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$Sc(OTf)_3$-Catalyzed or *t*-BuOK Promoted Tandem Reaction of 2-(2-(Alkynyl)benzylidene)malonate with Indole

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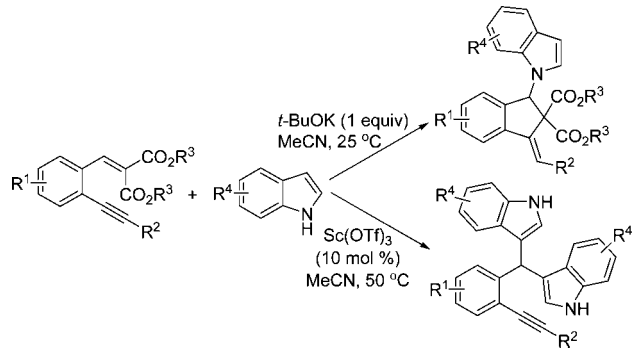
ABSTRACT



Tandem reaction of 2-(2-(alkynyl)benzylidene)malonate with indole was investigated. (*Z*)-1-Benzylidene-3-(1*H*-indol-1-yl)-1*H*-indene-2,2(3*H*)-dicarboxylate was generated in the presence of *t*-BuOK at room temperature; whereas 3-((1*H*-indol-3-yl)(2-(alkynyl)aryl)methyl)-1*H*-indole was obtained when $Sc(OTf)_3$ was utilized as catalyst at 50 °C.

Diversity-oriented chemical synthesis has been used as an engine to efficiently synthesize complex and diverse small molecules in the field of chemical genetics.[1] Among the strategies used in diversity-oriented synthesis, design and synthesis of natural products and complex compounds via tandem reactions has attracted much attention, and the development of tandem reactions has been a fertile area in organic synthesis.[2]

Recently, we have described efficient synthesis of 1,2-dihydroisoquinolines via multicomponent reactions of 2-(1-alkynyl)benzaldehydes, amines, and various nucleophiles.[3] The key intermediate in the reaction process was believed to be 2-(1-alkynyl)arylaldimine **1**. Prompted by these results, we envisioned that 2-(2-(alkynyl)benzylidene)malonate **2** might be utilized in similar tandem reactions because of the structural similarity of 2-(1-alkynyl)arylaldimine **1** (Figure 1). Herein, we disclose that 2-(2-(alkynyl)benzylidene)malonate **2** undergoes a tandem reaction with indole under acid-

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(1) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Schreiber, S. L. *Chem. Eng. News* **2003**, *81* (9), 51.

(2) For selected examples, see: (a) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137–166. (b) Porco, J. A., Jr.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410–7411. (c) Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1996**, *118*, 4059–4071. (d) Chen, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7424–7425. (e) Shi, F.; Li, X.; Xia, Y.; Zhang, L.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 15503–15504.

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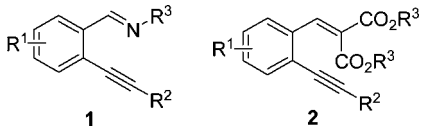
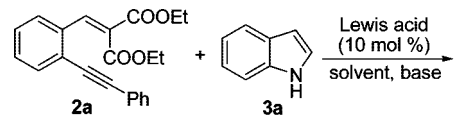


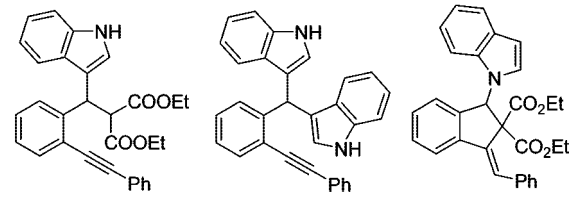
Figure 1. Structure of 2-(1-alkynyl)arylaldimine **1** and 2-(2-(alkynyl)benzylidene)malonate **2**.

or base-controlled conditions, thus offering an unprecedented and straightforward route for the synthesis of (*Z*)-1-benzylidene-3-(1*H*-indol-1-yl)-1*H*-indene-2,2(3*H*)-dicarboxylate or 3-((1*H*-indol-3-yl)(2-(alkynyl) aryl)methyl)-1*H*-indole.

