Synthetic Methods

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Direct Alkenylation of Indoles with α-Oxo Ketene Dithioacetals: Efficient Synthesis of Indole Alkaloids Meridianin Derivatives**

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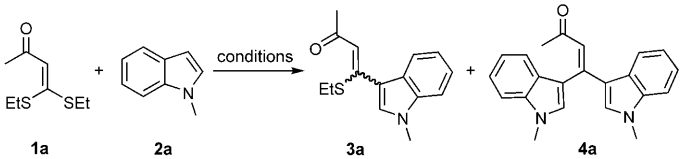
α-Oxo ketene dithioacetals have recently emerged as versatile reagents[1] in the synthesis of heterocycles[2] and aromatic compounds,[3] as well as odorless thiol equivalents.[4] Indole derivatives are potentially bioactive[5] and have been used as synthons of complex molecules.[6] Recently, bisindoles have attracted interest because of their potent antitumor bioactivity.[7,8] Although alkylation and arylation of indoles have been well-documented,[6,9] there are only a few reports on their alkenylation.[10] These alkenylation reactions include palladium-catalyzed vinylation using alkenes,[10a,c] nickel-catalyzed addition of indole to alkynes,[10b] acid-promoted reactions,[10d,g] or indirect transformations.[10e,f] Meridianins are marine natural products that represent a new family of protein kinase inhibitors and have been exhibited promising anticancer activity,[11] therefore making their syntheses an attractive challenge.[12] On the basis of the electronic and structural features, we envisioned that α-oxo ketene dithioacetals might react with indoles to generate new classes of indole derivatives potentially useful for the synthesis of meridianin derivatives. As a continuation of our interest in the functionalization of indoles,[13] we disclose herein the acid-mediated direct alkenylation of indoles with 2,α-oxo ketene dithioacetals, providing a new efficient route to derivatives of the meridianin indole alkaloids.

The reaction of α-oxo ketene dithioacetal **1a** and *N*-methylindole (**2a**) was initially conducted (Table 1). The first reaction was carried out in trifluoroacetic acid (TFA), which has been reported to be used as the solvent for the electrophilic substitution of arene C–H bonds under transition-metal catalysis.[14] The reaction of **1** and **2a** (1:1 molar ratio) occurred at room temperature, exclusively affording an isomeric mixture of monosubstituted product **3a** in 69% yield within 10 hours (Table 1, entry 1). The reaction proceeded more efficiently to give **3a** by using refluxing TFA at 72 °C (Table 1, entry 2). The reaction run in dichloromethane produced **3a** in a lower yield albeit with a higher stereoselectivity, and unexpectedly, bisindole **4a** was formed in 5% yield (Table 1, entry 3). A variation of the acidity of the reaction medium, through the reduction of the amount of TFA used, favored the formation of (*Z*)-**3a**, but the transformation was slower at room temperature (Table 1, entries 3–6). Additional reduction of the amount of TFA in the reaction medium led to **4a** as the major product (Table 1, entries 7 and 8). These results have demonstrated that stronger acidic conditions facilitate the monosubstitution of **1a** by **2a**, used in a 1:1 molar ratio, to afford **3a**. To obtain **4a** in a decent yield, the reaction of **1a** and **2a** in a 1:2 molar ratio was carried out in CH_2Cl_2 with TFA as the promoter, providing **4a** in yields ranging from 86 to 90% (Table 1, entries 9–13). By using *p*-TsOH or $BF_3{\cdot}OEt_2$ as the acid promoter, the same reaction proceeded but less efficiently (Table 1, entries 14 and 15). The reaction did not occur when THF was used as the solvent (Table 1, entry 16). Accordingly, the reaction conditions were optimized as follows: condi-

Table 1: Screening of reaction conditions.[a]



