme 1**.

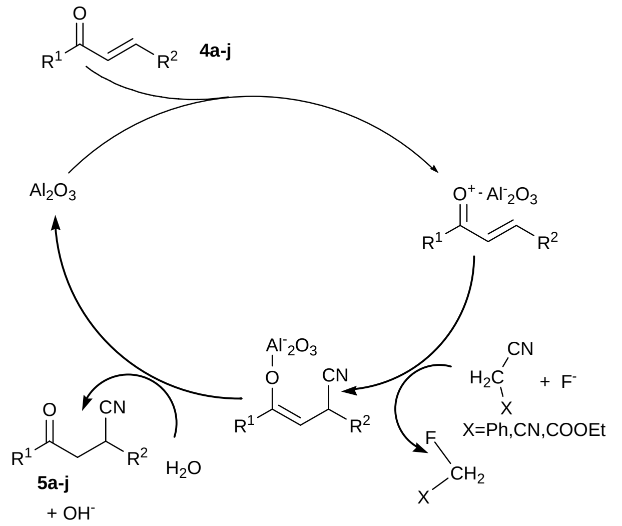
Table 2. Cyano-Michael Addition Catalyzed by KF-Al_2O_3



Ar^1	Ar^2	Product	Time(h)	Yield(%)[a]
C_6H_5	C_6H_5	**4a**	6	92
		5a	8	62
C_6H_5	4-$CH_3C_6H_4$	**4b**	6	86
		5b	8	63
C_6H_5	4-ClC_6H_4	**4c**	6	90
		5c	8	70
4-$CH_3C_6H_4$	C_6H_5	**4d**	6	90
		5d	8	74
4-$CH_3C_6H_4$	4-ClC_6H_4	**4e**	6	79
		5e	7	65
4-ClC_6H_4	C_6H_5	**4f**	6	89
		5f	6	74
2-ClC_6H_4	4-$CH_3C_6H_4$	**4g**	6	92
		5g	6	79
2-ClC_6H_4	4-ClC_6H_4	**4h**	6	95
		5h	8	77
4-$C_2H_5OC_6H_4$	4-ClC_6H_4	**4i**	6	95
		5i	6	64

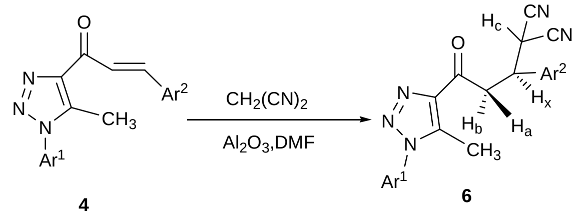
[a] Isolated yield.

Scheme 1. Mechanism postulated for KF-Al_2O_3-catalyzed conjugate addition.



To investigate the reaction mechanism, we reacted **4** (1 equiv), malononitrile (1.2 equiv) and Al_2O_3 (2 equiv) under the same conditions. Instead of the targets **5**, 2-[1-aryl-3-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)-3-oxopropyl]malononitriles **6** were obtained (**Table 3**). Al_2O_3 has sufficient Lewis acidity to activate the carbonyl group in chalcones and generate an electrophilic substrate (Michael acceptor) (**Scheme 1**). Malononitrile was attacked by the high-nucleophilic F^- ion to give a negatively charged CN^- ion. Finally, the activated chalcone was attacked by CN^- as a Lewis base or nucleophile (Michael donor) during addition. The cyano group in malononitrile can be removed by the action of KF-Al_2O_3 and the cyano group linked to the other active methylene can also be removed in a one-pot tandem reaction. The cyano group linked to active methylene removed by KF action is then directly added to enones(X=Ph, isolate, identified by NMR; $PhCH_2CN + F^- = PhCH_2F + CN^-$). The reaction capability for nucleophilic attack is $F^- > CN^-$ in DMF($CN^- > Cl^- > I^-$, F^- is not reported), but reaction capability for nucleophilic attack is $CN^- > F^-$ in H_2O($CN^- > I^- > Cl^-$).[19]

