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Copper-Mediated Direct C(sp^3)–H and C(sp^2)–H Acetoxylation

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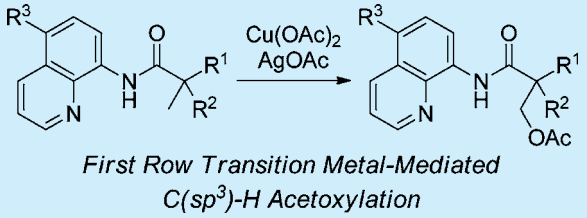
Supporting Information

ABSTRACT: A copper-mediated terminal position-selective C(sp^3)–H acetoxylation using a bidentate directing group and AgOAc as an oxidant was achieved. This reaction has high functional group tolerance and is not affected by steric hindrance. The reaction proceeds in excellent yield, even in gram scale, and the directing group can be removed after the reaction. Aromatic C(sp^2)–H acetoxylation also proceeded under similar reaction conditions.



First Row Transition Metal-Mediated C(sp^3)-H Acetoxylation

Direct C–H bond transformations are highly efficient and ideal methods for synthesizing organic molecules. Second- and third-row transition metal complexes or salts are often used as catalysts or mediators to promote direct C–H transformation. The abundance and low cost of first-row transition metals compared with second- and third-row transition metals, and the few examples of first-row transition-metal-catalyzed or -mediated C–H transformations, have recently prompted researchers to concentrate their effort on developing direct C–H (especially C(sp^2)–H) transformations using first-row transition metals,[1] including copper-catalyzed or -mediated reactions.[2] To date, however, there are still only a few examples of first-row transition-metal-catalyzed or -mediated unactivated C(sp^3)–H transformations: for examples of catalytic reactions, Nakamura and co-workers reported iron-catalyzed arylation, alkenylation, and alkylation at C(sp^3)–H bonds;[3] the Chatani[4] and Ge[5] groups independently reported nickel-catalyzed C(sp^3)–H arylation and alkylation; we reported copper-catalyzed intramolecular C(sp^3)–H amidation;[6] and Ge's group subsequently reported a similar C(sp^3)–H amidation.[7]

Organic molecules bearing acetoxy group(s) are important as natural products, drugs, and agricultural chemicals. For example, cytochalasin D[8] is a cell-permeable and potent inhibitor of actin polymerization, and decazolin[9] is a herbicide (Figure 1).

To introduce acetoxy groups into the desired C(sp^3)-site(s) of organic molecules, C(sp^3)–H acetoxylation is the most direct and efficient method, and acetoxylated products can be synthesized from simple substrates. Among them are the recently reported palladium-catalyzed oxidative C(sp^3)–H acetoxylations,[10−13] but there has been no report on C(sp^3)–H acetoxylation promoted by a first-row transition metal complex or salt.[14,15] The first example of copper-catalyzed C(sp^2)–H acetoxylation was previously reported by Yu and co-workers.[16] Here we report copper-mediated unactivated C(sp^3)–H acetoxylation using a chelating directing group and AgOAc as an oxidant.[17−19] In this reaction system, C(sp^2)–H acetoxylation also proceeded.[20]

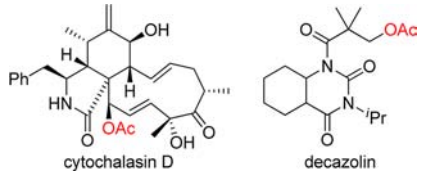


Figure 1. Bioactive compounds containing an acetate group.