Entry	Solv.	Acid	**1a**/**2a**/acid (mol ratio)	*T* [°C]	*t* [h]	Yield [%][b] **3a**	**4a**
1	TFA	TFA	1:1:40	RT	10	69 (3:2)[c]	–
2	TFA	TFA	1:1:40	reflux	1.0	83 (3:2)[c]	–
3	CH_2Cl_2	TFA	1:1:40	reflux	0.5	62 (9:2)[c]	5
4	CH_2Cl_2	TFA	1:1:30	reflux	0.5	78 (8:1)[c]	8
5	CH_2Cl_2	TFA	1:1:20	reflux	0.5	84 (9:1)[c]	8
6	CH_2Cl_2	TFA	1:1:20	RT	2.5	82 (9:1)[c]	7
7	CH_2Cl_2	TFA	1:1:10	reflux	0.5	36	24
8	CH_2Cl_2	TFA	1:1:2	reflux	2.5	9	45
9	CH_2Cl_2	TFA	1:2:2	reflux	8.0	–	86
10	CH_2Cl_2	TFA	1:2:3	reflux	7.0	–	89
11	CH_2Cl_2	TFA	1:2:4	reflux	2.5	–	90
12	CH_2Cl_2	TFA	1:2:5	reflux	1.8	–	85
13	CH_2Cl_2	TFA	1:2:4	RT	30	–	89
14	CH_2Cl_2	*p*-TsOH	1:2:4	RT	32	–	20
15	CH_2Cl_2	$BF_3{\cdot}OEt_2$	1:2:4	RT	30	–	69
16	THF	TFA	1:2:4	RT	30	–	–

[a] Reaction conditions: **1a** (0.5 mmol), solvent (5 mL). [b] Yield of isolated products. [c] Molar ratio of *Z*/*E*-**3a** isomers determined by ^{1}H NMR analysis. THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

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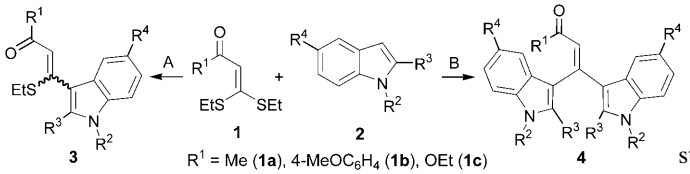
tion A: **1a**/**2a**/TFA = 1:1:20 in refluxing CH_2Cl_2 for the synthesis of **3a** with a high *Z*/*E* ratio; condition B: **1a**/**2a**/TFA = 1:2:4 in refluxing CH_2Cl_2 for synthesis of **4a**.

Next, the reactions of 2,α-oxo ketene dithioacetals **1a–c** and indoles **2a–i** were carried out under the optimized reaction conditions to define the scope of the reaction (Table 2). The reactions of **1a** and **1b** with **2** (R^3 = H) efficiently afforded the mono and bisindole products **3** (64–87% yield) and **4** (61–90% yield), respectively (Table 2, entries 1–11). The products (*Z*)-**3** were always obtained as the major products for the reactions run in a 1:1 molar ratio, reaching the highest *Z*/*E* ratio of 30:1 (Table 2, entry 8). Unexpectedly, the 1:1 molar ratio reactions of **1c** with **2a** and **2d** did not give the desired products **3l** and **3m**, respectively; instead the hydrolysis products **5a** (81% yield) and **5b** (84% yield), respectively, were formed [Table 2, entries 12 and 13, Eq. (1)]. When a bulky group such as phenyl was introduced to the C2-position of the indole (e.g., **2h**), the reactions of **1a** and **2h** only produced monoindole **3n** (Table 2, entry 14). The steric bulk of the C2 substituent of **2h** excluded the disubstitution of **1a** to form the expected bisindole **4n**. When an electron-withdrawing tosyl group was present (**2i**) on one nitrogen atom of the indole the reaction of **1a** and **2i** did not occur, suggesting that an electron-withdrawing substituent within **2** decreases its nucleophilicity and thus does not favor its substitution reaction with **1**. Product (*Z*)-**3a** was successfully isolated by recrystallization of a (*Z*/*E*)-**3a** mixture, and the molecular structures of (*Z*)-**3a** and **4g** were confirmed by X-ray crystallographic analysis (Figure 1 and see the Supporting Information).[19] In (*Z*)-**3a** the indolyl and acetyl groups are positioned *anti* to each other, and in **4g** the two indolyl moieties are arranged in a way so as to reduce the steric interactions by positioning the benzyl groups far away from each other.