Table 3. Carbon Michael addition catalyzed by Al_2O_3



Ar^1	Ar^2	Product	Time (h)	Yield (%)[a]
C_6H_5	C_6H_5	**6a**	7	72
C_6H_5	4-$CH_3C_6H_4$	**6b**	7	62
C_6H_5	4-ClC_6H_4	**6c**	6	73
4-$CH_3C_6H_4$	C_6H_5	**6d**	6	72

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4-$CH_3C_6H_4$	4-ClC_6H_4	**6e**	6	62
4-ClC_6H_4	C_6H_5	**6f**	6	79
2-ClC_6H_4	4-$CH_3C_6H_4$	**6g**	6	70
2-ClC_6H_4	4-ClC_6H_4	**6h**	6	78
4-$C_2H_5OC_6H_4$	4-ClC_6H_4	**6i**	6	77

[a] Isolated yield.

Reaction of **4f** (1 equiv), KF-Al_2O_3 (2 equiv) and ethyl cyanoacetate or 2-phenyl acetonitrile (1.2 equiv) under the same conditions (**Scheme 2**) gave **5f** in yield of 25% and 87%, respectively, but CH_3CN, CH_2=CH-CN did not give yield. Yield of compound **5g** is a function of the **5g** and KF/Al_2O_3 ratio (**Table 4**). Highly toxic HCN and metal cyanides are replaced by low-toxicity malononitrile, 2-phenyl acetonitrile or ethyl cyanoacetate. The reaction capability for cyano group removal by KF is 2-phenyl acetonitrile > malononitrile > ethyl cyanoacetate(2-phenyl acetonitrile, malononitrile, ethyl cyanoacetate is 87%, 74%, 25%).

Scheme 2. Reaction of **4f** and ethyl cyanoacetate or 2-phenyl acetonitrile under the same conditions.

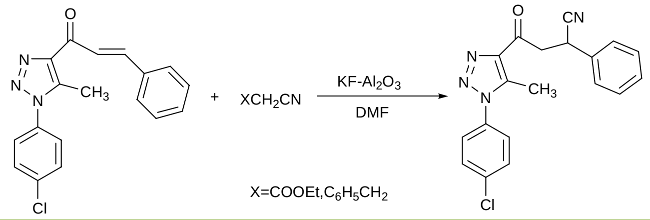

Table 4. Yield of compound **5g** as a function of the KF/Al_2O_3 ratio

Entry	KF/Al_2O_3 (mol%)	Yield (%)[a]
1	15	8
2	50	13
3	**100**	**21**
4	200	31
5	300	55
6	400	71
7	500	79
8	600	77
9	700	73

[a] Isolated yield.

Conclusions

In conclusion, a novel tandem nucleophilic addition was used for four-component KF–Al_2O_3-catalyzed environmentally friendly synthesis of polysubstituted β-cyanopropan-1-one. The tandem nucleophilic addition involves removal of the cyano group linked to active methylene by the action of KF, and then direct addition to enones. The reaction uses reagents of low toxicity and is thus more environmentally friendly than some traditional approaches.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedure, characterization data, ^1H and ^{13}C NMR spectra of products See DOI: 10.1039/b000000x/

