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One-pot synthesis of benzoylacetonitriles through sequential Pd-catalyzed carbonylation and decarboxylation

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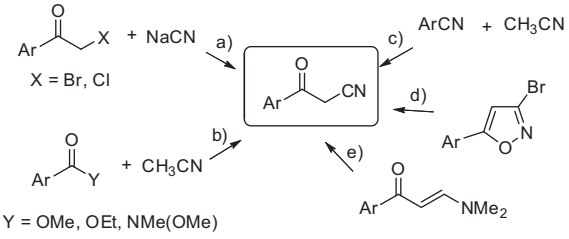
ABSTRACT

Benzoylacetonitrile were prepared through sequential carbonylation and decarboxylation. The palladium-catalyzed carbonylation of aryl iodides and methyl cyanoacetate using $Mo(CO)_6$ as a carbon monoxide source afforded beta-keto cyanoesters, and then the subsequent reaction with Li/H_2O produced the desired benzoylacetonitriles.

Introduction

Benzoylacetonitrile is an important building block because it can be converted to a variety of heterocyclic compounds such as cytosine,[1] triazole,[2] imidazole,[3] furan,[4] aminopyrazole,[5] aminoisoxazole,[6] isoxazole,[7] and pyridine.[8] In addition, it has been employed as a starting material for the preparation of biologically active materials, such as antimicrobial,[9] antineoplastic,[10] and anti-inflammatory agents,[11] and HIV inhibitors.[12] A number of preparation methods have been developed as shown in Scheme 1. The substitution of α-haloacetophenones with cyanide (Scheme 1a),[13] the coupling of an ester (or *N*-methoxy-*N*-methylbenzamide) and acetonitrile in the presence of a strong base (Scheme 1b),[14] the reaction between benzonitriles and acetonitrile (Scheme 1c),[15] the ring opening of 3-bromoisoxazole (Scheme 1d),[16] and the reaction of enaminones with hydroxylamine hydrochloride (Scheme 1e) have been employed to produce benzoylacetonitriles.[17]

Recently, we first reported the synthesis of benzoylacetonitriles through palladium-catalyzed carbonylation with aryl halides and trimethylsilyl acetonitrile (Scheme 2a).[18] Palladium-catalyzed carbonylation has been used in the synthesis of carbonyl compounds such as amides, esters, and ketones via the couplings of aryl halides and nucleophiles in the presence of carbon monoxide.[19] Although it is a simple and straightforward method, the handling of carbon monoxide gas requires special equipment and is a safety issue. In order to address the use of toxic carbon monoxide, we developed an alternative method that utilizes $Mo(CO)_6$ as a carbon monoxide surrogate. A number of carbonylation methods using $Mo(CO)_6$ have been reported.[20] Although these two methods provided straightforward protocols for the synthesis of benzoylacetonitriles from aryl halides, they required trimethylsilyl acetonitrile, which may give rise to cost issues. Therefore, the development of a synthetic method that uses much less expensive reagents is still in demand. To meet this requirement, we focused our attention on the carbonylation of aryl iodides with methyl cyanoacetate (**2**) and the subsequent decarboxylation.



Scheme 1. Classical methods for the synthesis of benzoylacetonitriles.

The palladium-catalyzed coupling reaction of aryl halides with alkyl cyanoacetates has been reported by other groups.[21] However, the carbonylation of aryl halides and cyanoacetate in the presence of a carbon monoxide has never been reported. Here, we first report the direct synthesis of benzoylacetonitriles through the car-

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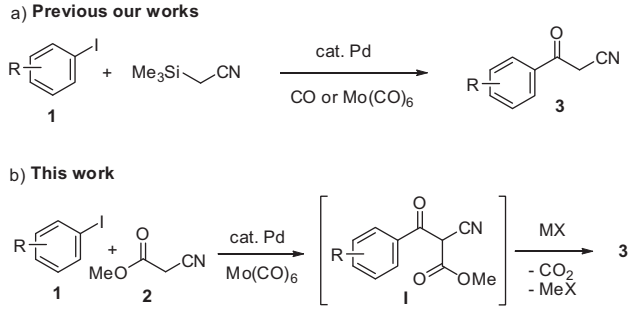
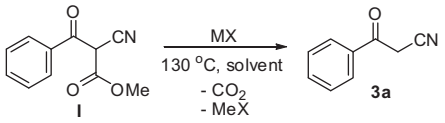


Scheme 2. Synthesis of benzoylacetonitriles through carbonylation.

