Reaction of 2-Alkynylbenzoyl Cyanides with Carboxylic Acids Producing Functionalized Indenones

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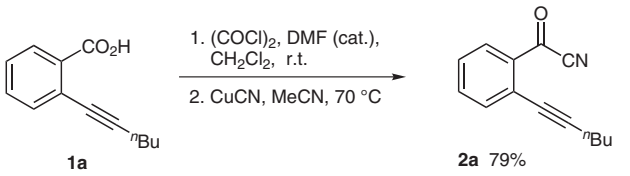
Abstract: 2-Alkynylbenzoyl cyanides react with carboxylic acids via a cyclic allene intermediate to produce 2-acylamino-3-acylindenones in good yield. The high reactivity of the 2-acylamino moiety of the product for a substitution reaction can be utilized for the synthesis of fused heterocycles.

Key words: cyclization, carboxylic acids, heterocycles, benzoyl cyanides, indenones

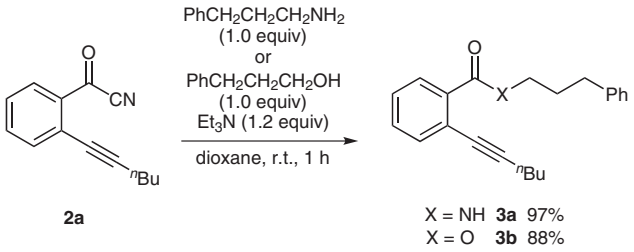
The cyanocarbonyl group is an interesting ambident electrophilic functionality; its cyano and carbonyl groups are both electrophilic enough to accept nucleophiles, and their electron-withdrawing nature reinforces the electrophilic reactivities.[1,2] As an extension of our previous studies on the rhodium-catalyzed reaction of cyanoformate with arylboronic acids,[3] we prepared 2-alkynylbenzoyl cyanide in order to develop a cascade reaction. Careful examination of its reactivity, however, disclosed an unexpected acid-mediated cyclization reaction. In this paper, we report the reaction of 2-alkynylbenzoyl cyanide with a carboxylic acid, which furnishes a functionalized indenone as the cyclized product.

2-(1-Hexyn-1-yl)benzoyl cyanide (**2a**) was readily prepared from 2-(1-hexyn-1-yl)benzoic acid (**1a**);[4] treatment of **1a** with oxalyl chloride in the presence of DMF in CH_2Cl_2 and subsequent removal of volatile compounds under reduced pressure afforded the corresponding acid chloride as the crude product. The crude acid chloride was directly reacted with CuCN in MeCN at 70 °C.[5] Isolation by column chromatography on silica gel afforded the desired benzoyl cyanide **2a** in 79% yield (Equation 1).

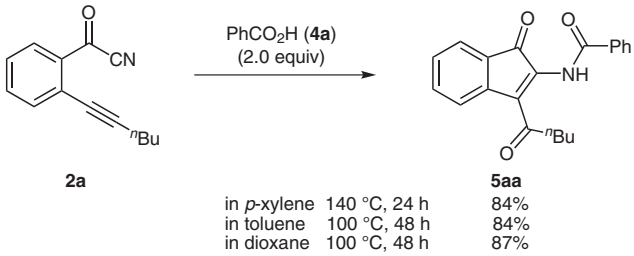
When 2-(1-hexyn-1-yl)benzoyl cyanide (**2a**) thus obtained was treated with 3-phenylpropylamine, the amino group attacked the carbonyl group of **2a**, with the cyano group acting as a leaving group to afford the corresponding amide **3a** in 97% yield. The related reaction between 3-phenylpropanol and **2a** in the presence of Et_3N proceeded in a similar manner producing ester **3b** (Equation 2). Thus, relatively active nucleophiles attacked the carbonyl group of **2a** under basic conditions. In contrast, when **2a** was heated with benzoic acid **4a**, a cyclization reaction occurred to afford 2-benzoylamino-3-pentanoylindenone **5aa** as shown in Equation 3.[6]



Equation 1 Preparation of 2-(hexyn-1-yl)benzoyl cyanide (**2a**)