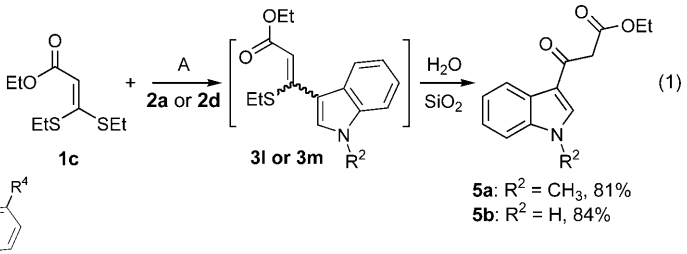
The reaction mechanism was explored by studying different substitution reactions of **1a** or **3a** with **2**. Indoles can be

Table 2: Alkenylation of indoles with α-oxo ketene dithioacetals.[a]



Entry	1	2		Cond.	Product	Yield [%][b]
1	**1a**	**2a**	R^2 = CH_3	A	**3a**	84 (9:1)[c]
			R^3 = R^4 = H	B	**4a**	90
2	**1a**	**2b**	R^2 = Bn	A	**3b**	78 (3:1)[c]
			R^3 = R^4 = H	B	**4b**	88
3	**1a**	**2c**	R^2 = allyl	A	**3c**	74 (3:2)[c]
			R^3 = R^4 = H	B	**4c**	74
4	**1a**	**2d**	R^2 = H	A	**3d**	75 (4:1)[c]
			R^3 = R^4 = H	B	**4d**	61
5	**1a**	**2e**	R^2 = R^3 = H	A	**3e**	64 (3:2)[c]
			R^4 = OMe	B	**4e**	67
6	**1a**	**2f**	R^2 = R^3 = H	A	**3f**	82 (3:1)[c]
			R^4 = Br	B	**4f**	77
7	**1a**	**2g**	R^2 = Bn, R^3 = H, R^4 = Br	A	**3g**	81 (6:5)[c]
				B	**4g**	88
8	**1b**	**2a**	R^2 = CH_3	A	**3h**	87 (30:1)[c]
			R^3 = R^4 = H	B	**4h**	88
9	**1b**	**2b**	R^2 = Bn	A	**3i**	78 (15:2)[c]
			R^3 = R^4 = H	B	**4i**	86
10	**1b**	**2d**	R^2 = H	A	**3j**	74 (11:5)[c]
			R^3 = R^4 = H	B	**4j**	79
11	**1b**	**2g**	R^2 = Bn, R^3 = H, R^4 = Br	A	**3k**	76 (14:1)[c]
				B	**4k**	89
12	**1c**	**2a**	R^2 = CH_3	A	**3l**	–[d]
			R^3 = R^4 = H	B	**4l**	84
13	**1c**	**2d**	R^2 = H	A	**3m**	–[d]
			R^3 = R^4 = H	B	**4m**	80
14	**1a**	**2h**	R^2 = Et,	A	**3n**	97 (20:1)[c]
			R^3 = Ph, R^4 = H	B	**3n**	95 (20:1)[c]
15	**1a**	**2i**	R^2 = Ts,	A	**3o**	
			R^3 = R^4 = H	B	**4o**	

[a] Reaction condition A: **1** (0.5 mmol), molar ratio **1**/**2**/TFA = 1:1:20, CH_2Cl_2 (5 mL), reflux, 0.5 h. Reaction condition B: **1** (0.5 mmol), molar ratio **1**/**2**/TFA = 1:2:4; CH_2Cl_2 (5 mL), reflux, 2.5–5.0 h. [b] Yield of isolated product. [c] Molar ratio of *Z*/*E*-**3** isomers determined by ^{1}H NMR analysis. [d] Hydrolysis, see Equation (3). Bn = benzyl.