Table 1
Optimization of Krapcho decarboxylation[a]



Entry	MX	Solvent	Yield[b] (%)
1	NaCN	DMSO/H_2O	43
2	NaCl	DMSO/H_2O	90
3	LiCl	DMSO/H_2O	84
4	KI	DMSO/H_2O	43
5	LiI	DMSO/H_2O	55
6	NaCN	DMF/H_2O	23
7	NaCl	DMF/H_2O	43
8	LiCl	DMF/H_2O	38
9	KI	DMF/H_2O	77
10	LiI	DMF/H_2O	88
11	NaCl	NMP/H_2O	51
12	LiI	NMP/H_2O	91

[a] Reaction conditions: **I** (0.3 mmol) and MX (0.6 mmol) were reacted at 120 °C for 6 h.
[b] Determined by gas chromatography with an internal standard.

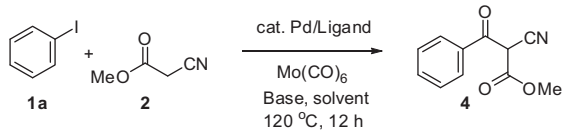
bonylation of aryl halides with alkyl cyanoacetates and a subsequent decarboxylation.

To achieve this goal, we first attempted to find the optimized conditions for the decarboxylation of methyl 2-cyano-3-oxo-phenylpropanoate (**I**), which can be obtained through the coupling reaction of an aryl halide and the corresponding cyanoacetate in the presence of a carbon monoxide source. This decarboxylation of an ester bearing an electron-withdrawing group at the β-position is known as the Krapcho reaction.[22] The results are summarized in Table 1.

When NaCN, NaCl, and LiCl, which showed good activity in the Krapcho decarboxylation, were employed in DMSO, desired product **3a** was formed in 43%, 90%, and 84% yields, respectively (entries 1–3). However, KI and LiI gave product **3a** in 43% and 55% yields, respectively (entries 4 and 5). Bearing in mind the subsequent reaction, the decarboxylation was tested in DMF, which was a good solvent in the palladium-catalyzed carbonylation for the synthesis of benzoylacetonitriles. We found that NaCN, NaCl, and LiCl provided lower yields of the product than they did in DMSO (entries 6–8). KI and LiI showed good yields in DMF (entries 9 and 10). When the reaction was conducted in NMP (*N*-methyl-2-pyrrolidinone), NaCl was inferior to LiI (entries 11 and 12).

In order to accomplish the one-pot sequential synthesis of benzoylacetonitriles, we attempted the palladium-catalyzed carbonylation of an aryl iodide and a cyanoacetate in the presence of $Mo(CO)_6$ (Table 2). As a model reaction, iodobenzene and methyl cyanoacetate were tested in the synthesis of the intermediate,

Table 2
Optimization of the carbonylation[a]



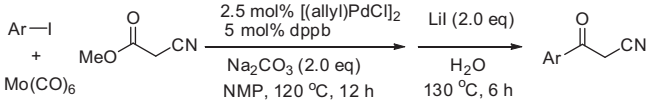
Entry	Catalyst	Ligand	Base	Solvent	Yield[b] (%)
1	$Pd(PPh_3)_2Cl_2$	PPh_3	Na_2CO_3	NMP	40
2	$Pd(PPh_3)_2Cl_2$	dppb	Na_2CO_3	NMP	54
3	$Pd_2(dba)_3$	PPh_3	Na_2CO_3	NMP	36
4	$Pd_2(dba)_3$	dppb	Na_2CO_3	NMP	57
5	$[(allyl)PdCl]_2$	PPh_3	Na_2CO_3	NMP	55
6	$[(allyl)PdCl]_2$	dppb	Na_2CO_3	NMP	87
7	$[(allyl)PdCl]_2$	dppf	Na_2CO_3	NMP	60
8	$[(allyl)PdCl]_2$	Xantphos	Na_2CO_3	NMP	70
9	$[(allyl)PdCl]_2$	BINAP	Na_2CO_3	NMP	62
10	$[(allyl)PdCl]_2$	dppb	K_2CO_3	NMP	61
11	$[(allyl)PdCl]_2$	dppb	Cs_2CO_3	NMP	73
12	$[(allyl)PdCl]_2$	dppb	Na_3PO_4	NMP	51
13	$[(allyl)PdCl]_2$	dppb	Na_2CO_3	DMF	81
14	$[(allyl)PdCl]_2$	dppb	Na_2CO_3	DMSO	53