Equation 2 Reaction of **2a** with an amine and an alcohol



Equation 3 Reaction of **2a** with benzoic acid **4a**

The results obtained with other carboxylic acids **4** and **2a** are summarized in Table 1.[7] Not only substituted benzenecarboxylic acids (entries 1–5) but also heteroaromatic (entries 6 and 7), cinnamic (entry 8), and aliphatic (entries 9–11) carboxylic acids reacted with **2a** to give the corresponding 2-acylamino-3-pentanoylindenone (**5aa**–**ak**) in yields ranging from 60% to 92%. Thus, a wide range of carboxylic acids effectively mediated the cyclization reaction of **2a**.

In order to further probe the scope of the reaction, benzoyl cyanides possessing other alkynyl groups were also examined. 2-Alkynylbenzoyl cyanide **2b**[4] having an isopropyl substituent was a suitable substrate, giving **5ba** and **5bi** at 120 °C (Equation 4). When the reaction of **2b** with benzoic acid **4a** was carried out at a lower temperature (100 °C), enol ester **6ba** was isolated in 71% yield. Furthermore, on

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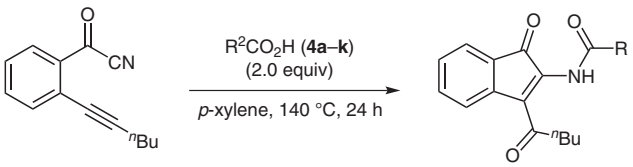
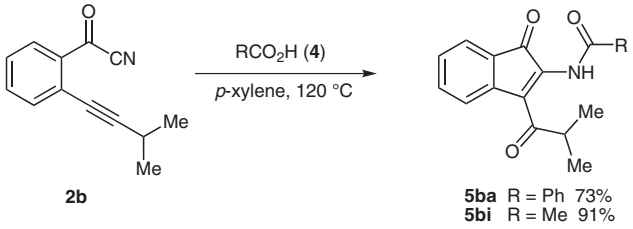
Table 1 Reaction of **2a** with Various Carboxylic Acids **4**



2a **5aa–5ak**

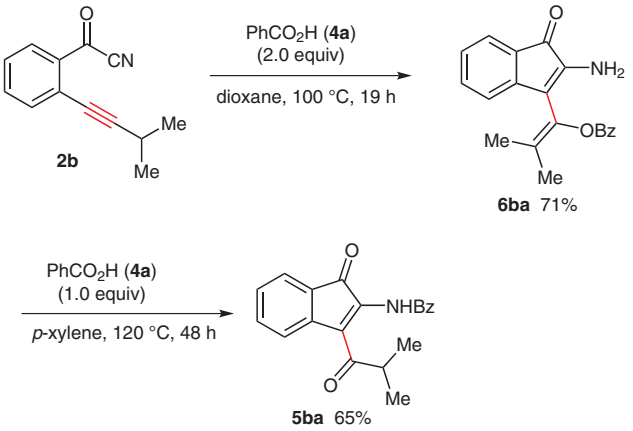
Entry	**4**	R^2	Product **5**	Yield (%)[a]
1	**4a**	Ph	**5aa**	84
2	**4b**	4-$MeOC_6H_4$	**5ab**	64
3	**4c**	4-ClC_6H_4	**5ac**	89
4	**4d**	4-BrC_6H_4	**5ad**	88
5	**4e**	4-$MeO_2CC_6H_4$	**5ae**	60
6	**4f**	Pyrid-2-yl	**5af**	62
7	**4g**	Thien-2-yl	**5ag**	83
8	**4h**	(*E*)-PhCH=CH	**5ah**	87
9	**4i**	Me	**5ai**	92[b]
10	**4j**	*i*-Pr	**5aj**	83
11	**4k**	*t*-Bu	**5ak**	87

[a] Isolated yield.
[b] Reaction at 120 °C.