Treatment of amide **1a** with a mixture of CuCl, AgOAc, and NaOAc in hexamethylphosphoric triamide (HMPA) at 145 °C for 24 h gave mono- and diacetoxylated products **2a** and **3a** in 30% and 14% yield, respectively (Table 1, entry 1). In this reaction, acetoxylation occurred only at the terminal C(sp^3)–H bond, and internal C(sp^3)–H acetoxylation of the ethyl group, C(sp^2)–H acetoxylation of the quinolyl group,[21] and intramolecular C(sp^3)–H amidation[6,7] did not proceed at all. Based on the screening of several copper salts (entries 2–8), Cu(OAc)$_2$ was the best catalyst, and **2a** and **3a** were obtained in 48% and 33% yield, respectively (entry 8). In this reaction, sodium acetate was not indispensable; however, the yields of **2a** and **3a** decreased slightly when sodium acetate was not used (entry 9). Because HMPA is a carcinogen, it was replaced with another solvent (entries 10–13), *N*-methylpyrrolidone (NMP), which exhibited similar reactivity as HMPA (entry 13). Unfortunately, the yields of **2a** and **3a** were decreased by decreasing the amount of Cu(OAc)$_2$ (entry 14). Only a trace amount of **2a** was formed without adding AgOAc. In addition, the desired reaction did not proceed in the absence of Cu(OAc)$_2$.

We then investigated the substrate scope of the acetoxylation (Table 2). Amides with a tertiary alkyl group gave the

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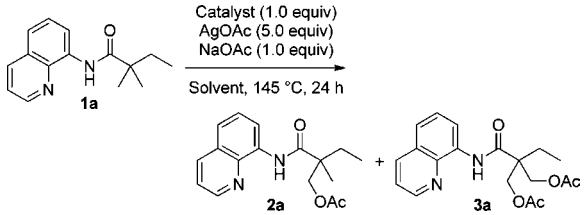
Table 1. Optimization of Reaction Conditions



entry	catalyst	solvent	yield (%) Mono-OAc (2a)	yield (%) Di-OAc (3a)
1	CuCl	HMPA	30	14
2	$CuCl_2$	HMPA	22	15
3	CuBr	HMPA	35	32
4	$CuBr_2$	HMPA	26	27
5	CuCN	HMPA	21	5
6	$Cu(OH)_2$	HMPA	10	5
7	$Cu_2(OH)_2(CO_3)$	HMPA	37	3
8	$Cu(OAc)_2$	HMPA	48	33
9[a]	$Cu(OAc)_2$	HMPA	36	18
10	$Cu(OAc)_2$	DMSO	28	trace
11	$Cu(OAc)_2$	DMA	34	22
12	$Cu(OAc)_2$	DMF	34	32
13	$Cu(OAc)_2$	NMP	46	32
14	$Cu(OAc)_2$[b]	NMP	31	18

[a]NaOAc was not added. [b]0.50 equiv.

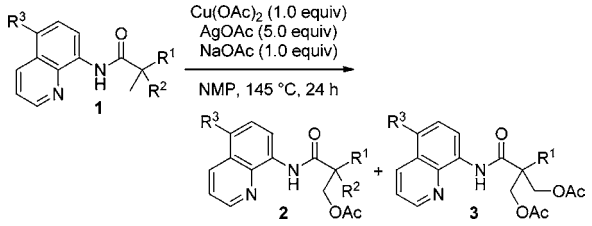
corresponding mono- and diacetoxylated products **2b**–**2e**, **2g**, and **3b**–**3e**, **3g**, respectively (entries 1–4 and 6).[22] In the case of substrates **1d** and **1e**, acetoxylation did not occur at the benzylic C(sp^3)–H bonds (entries 3 and 4). In the case of tertiary alkyl amides **1f** and **1h**–**1n** bearing a trifluoromethyl or benzylic group, only monoacetoxylated products **2f** and **2h**–**2n** were obtained in 62%–83% yield with high functional group tolerance (entries 5 and 7–13). The yields of the acetoxylated products increased with an increase in the electron-withdrawing ability of the functional group. The results of substrates **1o**–**1r** revealed that the reaction occurred preferentially at the methyl groups, and acetoxylation did not proceed at the terminal position of the ethyl groups, methylene moieties (internal position), or benzylic C(sp^3)–H bonds (entries 14–17). The corresponding acetoxylated product **2s** was obtained in 68% yield when an amide bearing a methoxy group on the quinolyl group was used as a substrate (entry 18).