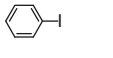
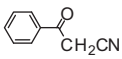
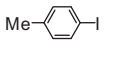
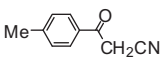
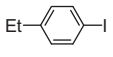
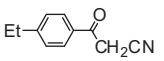
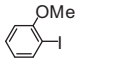
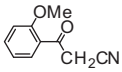
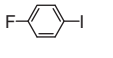
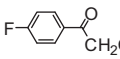
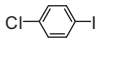
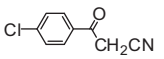
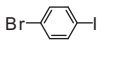
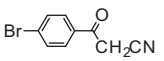
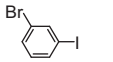
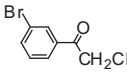
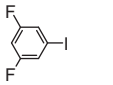
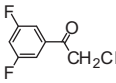
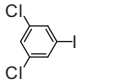
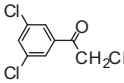
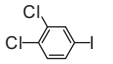
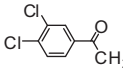
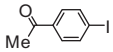
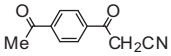
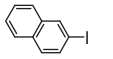
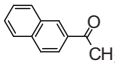
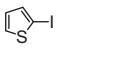
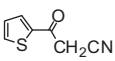
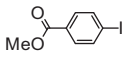
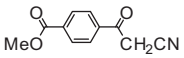
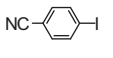
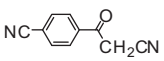
[a] Reaction conditions: iodobenzene (0.3 mmol), methyl cyanoacetate (0.6 mmol), $Mo(CO)_6$ (0.3 mmol), palladium catalyst (0.015 mmol), ligand (0.015 mmol), and base (0.6 mmol) were reacted in NMP (1.0 mL) at 120 °C for 12 h.
[b] Isolated yield.

methyl 2-cyano-3-oxo-3-phenylpropanoate, in the subsequent reaction. First, we employed $Pd(PPh_3)_2Cl_2$, which had shown good activity in the coupling reaction in the presence of $Mo(CO)_6$, as the palladium catalyst. When PPh_3 and 1,4-bis(diphenylphosphino) butane (dppb) were used as ligands, desired carbonyl compound **4** was formed in 40% and 54% yields, respectively (entries 1 and 2). When the palladium catalyst was changed to $Pd_2(dba)_3$ with PPh_3 and dppb as ligands, the yields did not improve (entries 3 and 4). When $[(allyl)PdCl]_2$ was employed as the palladium catalyst, the reactions with PPh_3 and dppb as ligands afforded the desired product in 55% and 87% yields, respectively (entries 5 and 6). However, other chelating phosphine ligands such as 1,1′-bis(diphenylphosphino)ferrocene (dppf), Xantphos, and BINAP were not superior to dppb and did not give satisfactory results (entries 7–9). When K_2CO_3, Cs_2CO_3, and Na_3PO_4 were used as bases instead of Na_2CO_3, the desired product was formed in 61%, 73%, and 51% yield, respectively (entries 10–12). The reaction in DMF gave an 81% yield of the product (entry 13). However, the reaction in DMSO, which is a good solvent in the decarboxylation, did not give a satisfactory result (entry 14).