(1)

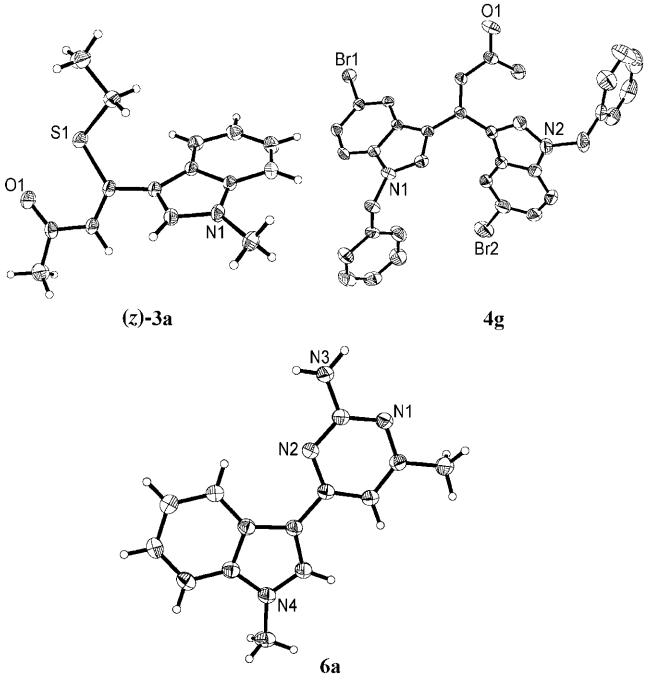
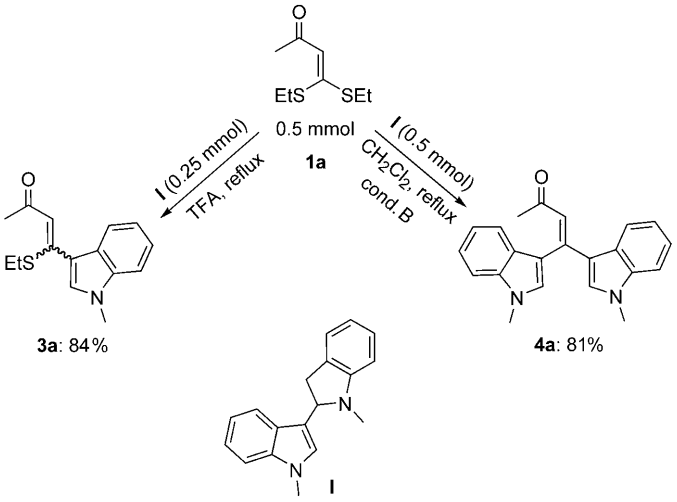


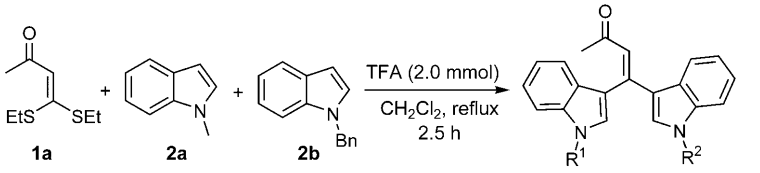
Figure 1. Molecular structures of (*Z*)-**3a**, **4g**, and **6a**. The thermal ellipsoids are at 30% probability.

readily protonated in concentrated acidic solutions, whereas indole dimers are usually formed under dilute acidic conditions.[15,16] Therefore treatment of **2a** in a dilute TFA solution in CH_2Cl_2 at room temperature conveniently afforded the dimeric **I** (see the Supporting Information), which was used to react with **1a** in TFA or under reaction condition B (Scheme 1). Within 30 minutes the reaction of **1a**



Scheme 1. Reactions of **1a** and the dimer **I**.

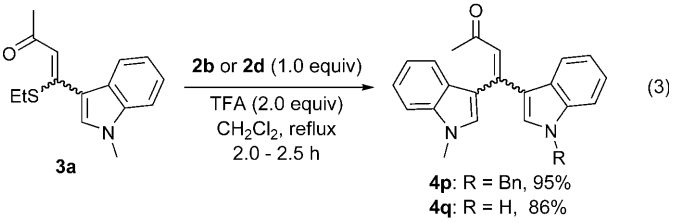
with 0.5 equivalents of **I** in refluxing TFA gave **3a** in 84% yield, whereas the treatment of **1a** with 1.0 equivalent of **I** in refluxing CH_2Cl_2 and using TFA as the promoter afforded **4a** in 81% yield. These results are comparable with those obtained by using **2a** as the substrate (Table 2, entry 1), presumably because of the facile thermal conversion of the indole dimer into the monomer units.[16] A competition reaction of **1a** with **2a**/**2b** (**2a**/**2b** 1:1) under intermediate acidic conditions produced homo- and hetero-bisindole products **4a**, **4b**, and **4p** [Eq. (2)], revealing that increasing