2b

Equation 4 Reaction of **2b** with carboxylic acids



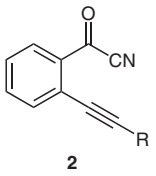
2b

Scheme 1 Formation of **5ba** from **2b** and **4a** via enol ester **6ba**

heating a mixture of **6ba** and benzoic acid **4a** at 120 °C, 2-acylaminoindenone **5ba** was produced in 65% yield (Scheme 1). Unlike **2a** and **2b**, 2-alkynylbenzoyl cyanides **2c**–**e**[4] (Figure 1) failed to react with benzoic acid (**4a**), and **2c**–**e** were recovered, suggesting the need for a hydrogen at the propargylic position in order for the cyclization reaction to occur. The attempted reaction of benzoyl cyanide **2f**[8] bearing a terminal alkyne resulted in the formation of a mixture of intractable compounds.

In order to gain a further insight into the mechanism, we treated **2a** with acetic acid-d_1 **4i-D** (5 equiv) in *p*-xylene at 120 °C for 7 hours. Under these conditions, **5ai-D** which incorporated a deuterium at the α-position of the carbonyl group (67% D), was isolated in 83% yield (Equation 5).[9] The deuterium incorporation also indicated the intermediacy of an enol ester such as **6ba**. On the basis of these results, we propose the pathway shown in Scheme 2 to explain the formation of 2-acylamino-3-acylindenone **5** from **2.** Initially, carboxylic acid **4** mediates isomerization of 2-alkynylbenzoyl cyanide **2** to cyclic allene **7**. Then, carboxylic acid **4** attacks the sp-carbon of the allene moiety to form enol ester **6**. Finally, the acyl group migrates to the amino group to afford 2-acylamino-3-acylindenone **5**.

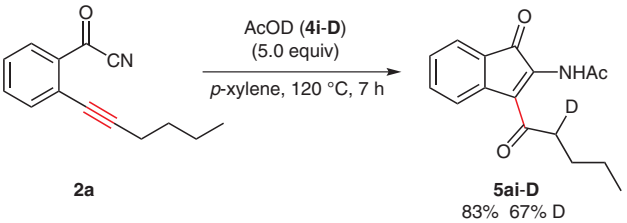
We next examined the reactivities of the product. Treatment of **5aa** with a primary amine resulted in a facile substitution reaction of the acetylamino group to give 2-alkylamino-3-pentanoylindenone **11** in high yield (Equation 6).[10] The substitution reaction probably proceeds via an addition–elimination mechanism. The substitutive reactivity of the acylamino group with primary amines was next utilized for construction of heterocyclic structures.[11] Treatment of 2-acetylamino-3-acylindenone **5ai** and **5bi** with amidine hydrochlorides **8** in pyridine at 100 °C afforded the corresponding indenopyrimidine **9** as exemplified in Equation 7.[12] When **5ai** and **5bi** were reacted with methylhydrazine, the primary amino group initially replaced the acetylamino group to furnish indenopyrazole derivatives **12** possessing a methyl group at the 2-position (Equation 8).[13,14]



2

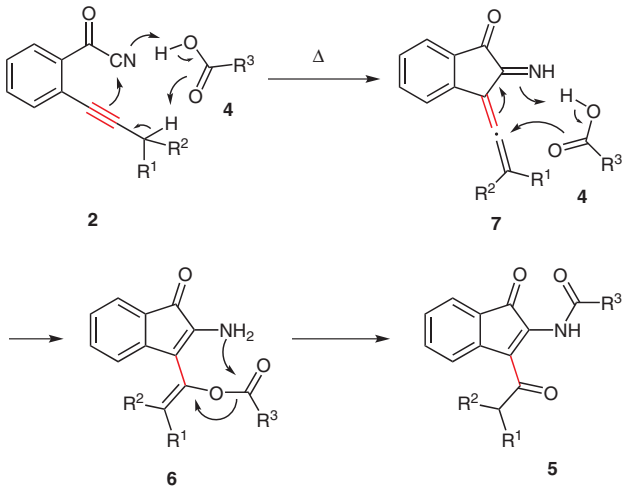
2c R = ^{t}Bu
2d R = Ph
2e R = TMS
2f R = H