1. For recent reviews, see: (a) H. Pellissier, *Adv. Synth. Catal.,* 2012, **354**, 237-294; (b) H. Clavier and H. Pellissier, *Adv. Synth. Catal.,* 2012, **354**, 3347-3403; (c) W. Raimondi, D. Bonne and J. Rodriguez, *Angew. Chem. Int. Ed*., 2012, **51**, 40-42; (d) A. Grossmann and D. Enders, *Angew. Chem. Int. Ed.,* 2012, **51**, 314-325; (e) M. Platon, R. Amardeil, L. Djakovitch and J. C. Hierso, *Chem. Soc. Rev.,* 2012, **41**, 3929-3968; (f) D. Tejedor, G. Méndez-Abt, L. Cotos and F. Garcia-Tellado, *Chem. Soc. Rev.,* 2013, **42**, 458-471; (g) M. Malacria, *Chem. Rev.* 1996, **96**, 289-306; (h) K. C. Nicolaou, T. Montagnon and S. A. Snyder, *Chem. Commun*., 2003, 551-564; (i) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed*., 2006, **45**, 7134-7186; (j) D. Enders, C. Grondal and M. R. M. Hüttl, *Angew. Chem., Int. Ed.,* 2007, **46**, 1570-1581.
2. (a) W. Nagata and M. Yoshioka, *In Organic Reactions*, (ED.: W. O. Dauben), John Wiley and Sons Inc., New York, 1977; Vol. **25**, 255; (b) A. Lapworth and E. Wechsler, *J. Chem. Soc*. Trans., 1910, **97**, 38-48; (c) H. Ishii, I. S. Chen and T. Ishikawa, *J. Chem. Soc*., Perkin Trans., 1, 1987, 671-676; (d) W. Davey and D. J. Tivey, *J. Chem. Soc*., 1958, 1230-1235; (e) I. N. Nazarov and S. I. Zav'yalov, *J. Gen. Chem*., USSR (Engl. Transl.) 1954, **24**, 475-478 (*Chem. Abstr*., 1955, **49**, 6139f); (f) B. E. Betts and W. Davey, *J. Chem. Soc*., 1958, 4193-4196; (g) C. L. Liotta, A. M. Dabdoub and L. H. Zalkow, *Tetrahedron Lett.*, 1977, 1117-1120.
3. (a) Y. Tanaka, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.,* 2008, **130**, 6072-6073; (b) T. Mita, K. Sasaki, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.,* 2005, **127**, 514-515.
4. (a) G. M. Sammis and E. N. Jacobsen, *J. Am. Chem. Soc*., 2003, **125**, 4442-4443; (b) G. M. Sammis, H. Danjo and E. N. Jacobsen, *J. Am. Chem. Soc.,* 2004, **126**, 9928-9929.
5. K. Utimoto, Y. Wakabayashi, T. Horie, M. Inoue, Y. Shishiyama, M. Obayashi and H. Nozaki, *Tetrahedron,* 1983, **39**, 967-973.
6. (a) H. Iida, T. Moromizato, H. Hamana and K. Matsumoto, *Tetrahedron Lett.,* 2007, **48**, 2037-2039; (b) Y. Tanaka, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc*., 2008, **130**, 6072-6073.
7. (a) A. Loudet, R. Bandichhor, L. X. Wu and K. Burgess, *Tetrahedron,* 2008, **64**, 3642-3654; (b) E. M. Davis and J. E. Ellis, Patent *WO* 9815524, 1998.
8. (a) K. Hino, Y. Nagai, H. Uno, Y. Masuda, M. Oka and T. Karasawa, *J. Med. Chem*., 1988, **31**, 107-117; (b) J. A. Ciller, N. Martin, M. Quinteiro, C. Seoane and J. L. Soto, *Org. Prep. Procedures Int*., 1986, **18**, 227-236; (c) M. A. I. Salem, H. M. F. Madkour, E. S. A. Soliman and N. F. H. Mahmoud, *Heterocycles,* 2000, **53**, 1129-1143.
9. (a) J. H. Clark, *Chem. Rev*., 1980, **80**, 429-452; (b) J. W. Apsimon, J. W. Hooper and B. A. Laishes, *Can. J. Chem*., 1970, **48**, 3064-3075.
10. (a) D. Villemin and M. Ricard, *Tetrahedron Lett*., 1984, **25**, 1059-1060; (b) J. A. Cabello, J. M. Campelo, A. Garcia, D. Luna and J. M. Marinas, *J. Org. Chem*., 1984, **49**, 5195-5197.
11. Y. Gao, D. Q. Shi, L. H. Zhou and G. Y. Dai, *Chin. J. Org. Chem.,* 1996, **16**, 548-551.