Finally, we combined the carbonylation and the decarboxylation for the sequential one-pot synthesis of benzoylacetonitriles. The optimized conditions were as follows: aryl iodide, methyl cyanoacetate, $Mo(CO)_6$, $[(allyl)PdCl]_2$, dppb, and Na_2CO_3 were reacted in NMP at 120 °C for 12 h, and then LiI/H_2O was added to the resulting mixture and stirred at 130 °C for 6 h. To evaluate this methodology, a variety of aryl iodides was tested under the optimized conditions. As shown in Table 3, moderate yields were obtained in most cases. As expected, iodobenzene provided the desired benzoylacetonitrile in 76% isolated yield (entry 1). Methyl-, ethyl-, and methoxy-substituted iodobenzenes gave desired products **3b**, **3c**, and **3d** in 70%, 71%, and 69% yields, respectively (entries 2–4). Halide-substituted aryl iodides afforded the desired benzoylacetonitriles in yields ranging from 55% to 71% (entries 5–11). 4-Iodoacetophenone gave desired product **3l** in 57% yield (entry 12). 2-Naphthyl iodide and 2-thiophenyl iodide provided corresponding products **3m** and **3n** in 83% and 44% yields, respectively (entries 13 and 14). However, aryl iodides bearing ester or cyano groups did not give the desired products (entries 15 and 16).[23]

Table 3
Synthesis of benzoylacetonitriles[a]

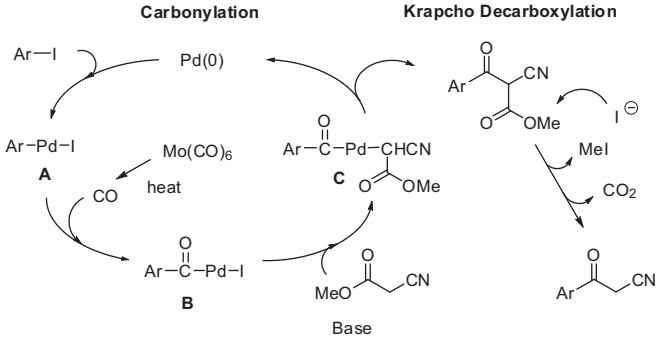


Entry	R	Product		Yield[b] (%)
1			**3a**	76
2			**3b**	70
3			**3c**	71
4			**3d**	69
5			**3e**	61
6			**3f**	63
7			**3g**	71
8			**3h**	62
9			**3i**	62
10			**3j**	59
11			**3k**	55
12			**3l**	57
13			**3m**	83
14			**3n**	44
15			**3o**	0
16			**3p**	0

[a] Reaction conditions: aryl iodide (3.0 mmol), methyl cyanoacetate (6.0 mmol), $Mo(CO)_6$ (3.0 mmol), $[(allyl)PdCl]_2$ (0.075 mmol), dppb (0.15 mmol), and Na_2CO_3 (6.0 mmol) were reacted in NMP (8.0 mL) at 120 °C for 12 h, and then LiI (6.0 mmol) and H_2O (3.0 mL) were added and stirred at 130 °C for 6 h. The conversion of all aryl iodides was >99%.
[b] Isolated yield.

The proposed reaction pathway is shown in Scheme 3. The aryl iodide reacts with palladium to give oxidative aryl palladium complex **A**, and then carbon monoxide, which is generated from Mo $(CO)_6$, is inserted into palladium complex **A** to produce acyl palladium complex **B**. This acyl palladium complex reacts with methyl cyanoacetate in the presence of a base to give palladium complex **C**, and then carbonylated compound **I** is formed through reductive elimination. Compound **I** reacts with LiI in the presence of H_2O to give the desired benzoylacetonitrile through the Krapcho decarboxylation.

In summary, we have developed a one-pot synthesis of benzoylacetonitriles through sequential carbonylation and



Scheme 3. Proposed mechanism.

decarboxylation. Methyl cyanoacetate, which is less expensive than trimethylsilyl acetonitrile, reacted with an aryl iodide and $Mo(CO)_6$ in the presence of a palladium catalyst to give a beta-keto cyanoester, which was treated with LiI/H_2O to provide the benzoylacetonitrile in a moderate to good yield. The utilization of $Mo(CO)_6$ and a cyanoacetate as the carbon monoxide and acetonitrile source, respectively, provided a convenient-handling and low-cost reaction method for the synthesis of benzoylacetonitriles from aryl iodides. To the best of our knowledge, this is the first Letter of sequential carbonylation and decarboxylation for the synthesis of benzoylacetonitriles.