Because the indole skeleton is an important substructure in both natural products and therapeutic agents,[4] at the beginning a set of experiments was carried out using diethyl 2-(2-(2-phenylethynyl)benzylidene)malonate **2a** and indole **3a** as model substrates. This preliminary survey, carried out in the presence of a Lewis acid as the catalyst, allowed us to evaluate and optimize the most efficient catalytic system. In an initial experiment, the reaction was performed in acetonitrile at room temperature catalyzed by $Yb(OTf)_3$ (Table 1, entry 1). The generated product was the normal Michael addition adduct **4a** (53% yield). A similar result was obtained when the catalyst was replaced by $Dy(OTf)_3$ or $Sc(OTf)_3$ (Table 1, entries 2 and 8). This normal Michael addtion reaction is well-established in the literature.[5] No reaction occurred or only a trace amount of product was detected when other Lewis acids ($LiClO_4$, $Mg(ClO_4)_2$, $ZnCl_2$, $YbCl_3$, CAN) were utilized as catalyst (Table 1, entries 3−7). Interestingly, compound **5a** was formed when the reaction was performed at 50 or 70 °C catalyzed by $Sc(OTf)_3$ or $Yb(OTf)_3$ (Table 1, entries 9 and 10). The alkynyl group in the substrate is not a specific factor for the outcome of double addition. The same outcome was observed with the parent benzylidenemalonate. It seems that the difference for generation of compound **4a** or **5a** depends on the temperature employed. Further investigation revealed that the tandem addition-cyclization could occur via 5-*exo*-cyclization[6] when *t*-BuOK was added as a base in the $Yb(OTf)_3$-catalyzed reaction (Table 1, entry 11). The corresponding product was afforded in 77% yield, and the structure was verified as **6a** by ^1H and ^{13}C NMR, mass spectroscopy, and X-ray diffraction analysis (see Supporting Information). The yield could

Table 1. Screening Conditions for Reaction of **2a** with Indole **3a**[a]





entry	Lewis acid	base	solvent	temp (°C)	time (h)	yield (%)[b]
1	$Yb(OTf)_3$		MeCN	25	70	53 (**4a**)
2	$Dy(OTf)_3$		MeCN	25	72	71 (**4a**)
3	$LiClO_4$		MeCN	25	24	NR
4	$Mg(ClO_4)_2$		MeCN	25	24	NR
5	$ZnCl_2$		MeCN	25	24	NR
6	$YbCl_3$		MeCN	25	24	trace
7	CAN		MeCN	25	24	trace
8	$Sc(OTf)_3$		MeCN	25	24	87 (**4a**)
9	$Sc(OTf)_3$		MeCN	50	5	99 (**5a**)
10	$Yb(OTf)_3$		MeCN	70	48	80 (**5a**)
11	$Yb(OTf)_3$	^{t}BuOK	MeCN	25	20	77 (**6a**)
12	$Yb(OTf)_3$	K_2CO_3	MeCN	25	24	NR
13	$Yb(OTf)_3$	Cs_2CO_3	MeCN	60	48	85 (**6a**)
14	$Yb(OTf)_3$	NaH	MeCN	25	24	NR
15	$Yb(OTf)_3$	Et_3N	MeCN	25	24	NR
16	$Yb(OTf)_3$	$^i Pr_2NEt$	MeCN	25	24	NR
17	AgOTf	^{t}BuOK	MeCN	25	24	61 (**6a**)
18	CuI	^{t}BuOK	MeCN	25	7	63 (**6a**)
19	$FeCl_3$	^{t}BuOK	MeCN	25	7	63 (**6a**)
20	$Mg(ClO_4)_2$	^{t}BuOK	MeCN	25	7	85 (**6a**)
21		^{t}BuOK	MeCN	25	24	76 (**6a**)
22		^{t}BuOK	^{t}BuOH	25	24	17 (**6a**)
23		^{t}BuOK	DCE	25	48	trace
24		^{t}BuOK	THF	25	48	trace
25		^{t}BuOK	toluene	25	48	trace
26		^{t}BuOK	DMF	25	24	70 (**6a**)
27[c]		^{t}BuOK	MeCN	25	9	97 (**6a**)

[a] Reaction conditions: 2-(2-(alkynyl)benzylidene)malonate **2a** (0.3 mmol), indole **3a** (0.33 mmol, 1.1 equiv), Lewis acid (10 mol %), base (1.0 equiv). [b] Isolated yield based on 2-(2-(alkynyl)benzylidene)malonate **2a**. [c] Reaction conditions: 2-(2-(alkynyl)benzylidene)malonate **2a** (0.3 mmol), indole **3a** (0.25 mmol), base (1.0 equiv). Isolated yield based on indole **3a**.