Green Chemistry Accepted Manuscript

12. J. M. Melot, F. M. Boullet and A. Foucaud, *Tetrahedron Lett*., 1986, **27**, 493-496.
13. J. Yamawaki, T. Kawate, T. Ando and T. Hanafusa, *Bull. Chem. Soc. Jpn*., 1983, **56**, 1885-1886.
14. F. Texier-boullet, D. Villemin, M. Ricard, H. Moison and A. Foucaud, *Tetrahedron,* 1985, **41**, 1259-1266.
15. (a) T. Ando, J. Yamawaki, T. Kawate, S. Sumi and T. Hanafusa, *Bull. Chem. Soc. Jpn.,* 1982, **55**, 2504-2507; (b) J. Yamawaki, T. Ando and T. Hanafusa, *Chem. Lett*., 1981, **(8)**, 1143-1146; (c) D. Villemin, *J. Chem. Soc. Chem. Commun*., 1985, **(13)**, 870.
16. (a) X. S. Wang, D. Q. Shi and S. J. Tu, *Chin. J. Org. Chem*., 2002, **22**, 909-912; (b) X. S. Wang, D. Q. Shi and S. J. Tu, *Synth. Commun*., 2003, **33**, 119-126; (c) X. S. Wang, D. Q. Shi and S. J. Tu, *Chin. J. Org. Chem.,* 2003, **23**, 203-206; (d) S. H. Wang, X. S. Wang, D. Q. Shi, S. J. Tu, *Chin. J. Chem*. 2003, **23**, 1146-1148; (e) X. S. Wang, D. Q. Shi, H. Z. Yu, G. F. Wang and S. J. Tu, *Synth. Commun*., 2004, **34**, 509-514.
17. (a) R. Alonso, M. J. Camarasa, G. Aloso and F. G. de Las Heras, *Eur. J. Med. Chem*., 1980, **15**, 105-109; (b) T. Araki and Y. Kinoshita, Patent *WO* 0142227, 2001; (c) C. S. Andotra, R. Kumar, S. Dham and P. Sharma, *J. Heterocycl. Chem*., 1998, **8**, 139–142; (d) F. E. Tisdell, J. R. Schoonover, L. P. Jr. Dintenfass, J. T. Pechacek, V. B. Hegde, J. M. Gifford, M. C. Yap, D. H. Devries, C. T. Hamilton, N. R. Pearson and M. L. Ash, Patent *WO* 00 247204, 2000; (e) F. E. Tisdell, J. T. Pechack, P. L. Johnson, S. J. Bis, V. B. Hedge, J. R. Schoonover, L. P. Jr. Dintenfass, P. V. Ripe, L. P. Dintenfass, T. D. Thibault, M. L. Ash, D. H. Devries and T. P. Martin, Patent *WO* 00 247374, 2000; (f) A. San-Félix, R. Aelarez, S. Velázquez, E. De Clerq, J. Balzarini and M. J. Camarasa, *Nucleosides & Nucleotides,* 1995, **14**, 595-598.
18. (a) H. S. Dong, D. D. Wang and C. Q. Jin, *J. Chin. Chem. Soc*., 2005, **52**, 1011-1016; (b) H. S. Dong and B. Wang, *J. Chin. Chem. Soc.,* 2005, **52**, 103-108; (c) B. Quan, H. S. Dong, B. Wang and T. Q. Zhang, *Indian J. Heterocycl. Chem.,* 2004, **13**, 393-394; (e) G.-L. Shen, Z.-B. Chen, Z.-F. Wu and H.-S. Dong, *J. Heterocyclic Chem.*, 2013, **50**, 781-786.
19. D. Landini, A. Maia and F. Montanari, *J. Am. Chem. Soc.,* 1978, **100**, 2796-2801.

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