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References and notes

1. Ji, Y.; Trenkle, W. C.; Vowles, J. V. *Org. Lett.* **2006**, *8*, 1161–1163.
2. (a) Danence, L. J. T.; Gao, Y.; Li, M.; Huang, Y.; Wang, J. *Chem. Eur. J.* **2011**, *17*, 3584–3587; (b) Lang, S. A., Jr.; Lovell, F. M.; Cohen, E. *J. Heterocycl. Chem.* **1977**, *14*, 65–69.
3. Laufer, S. A.; Zimmermann, W.; Ruff, K. J. *J. Med. Chem.* **2004**, *47*, 6311–6325.
4. (a) Hu, J.; Wei, Y.; Tong, X. *Org. Lett.* **2011**, *13*, 3068–3071; (b) Ballini, R.; Gabrielli, S.; Palmieri, A. *Synlett* **2010**, 2468–2470; (c) Arcadi, A.; Cerichelli, G.; Chiarini, M.; Di Giuseppe, S.; Marinelli, F. *Tetrahedron Lett.* **2000**, *41*, 9195–9198.
5. (a) Ranatunge, R. R.; Garvey, D. S.; Janero, D. R.; Letts, L. G.; Martino, A. M.; Murty, M. G.; Richardson, S. K.; Young, D. V.; Zemetseva, I. S. *Bioorg. Med. Chem.* **2004**, *12*, 1357–1366; (b) Kordik, C. P.; Luo, C.; Zanoni, B. C.; Dax, S. L.; McNally, J. J.; Lovenberg, T. W.; Wilson, S. J.; Reitz, A. B. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2283–2286; (c) Bagley, M. C.; Davis, T.; Dix, M. C.; Widdowson, C. S.; Kipling, D. *Org. Biomol. Chem.* **2006**, *4*, 4158–4164; (d) Sharma, P. K.; Singh, K.; Kumar, S.; Kumar, P.; Dhawan, S. N.; Lal, S.; Ulbrich, H.; Dannhardt, G. *Med. Chem. Res.* **2011**, *20*, 239–244.
6. Eddington, N. D.; Cox, D. S.; Roberts, R. R.; Butcher, R. J.; Edafiogho, I. O.; Stables, J. P.; Cooke, N.; Goodwin, A. M.; Smith, C. A.; Scott, K. R. *Eur. J. Med. Chem.* **2002**, *37*, 635–648.
7. Takikawa, H.; Hikita, K.; Suzuki, K. *Synlett* **2007**, 2252–2256.
8. Khidre, R. E.; Abdel-Wahab, B. F. *Curr. Org. Chem.* **2013**, *17*, 430–445.
9. (a) Logoglu, E.; Yilmaz, M.; Katircioglu, H.; Yakut, M.; Mercan, S. *Med. Chem. Res.* **2010**, *19*, 490–497; (b) El-Hawash, S. A.; Habib, N. S.; Fanaki, N. H. *Pharmazie* **1999**, *54*, 808–813.
10. Kalwania, G. S.; Gorsi, B. L.; Sharma, Savita; Sharma, M. *Pharmazie* **1994**, *49*, 452–453.
11. Ross, J. R.; Sowell, J. W. *J. Heterocycl. Chem.* **1987**, *24*, 757–765.
12. (a) Yadav, M. R.; Pawar, V. P.; Marvaniya, S. M.; Halen, P. K.; Giridhar, R.; Mishra, A. K. *Bioorg. Med. Chem.* **2008**, *16*, 9443–9449; (b) Andreu, I.; Morera, I. M.; Boscà, F.; Sánchez, L.; Camps, P.; Miranda, M. A. *Org. Biomol. Chem.* **2008**, *6*, 860–867; (c) Norinder, J.; Bogar, K.; Kanupp, L.; Bäckvall, J.-E. *Org. Lett.* **2007**, *9*, 5095–5098; (d) Herschhorn, A.; Lerman, L.; Weitman, M.; Gleenberg, I. O.; Nudelman, A.; Hizi, A. *J. Med. Chem.* **2007**, *50*, 2370–2384.
13. (a) Kamila, S.; Koh, B.; Biehl, E. R. *J. Heterocycl. Chem.* **2006**, *43*, 1609–1612; (b) Gakhar, H. K.; Gill, G. S.; Multani, J. S. *J. Indian Chem. Soc.* **1971**, *48*, 953–956.
14. (a) Long, R. S. *J. Am. Chem. Soc.* **1947**, *69*, 990–995; (b) Dorsh, J. B.; McElvain, S. M. *J. Am. Chem. Soc.* **1932**, *54*, 2960–2964; (c) Turner, J. A.; Jacks, W. S. *J. Org. Chem.* **1989**, *54*, 4229–4231.