be increased to 85% when the base was changed to Cs_2CO_3, although prolonged reaction time was needed (48 h, Table 1, entry 13). However, no product was detected when other bases (K_2CO_3, NaH, Et_3N, $^i Pr_2NEt$) were employed (Table 1, entries 12, 14−16). Other Lewis acids (AgOTf, CuI, $FeCl_3$, $Mg(ClO_4)_2$) were also screened in the presence of *t*-BuOK, and the desired product **6a** was generated in moderate to good yield (Table 1, entries 17−20). From these results, the role of the Lewis acid in the reaction was doubted. Thus, the reaction without adding Lewis acid in the presence of *t*-BuOK was examined at room temperature. Surprisingly,

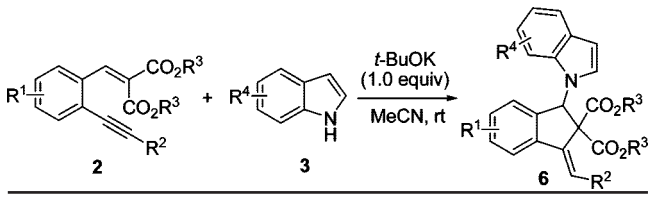
(3) (a) Ding, Q.; Wu, J. *Org. Lett.* **2007**, *9*, 4959–4962. (b) Gao, K.; Wu, J. *J. Org. Chem.* **2007**, *72*, 8611–8613. (c) Sun, W.; Ding, Q.; Sun, X.; Fan, R.; Wu, J. *J. Comb. Chem.* **2007**, *9*, 690–694.

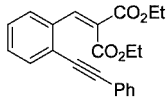
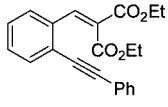
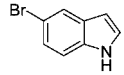
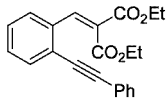
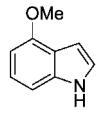
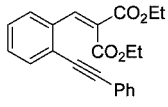
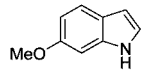
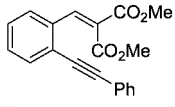
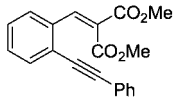
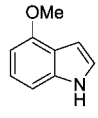
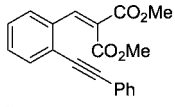
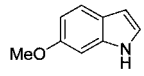
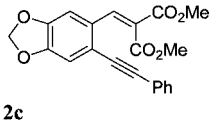
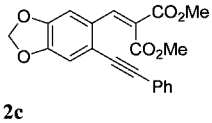
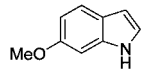
(4) (a) Saxton, J. E. *Nat. Prod. Rep.* **1997**, *14*, 559–590. (b) Toyota, M.; Ihara, N. *Nat. Prod. Rep.* **1998**, *15*, 327–340.

(5) (a) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780–10781. (b) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH Verlag GmbH: Weinheim, 2000.

(6) For selected examples, see: (a) Martinez, I.; Alford, P. E.; Ovaska, T. V. *Org. Lett.* **2005**, *7*, 1133–1135. (b) Bailey, W. F.; Longstaff, S. C. *J. Org. Chem.* **1998**, *63*, 432–433. (c) Duan, X.-H.; Guo, L.-N.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2006**, *8*, 5777–5780. (d) Bi, H.-P.; Guo, L.-N.; Duan, X.-H.; Gou, F.-R.; Huang, S.-H.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2007**, *9*, 397–400. (e) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2007**, *72*, 1538–1540. (f) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2006**, *71*, 3325–3327. (g) Bi, H.-P.; Liu, X.-Y.; Gou, F.-R.; Guo, L.-N.; Duan, X.-H.; Liang, Y.-M. *Org. Lett.* **2007**, *9*, 3527–3529.

Table 2. Reaction of Compound **2** with Indole **3** in the Presence of *t*-BuOK (1.0 equiv) at Room Temperature