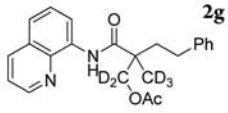
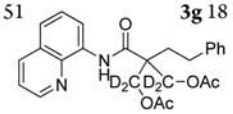
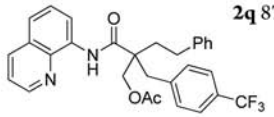
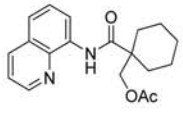
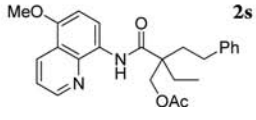
The proposed mechanism for the C(sp^3)–H acetoxylation is as follows (Scheme 1): (1) formation of a metallacyclic intermediate by the reaction of amide **1** with $Cu(OAc)_2$ and AgOAc via the elimination of 2 equiv of acetic acid via a concerted metalation–deprotonation pathway (including C-(sp^3)–H bond activation); (2) reductive elimination; and (3) protonation of the formed amide-copper intermediate to give the acetoxylated product.

We then performed kinetic isotope experiments to elucidate the rate-determining step of the C(sp^3)–H acetoxylation (for details, see the Supporting Information, Figures S1 and S2). The kinetic isotope effect value was calculated to be 1.3, suggesting that the C(sp^3)–H bond activation should not be the rate-determining step of the acetoxylation.[23]

The acetoxylation also proceeded in excellent yield without the formation of regioisomers and loss of the functional groups when a more complex molecule **4** was used as a substrate (Scheme 2). This finding suggests that the C(sp^3)–H

Table 2. Investigation of Substrate Scope



entry	2	yield (%)	3	yield (%)
1	R^1 = Me	**2b** 39		**3b** 38
2	R^1 = ^{n}C_3H_7	**2c** 55		**3c** 23
3	R^1 = $(CH_2)_2Ph$	**2d** 55		**3d** 21
4	R^1 = CH_2OCH_2Ph	**2e** 54		**3e** 22
5	R^1 = CF_3	**2f** 73		**3f** <1
6		**2g** 51		**3g** 18
7	X = OMe	**2h** 67		**3h** <1
8	X = Me	**2i** 71		**3i** <1
9	X = H	**2j** 74		**3j** <1
10	X = Br	**2k** 62		**3k** <1
11	X = Cl	**2l** 78		**3l** <1
12	X = F	**2m** 81		**3m**<1
13	X = CF_3	**2n** 83		**3n** <1
14	R^1 = $(CH_2)_2Ph$	**2o** 78		
15	R^1 = CH_2Ph	**2p** 86		
16		**2q** 87		
17		**2r** 79		
18		**2s** 68		

acetoxylation is applicable to late-stage functionalization of complex molecules. The acetoxylation also proceeded in excellent yield without decreasing the yield of the product

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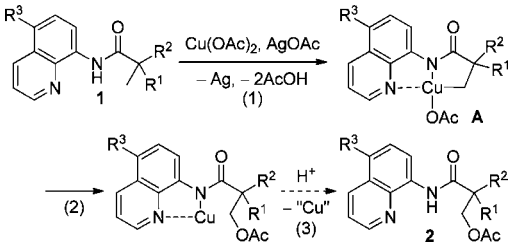
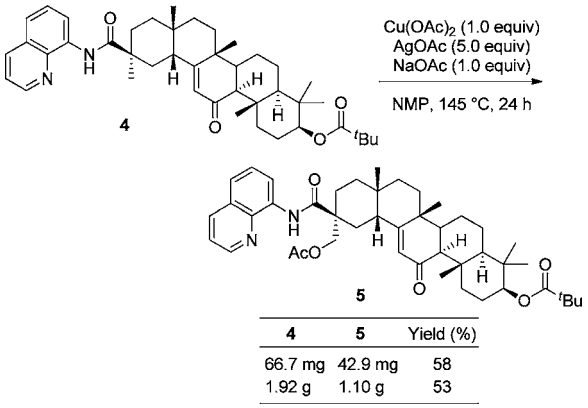
Scheme 1. Proposed Mechanism for C(sp^3)−H Acetoxylation



Scheme 2. Regioselective Acetoxylation of a Complex Molecule 4

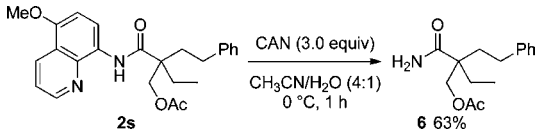


4	5	Yield (%)
66.7 mg	42.9 mg	58
1.92 g	1.10 g	53

even in gram scale (Scheme 2). By the reaction of amide **4** with a mixture of $Cu(OAc)_2$, AgOAc, and NaOAc, 1.10 g of acetoxylated product **5** was obtained in 53% yield. The yield of **5** on a large scale was comparable to that of **5** (42.9 mg, 58%) on a small scale.