15. Puterova, Z.; Andicsova, A.; Vegh, D. *Tetrahedron* **2008**, *64*, 11262–11269.
16. Kociolek, M. G.; Straub, N. G.; Marton, E. J. *Lett. Org. Chem.* **2005**, *2*, 280–282.
17. Al-Awadi, N. A.; Abdelkhalik, M. M.; Abdelhamid, I. A.; Elnagdi, M. H. *Synlett* **2007**, 2979–2982.
18. (a) Pyo, A.; Park, A.; Jung, H. M.; Lee, S. *Synthesis* **2012**, *44*, 2885–2888; (b) Park, A.; Lee, S. *Org. Lett.* **2012**, *14*, 1118–1121.
19. (a) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114–4133; (b) Shibata, T. *Adv. Synth. Catal.* **2006**, *348*, 2328–2336; (c) Strubing, D.; Beller, M. *Top. Organomet. Chem.* **2006**, *18*, 165–178; (d) Trzeciak, A. M.; Ziolkowski, J. J. *Coord. Chem. Rev.* **2005**, *249*, 2308–2322; (e) Schoenberg, A. I.; Bartoletti, R. F.; Heck *J. Org. Chem.* **1974**, *39*, 3318–3326; (f) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327–3331.
20. (a) Aakerbladh, L.; Nordeman, P.; Wejdemar, M.; Odell, L. R.; Larhed, M. *J. Org. Chem.* **2015**, *80*, 1464–1471; (b) Borhade, S. R.; Sandstrom, A.; Arvidssön, P. I. *Org. Lett.* **2013**, *15*, 1056–1059; (c) Jafarpour, F.; Rashidi-Ranjbar, P.; Kashani, A. O. *Eur. J. Org. Chem.* **2011**, 2128–2132; (d) Saevmarker, J.; Lindh, J.; Nilsson, P. *Tetrahedron Lett.* **2010**, *51*, 6886–6889; (e) Letavic, M. A.; Ly, K. S. *Tetrahedron Lett.* **2007**, *48*, 2339–2343; (f) Wu, X.; Ekegren, J. K.; Larhed, M. *Organometallics* **2006**, *25*, 1434–1439; (g) Wu, X.; Larhed, M. *Org. Lett.* **2005**, *7*, 3327–3329; (h) Wu, X.; Mahalingam, A. K.; Wan, Y.; Alterman, M. *Tetrahedron Lett.* **2004**, *45*, 4635–4638; (i) Georgsson, J.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2003**, *5*, 350–352; (j) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717–727.
21. (a) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003–8007; (b) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051–5053; (c) Stauffer, S. R.; Beare, N. A.; Stambuli, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4641–4642; (d) Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541–555.
22. (a) McClure, K. J.; Huang, L.; Arienti, K. L.; Axe, F. U.; Brunmark, A.; Blevitt, J.; Breitenbucher, J. G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1924–1928; (b) Chauder, B. A.; Boros, E. E.; Du, K. S.; Kazmierski, W. M.; Koble, C. S.; Thompson, J. B. *Synth. Commun.* **2006**, *36*, 279–284; (c) Krapcho, A. P. *Synthesis* **1984**, 805–822; (d) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138–147; (e) Krapcho, A. P.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Short, F. W. *Tetrahedron Lett.* **1974**, *15*, 1091–1094.
23. We obtained the black decomposed reaction mixture which was not identified.