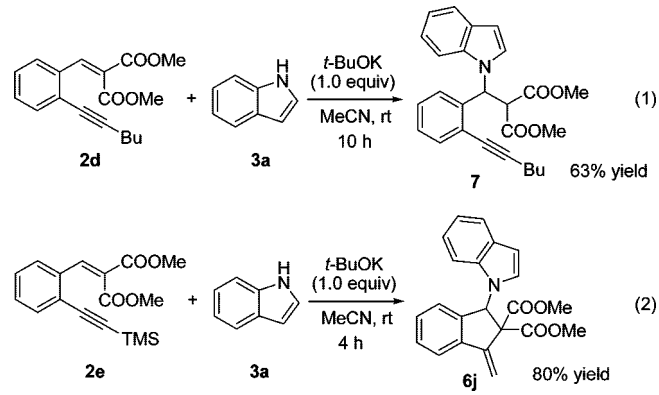
entry	substrate **2**	indole **3**	time (h)	yield (%)[a]
1	 **2a**	 **3a**	9	97 (**6a**, *Z*/*E*: 92/8)
2	 **2a**	 **3b**	12	50 (**6b**, *Z*/*E*: 91/9)
3	 **2a**	 **3c**	9	98 (**6c**, *Z*/*E*: 93/7)
4	 **2a**	 **3d**	5	94 (**6d**, *Z*/*E*: 91/9)
5	 **2b**	 **3a**	6	89 (**6e**, *Z*/*E*: 92/8)
6	 **2b**	 **3c**	13	88 (**6f**, *Z*/*E*: 94/6)
7	 **2b**	 **3d**	5	87 (**6g**, *Z*/*E*: >99/1)
8	 **2c**	 **3a**	6	99 (**6h**, *Z*/*E*: 94/6)
9	 **2c**	 **3d**	5	88 (**6i**, *Z*/*E*: >99/1)

[a] Isolated yield based on indole **3**. The *Z*/*E* ratio was determined by ^{1}H NMR.

the reaction also proceeded smoothly to give rise to the desired product **6a** in 76% yield (24 h, Table 1, entry 21). The presence of Lewis acid may accelerate the reaction. For instance, the reaction was complete in 7 h when $Mg(ClO_4)_2$ was added (Table 1, entry 20). Solvent effect was also investigated, and acetonitrile was demonstrated as the best choice for this transformation (Table 1, entries 21−26). The yield could be dramatically improved when the ratio of substrates was changed to 1.2:1 (97% yield, Table 1, entry 27).

To demonstrate generality of this method, we started to investigate the scope of this tandem addition-cyclization reaction under the optimized reaction conditions (*t*-BuOK, MeCN, room temperature), and the results are shown in Table 2. From Table 2, it was found that for most cases this base-promoted tandem reaction of 2-(2-(alkynyl)benzylidene)malonate **2** and indole **3** furnished the corresponding (*Z*)-1-benzylidene-3-(1*H*-indol-1-yl)-1*H*-indene-2,2(3*H*)-dicarboxylate **6** in good to excellent yields. A better result was observed when an indole with an electron-donating group attached on the aromatic ring was employed. For example, 98% or 94% yield of corresponding product **6c** or **6d** was obtained, respectively, when 2-(2-(alkynyl)benzylidene)malonate **2a** reacted with methoxy-substituted indole **3c** or **3d** (Table 2, entries 3 and 4). However, only moderate yield was observed when 5-bromoindole was utilized in the reaction of 2-(2-(alkynyl)benzylidene)malonate **2a** (50% yield, Table 2, entry 2). Substrate **2b** reacted with indole **3a**, leading to the formation of compound **6e** in 89% yield (Table 2, entry 5). A similar result was obtained when indole **3c** or **3d** was used as a replacement (Table 2, entries 6 and 7). Reaction of compound **2c** with indole **3a** or **3d** also proceeded smoothly and gave rise to the desired product **6h** or **6i** in 99% or 88% yield, respectively (Table 2, entry 8). We also tested the reactions of indole **3a** with other substrates, such as **2d** and **2e**. Interestingly, only normal Michael addition product **7** was furnished when substrate **2d** was employed (63% yield, Scheme 1, eq 1). Reaction of

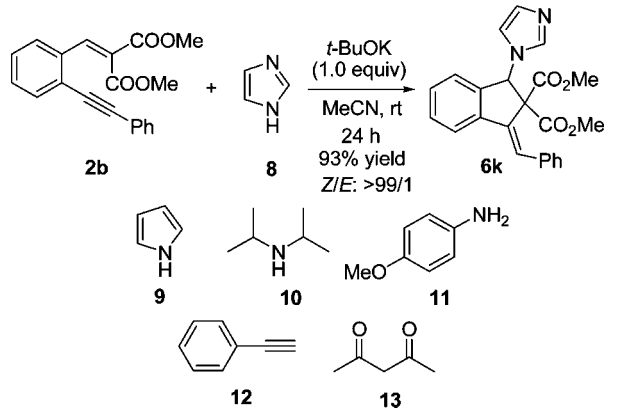
Scheme 1. Reaction of 2-(2-(Alkynyl)benzylidene)malonate **2d** and **2e** with Indole **3a** Promoted by *t*-BuOK



compound **2e** with indole **3a** generated the desilylated product **6j** in 80% yield (Scheme 1, eq 2).