When a 5-methoxyquinolyl group was used as the directing group, the directing group could be removed by oxidation (Scheme 3).[24] Treatment of the acetoxylated product **2s** with ceric ammonium nitrate afforded the deprotected compound **6** in 63% yield without the loss of an acetoxy group.

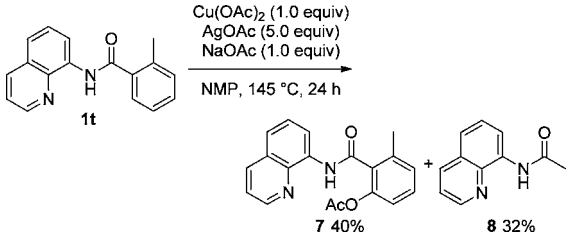
Scheme 3. Removal of a Directing Group



Acetoxylation also proceeded at an aromatic C(sp^2)−H bond. Treatment of aromatic amide **1t** with a mixture of $Cu(OAc)_2$, AgOAc, and NaOAc in NMP at 145 °C for 24 h gave an *ortho*-acetoxylated product **7** and amide **8** in 40% and 32% yield, respectively (Scheme 4).[25−27]

In summary, we successfully developed an intermolecular C(sp^3)−H acetoxylation by using a combination of stoichiometric amounts of $Cu(OAc)_2$ and AgOAc. This reaction has high functional group tolerance, and the reaction proceeded in excellent yield, even in gram scale. The directing group can be removed by oxidation using a 5-methoxyquinolyl group as a directing group. This acetoxylation can be applied to a complex molecule, which will lead to late-stage functionalization. Deuterium labeling experiments suggested that the C(sp^3)−H bond activation step is not the rate-determining step. Aromatic

Scheme 4. Regioselective C(sp^2)−H Acetoxylation



C(sp^2)−H acetoxylation also proceeded under similar reaction conditions. We believe that this reaction will provide useful insights into C−H bond transformations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for all compounds, and KIE experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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■ REFERENCES

(1) For a review, see: Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087.

(2) (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (b) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (c) Ban, I.; Sudo, T.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 3607. (d) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607. (e) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (f) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178. (g) Fukuzawa, S.; Shimizu, E.; Atsumi, Y.; Haga, M.; Ogata, K. *Tetrahedron Lett.* **2009**, *50*, 2374. (h) Miyasaka, M.; Hirano, K.; Satoh, T.; Kawalczyk, R.; Bolm, C.; Miura, M. *Org. Lett.* **2011**, *13*, 359. (i) Duong, H. Am.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 463. (j) Jeyachandran, R.; Potukuchi, H. K.; Ackermann, L. *Beilstein J. Org. Chem.* **2012**, *8*, 1771. (k) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237. (l) Takemura, N.; Kuninobu, Y.; Kanai, M. *Org. Lett.* **2013**, *15*, 844. (m) Zhu, R.; Wei, J.; Shi, Z. *Chem. Sci.* **2013**, *4*, 3706. (n) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4457. (o) Roane, J.; Daugulis, O. *Org. Lett.* **2013**, *15*, 5842. (p) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342. (q) Pan, C.; Jin, H.; Xu, P.; Liu, X.; Cheng, Y.; Zhu, C. *J. Org. Chem.* **2013**, *78*, 9494. (r) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 9797. (s) Odani, R.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2013**, *78*, 11045.

(3) (a) Yoshikai, N.; Mieczkowski, A.; Matsumoto, A.; Illies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2010**, *132*, 5568. (b) Shang, R.; Ilies, L.; Matsumoto, A.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 6030.

(4) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 898.

(5) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2014**, *136*, 1789.