Figure 1 The substrates which failed to react with carboxylic acids

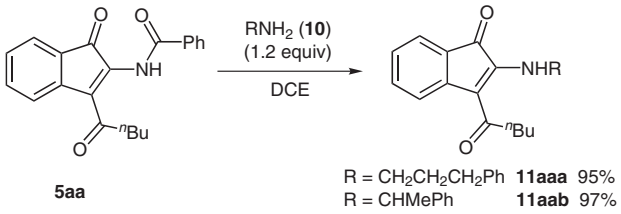


2a

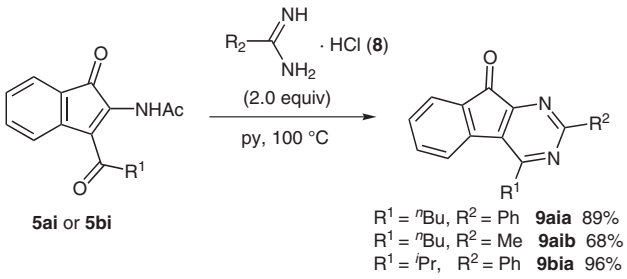
Equation 5 Deuterium experiment



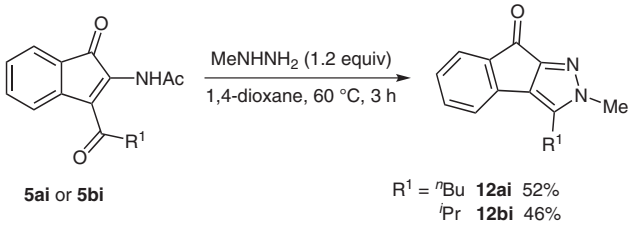
Scheme 2 Proposed mechanism for the formation of **5** from **2** and **4**



Equation 6 Reaction of **5aa** with primary amines **10**



Equation 7 Synthesis of 9-oxoindenopyrimidines (**9**) from 2-acetylamino-3-acylindenone (**5ai** and **5bi**) and amidine hydrochlorides **8**



Equation 8 Synthesis of 2-methyl-8-oxoindenopyrazoles (**12**) from 2-acetylamino-3-acylindenone (**5ai** and **5bi**) and methylhydrazine

In conclusion, we have found that 2-alkynylbenzoyl cyanides possessing a propargylic hydrogen react readily with carboxylic acids to provide 2-acylamino-3-acylindenones. The reaction proceeds via a cyclic allenyl intermediate, which is generated by assistance of the enhanced electrophilic nature of the cyano group. The produced 2-acylamino-3-acylindenones could be utilized for the synthesis of fused heterocycles with an indenone skeleton.

References and Notes

(1) For attack of carbon nucleophiles to the cyano group, see: (a) Veronese, A. C.; Callegari, R.; Basato, M.; Valle, G. *J. Chem. Soc., Perkin Trans. 1* **1994**, *13*, 1779. (b) Veronese, A. C.; Gandolfi, V.; Basato, M.; Corain, B. *J. Chem. Res., Synop.* **1988**, *8*, 246. (c) Basato, M.; Corain, B.; Cofler, M.; Veronese, A. C.; Zanotti, G. *J. Chem. Soc., Chem. Commun.* **1984**, *23*, 1593.

(2) For recent examples of attack of carbon nucleophiles to the carbonyl group, see: (a) Ikeda, Z.; Hirayama, T.; Matsubara, S. *Angew. Chem. Int. Ed.* **2006**, *45*, 8200. (b) Shen, Z.; Li, B.; Wang, L.; Zhang, Y. *Tetrahedron Lett.* **2005**, *46*, 8785. (c) Zhou, S.; Yan, B.; Liu, Y. *J. Org. Chem.* **2005**, *70*, 4006. (d) Duplais, C.; Bures, F.; Sapountzis, I.; Korn, T. J.; Cahiez, G.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2968. (e) Gohain, M.; Gogoi, B. J.; Prajapati, D.; Sandhu, J. S. *New J. Chem.* **2003**, *27*, 1038. (f) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Chem. Commun.* **2002**, 1034. (g) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Tetrahedron Lett.* **2002**, *43*, 2945. (h) Yoo, B. W.; Hwang, S. K.; Kim, D. Y.; Choi, J. W.; Ko, J. J.; Choi, K. I.; Kim, J. H. *Tetrahedron Lett.* **2002**, *43*, 4813.