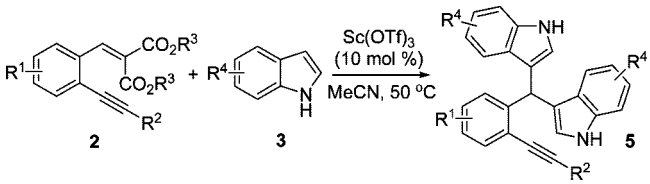
Other nucleophiles were also examined in the reaction of compound **2b** under the conditions shown in Table 2. As presented in Scheme 2, imidazole **8** was also a good partner for the reaction of 2-(2-(alkynyl)benzylidene)malonate **2b**, which gave rise to the desired product **6k** in 93% yield. However, only a trace amount of product was detected when pyrrole **9** was utilized. No reaction occurred when diisopropylamine **10**, *p*-anisidine **11**, or phenylacetylene **12** was employed as nucleophile. A complex mixture was observed for reaction of **2b** with pentane-2,4-dione **13**.

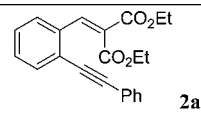
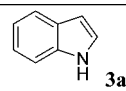
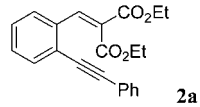
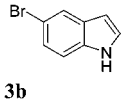
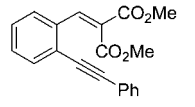
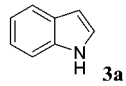
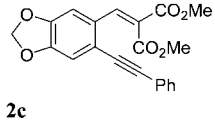
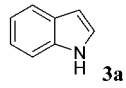
Scheme 2. Reaction of 2-(2-(Alkynyl)benzylidene)malonate **2b** with Other Nucleophiles



In a second set of experiments, the Lewis acid catalyzed reaction of 2-(2-(alkynyl)benzylidene)malonate **2** with indole **3** was examined (Table 3). This transformation was highly

Table 3. Reaction of Compound **2** with Indole **3** Catalyzed by $Sc(OTf)_3$ (10 mol %) at 50 °C



entry	substrate **2**	indole **3**	time (h)	yield (%)[a]
1	 **2a**	 **3a**	5	99 (**5a**)
2[b]	 **2a**	 **3b**	5	99 (**5b**)
3	 **2b**	 **3a**	14	99 (**5a**)
4	 **2c**	 **3a**	4	94 (**5c**)

[a] Isolated yield based on 2-(2-(alkynyl)benzylidene)malonate **2**.

effective and gave rise to the 3-((1*H*-indol-3-yl)(2-(alkynyl)aryl)methyl)-1*H*-indole **5** in excellent yield. Although the mechanism is not clear, our finding is similar to a report on the reactions of (*Z*)-ethyl 2-cyano-3-phenylacrylate with EtSH catalyzed by AkX_3 (X = Br, Cl).[7] In the reactions, double bonds activated by electron-withdrawing groups were cleaved on treatment with a hard Lewis acid and EtSH. For the results shown in Table 3, we reasoned that the formation of unexpected product **5** could be explained in a similar manner.[7] Initially, Michael addition of indole takes place to afford the normal adduct **4**, which is converted into the benzylidene-3*H*-indole species by the loss of the active methylene moiety in the presence of Lewis acid at higher temperature. Addition of another molecule of indole completes the overall transformation.

In conclusion, we have described an unprecedented and straightforward route for the synthesis of (*Z*)-1-benzylidene-3-(1*H*-indol-1-yl)-1*H*-indene-2,2(3*H*)-dicarboxylate via a tandem addition-cyclization reaction of 2-(2-(alkynyl)benzylidene)malonate with indole under base conditions. We also discover that 3-((1*H*-indol-3-yl)(2-(alkynyl)aryl)methyl)-1*H*-indole may be formed in the presence of Lewis acid via double sequential addition of indole to 2-(2-(alkynyl)benzylidene)malonate.

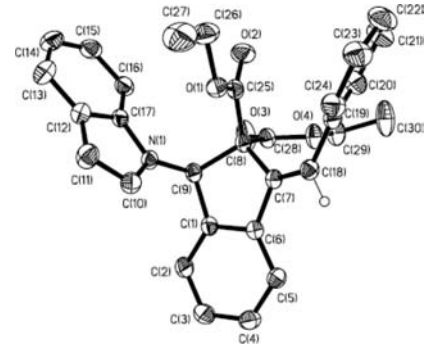


Figure 2. X-ray structure of compound **6a**.

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Supporting Information Available: Experimental procedures, characterization data including X-ray diffraction analysis data of compound **6a** in CIF format, and copies of ^1H and ^{13}C NMR of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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