(6) Wang, Z.; Ni, J.; Kuninobu, Y.; Kanai, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 3496.

dx.doi.org/10.1021/ol5022542 | *Org. Lett.* 2014, 16, 4790−4793

(7) Wu, X.; Zhao, Y.; Zhang, G.; Ge, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 3706.
(8) May, J. A.; Ratan, H.; Glenn, J. R.; Losche, W.; Spangenberg, P.; Heptinstall, S. *Platelets* **1998**, *9*, 227.
(9) Fuerst, E. P.; Arntzen, C. J.; Pfister, K.; Penner, D. *Weed Science* **1986**, *34*, 344.
(10) For an example of palladium-catalyzed benzylic C(sp^3)−H acetoxylation, see: Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300.
(11) For an example of palladium-catalyzed allylic C(sp^3)−H acetoxylation, see: Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346.
(12) For examples of palladium-catalyzed acetoxylation of C(sp^3)−H adjacent to a heteroatom, see: (a) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (b) Wang, D.-H.; Wu, D.-F.; Yu, J.-Q. *Org. Lett.* **2006**, *8*, 3387.
(13) For examples of palladium-catalyzed unactivated C(sp^3)−H acetoxylation, see: (a) Giri, R.; Liang, J.; Lei, J.-G.; Lei, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420. (b) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. *Org. Lett.* **2012**, *14*, 3724.
(14) For examples of copper-catalyzed C(sp^3)−H transformations, see: (a) Basle, O.; Li, C.-J. *Org. Lett.* **2008**, *10*, 3661. (b) Takemura, N.; Kuninobu, Y.; Kanai, M. *Org. Biomol. Chem.* **2014**, *12*, 2528.
(15) For examples of copper-mediated C(sp^2)−heteroatom bond formations, see: (a) Oda, Y.; Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *Synthesis* **2012**, *44*, 1515. (b) Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 3354.
(16) For the first example of copper-catalyzed C(sp^2)−H acetoxylation, see: Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790.
(17) There are several examples of pioneering researches using the directing group from Daugulis's group; see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (c) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem., Int. Ed.* **2013**, *52*, 6043. See also, refs 2k, 2o, and 2p.
(18) For a review of bidentate directing group-assisted transition-metal-catalyzed C−H transformations, see: Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726.
(19) During our submission, a similar reaction has appeared online. See: Wu, X.; Zhao, Y.; Ge, H. *Chem.—Asian J.*, in press, DOI: 10.1002/asia.201402510.
(20) For examples of palladium-catalyzed C(sp^2)−H acetoxylation, see: (a) Vickers, C. J.; Mei, T.-S.; Yu, J.-Q. *Org. Lett.* **2010**, *12*, 2511. (b) Richter, H.; Beckendorf, S.; Mancheno, O. G. *Adv. Synth. Catal.* **2011**, *353*, 295. (c) Emmert, M. H.; Cook, A. K.; Xie, Y. J.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 9409. (d) Wang, L.; Xia, X.-D.; Guo, W.; Chen, J.-R.; Xiao, W.-J. *Org. Biomol. Chem.* **2011**, *9*, 6895. (e) Yang, M.; Jiang, X.; Shi, W.-J.; Zhu, Q.-L.; Shi, Z.-J. *Org. Lett.* **2013**, *15*, 690. (f) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. *Org. Lett.* **2014**, *16*, 968. (g) Zhang, H.; Hu, R.-B.; Zhang, X.-Y.; Li, S.-X.; Yang, S.-D. *Chem. Commun.* **2014**, *50*, 4686. See also, ref 14.
(21) Rozen, S.; Hebel, D.; Zamir, D. *J. Am. Chem. Soc.* **1987**, *109*, 3789.
(22) *N*-(8-Quinolinyl)isobutyramide (amide with a secondary alkyl group) did not give the desired acetoxylated product, and amide **8** (for the structure, see Scheme 4) was obtained in 21% yield.
(23) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066.
(24) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 11124. See also, ref 6.
(25) (a) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149. (b) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141.
(26) The mechanism for the formation of amide **8** is not clear yet.
(27) In the case when 2-methyl-2-phenyl-*N*-(8-quinolinyl)propanamide was used as a substrate, intramolecular C(sp^2)−H amidation proceeded and the corresponding 2-indolinone derivative was obtained in 61% yield. See ref 6.

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