(3) Shimizu, H.; Murakami, M. *Chem. Commun.* **2007**, 2855.

(4) **Representative Procedure for the Preparation of 2-Alkynylbenzoyl Cyanide 2**
Oxalyl chloride (1.60 mL, 18.7 mmol) was added dropwise to a mixture of 2-(1-hexyn-1-yl) benzoic acid (**1a**, 3.43 g, 17.0 mmol) and DMF (2 drops) in CH_2Cl_2 (35 mL). The reaction mixture was stirred for 1.5 h at r.t. Then, volatile components were removed in vacuo to give crude acid chloride. A solution of the crude acid chloride in MeCN (20 mL) was added to a stirred suspension of CuCN (3.00 g, 33.5 mmol) in MeCN (20 mL) at r.t. After the mixture was stirred for 1 h at 70 °C, the resulting clear solution was cooled to r.t. and concentrated in vacuo. The residue was washed with Et_2O, filtrated and concentrated in vacuo again. The residue was purified rapidly by silica gel column chromatography (hexane and then hexane–Et_2O, 50:1) to afford 2-(1-hexyn-1-yl)benzoyl cyanide (**2a**) (2.83 g, 79%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (3 H, t, *J* = 7.2 Hz), 1.42–1.58 (2 H, m), 1.58–1.72 (2 H, m), 2.51 (2 H, t, *J* = 7.2 Hz), 7.42–7.52 (1 H, m), 7.54–7.67 (2 H, m), 8.05–8.12 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 19.8, 22.2, 30.4, 77.9, 101.6, 113.5, 125.9, 127.9, 132.6, 133.7, 135.2 (two signals overlapping), 166.9. IR (neat): 2959, 2220, 1682, 1663, 1482, 1231 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{14}H_{13}ON$ [M$^+$]: 211.0997; found: 211.0997. Compounds **2b–e** were prepared by a similar procedure.

(5) Normant, J. F.; Piechucky, C. *Bull. Soc. Chem. Fr.* **1972**, *6*, 2402.

(6) No reaction occurred at room temperature.

(7) **Representative Procedure for the Cyclization Reaction of 2 with 4**
A mixture of 2-(1-hexyn-1-yl)benzoyl cyanide (**2a**, 42.3 mg, 0.20 mmol) and benzoic acid (**4a**, 48.8 mg, 0.40 mmol) in *p*-xylene (1.0 mL) was stirred at 140 °C for 24 h under an argon atmosphere, and then the solvent was evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (toluene–EtOAc, 10:1) to afford 2-benzoylamino-3-pentanoylindenone **5aa** (55.9 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (3 H, t, *J* = 7.2 Hz), 1.38 (2 H, pseudo sext, *J* = 7.5 Hz), 1.74 (2 H, pseudo quin, *J* = 7.5 Hz), 2.75 (2 H, t, *J* = 7.5 Hz), 7.14 (2 H, t, *J* = 7.5

Hz), 7.35 (1 H, dt, *J* = 1.2, 7.5 Hz), 7.44–7.56 (3 H, m), 7.56–7.64 (1 H, m), 7.87–7.94 (2 H, m), 8.40 (1 H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.6, 25.8, 44.1, 121.9, 124.4, 126.8, 127.3, 127.6, 127.9, 129.1, 132.5, 132.7, 133.0, 135.6, 145.5, 164.9, 193.0, 201.1. IR (KBr): 3312, 2959, 1726, 1678, 1662, 1512, 1277 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{21}H_{19}O_3N$ [M$^+$]: 333.1365; found: 333.1361.

(8) Compound **2f** was prepared by the $SnCl_4$-catalyzed reaction of acid chloride with TMSCN: Olah, G. A.; Arvanaghi, M.; Prakash, G. K. S. *Synthesis* **1983**, 636.

(9) When **5ai** was exposed to same reaction conditions, a deuterium was incorporated only in 17% at the α-position of the carbonyl group.

(10) No reaction occurred with secondary amines such as a piperidine and *N*-benzylmethylamine.

(11) For cyclocondensation of β-enamino carbonyl compounds with amidines and hydrazines, see: (a) Bredereck, H.; Sell, R.; Effenberger, F. *Chem. Ber.* **1964**, *97*, 3407. (b) Kvita, V. *Synthesis* **1986**, 786. (c) Bredereck, H.; Herlinger, H.; Schweizer, E. *Chem. Ber.* **1960**, *93*, 1208. (d) Plath, P.; Rohr, W. *Synthesis* **1982**, 318.

(12) **Representative Procedure for the Synthesis of Indenopyrimidine**
A mixture of **5ai** (27.2 mg, 0.10 mmol) and benzamidine hydrochloride (**8a**, 38.5 mg, 0.20 mmol) in pyridine (1.0 mL) was stirred at 100 °C for 24 h under an argon atmosphere, and then the reaction mixture was cooled and diluted with EtOAc (5 mL) and H_2O (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined extracts were washed with H_2O and brine, and dried over $MgSO_4$. The solvent was evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (toluene–EtOAc, 20:1) to afford 4-butyl-2-phenyl-9*H*-indeno[2,1-*d*]pyrimidin-9-one (**9aia**, 28.1 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (3 H, t, *J* = 7.5 Hz), 1.45–1.65 (2 H, m), 1.92 (2 H, quin, *J* = 7.7 Hz), 3.13 (2 H, t, *J* = 7.5 Hz), 7.33–7.47 (1 H, m), 7.47–7.57 (3 H, m), 7.57–7.69 (2 H, m), 7.82 (1 H, d, *J* = 7.5 Hz), 8.47–8.62 (2 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 22.8, 29.4, 35.9, 123.7, 125.6, 128.6, 128.7, 129.7, 131.17, 131.23, 131.9, 136.3, 137.1, 141.8, 160.3, 165.3, 165.5, 193.4. IR (KBr): 2959, 1730, 1572, 1458, 1390, 1186 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{21}H_{18}ON_2$ [M$^+$]: 314.1419; found: 314.1422.

(13) **Representative Procedure for the Synthesis of Indenopyrazole**
To a stirred solution of **5ai** (27.2 mg, 0.10 mmol) in 1,4-dioxane (0.5 mL) under an argon atmosphere was added a solution of methylhydrazine (5.5 mg, 0.12 mmol) in 1,4-dioxane (0.5 mL) at 60 °C over 5 min. After being stirred for 3 h, the reaction mixture was cooled and diluted with EtOAc (5 mL) and H_2O (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (4 × 3 mL). The combined extracts were washed with H_2O and brine, and dried over $MgSO_4$. The solvent was evaporated in vacuo. The residue was purified by preparative thin-layer chromatography ($CHCl_3$–EtOAc, 10:1) to afford 3-butyl-2-methyl-8*H*-indeno[2,1-*c*]pyrazol-8-one (**12ai**, 12.4 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (3 H, t, *J* = 7.3 Hz), 1.39–1.49 (2 H, m), 1.63–1.73 (2 H, m), 2.74 (2 H, t, *J* = 7.5 Hz), 3.83 (3 H, s), 7.09–7.14 (2 H, m), 7.35 (1 H, dt, *J* = 1.1, 7.5 Hz), 7.52 (1 H, dd, *J* = 1.3, 7.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 22.3, 25.0, 30.7, 37.1, 120.2, 124.7, 126.8, 129.6, 134.4, 137.5, 138.0, 138.4, 152.3, 186.2. IR (KBr): 2939, 1714, 1603, 1491, 1317, 1169 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{15}H_{16}ON_2$ [M$^+$]: 240.1263; found: 240.1260. The position of the methyl group was identified by NOE measurement.

(14) For selective formation of N-substituted pyrazoles from *N*-methoxy-*N*-methyl-β-enaminoketoesters, see: Persson, T.; Nielsen, J. *Org. Lett.* **2006**, *8*, 3219.