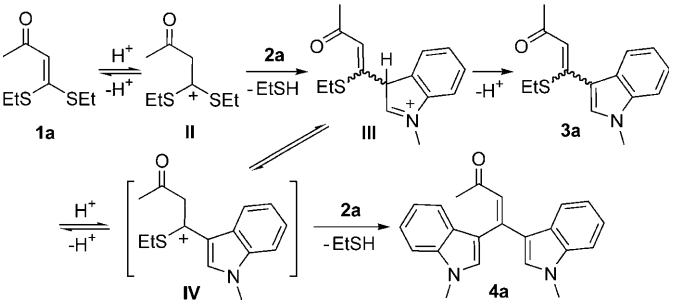
(2)

the steric bulk of indole **2** reduces formation of the desired bisindole product. The reactions of **3a** with **2b** or **2d** were also successfully pursued to prepare hetero-bisindoles **4p** and **4q** in approximately a 1:1 *Z*/*E* ratio, respectively [Eq. (3)].

A possible mechanism is proposed in Scheme 2. The reaction of **1a** and indole **2a** is presumably initiated by the protonation of the polarized C=C bond of **1a** to form carbocation **II**, which is additionally stabilized by the two adjacent electron-donating ethylthio groups. Nucleophilic



(3)

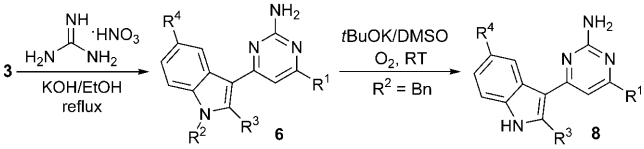


Scheme 2. Proposed mechanism.

attack at the cationic carbon atom of **II** by C3 of **2a** forms the β-indolyl monosubstituted product **3a** via intermediate **III** by elimination of an EtSH and a proton. In an acidic solution, an equilibrium is present between the indole, its protonated form, and the dimer.[15,16] In concentrated acidic solutions, the protonated indole is predominant and cannot nucleophilically attack carbocation **IV** to form bisindole **4a**, thereby forming **3a** when the reactants are used in a 1:1 molar ratio. However, in a dilute acidic solution the readily formed indole dimer easily undergoes thermal conversion into the monomer units, which nucleophilically attack **IV** to form **4a** as the major product. Notably, **3a** may also be protonated by the acid promoter to form **III** or **IV** which then reacts with **2a** to generate **4a**.

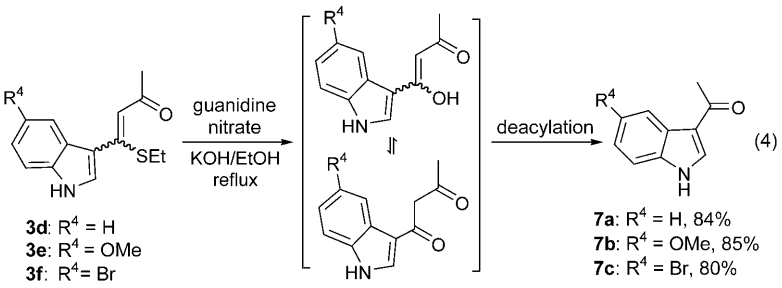
Meridianins and their derivatives are usually prepared by the condensation of functionalized indoles with guanidines,[12,17a,b] or by the Suzuki coupling of indolyl boronates with halopyrimidines.[17c] Compounds **3** can be considered as ketene monothioacetals or alkenylated indoles which may be used as versatile synthetic intermediates. Thus, we carried out the condensation reactions of **3** with guanidine, in an attempt to synthesize meridianin derivatives. The reaction of **3a** and guanidine nitrate under basic reaction conditions afforded the meridianin derivative **6a** in 71% yield upon isolation (Table 3, entry 1), and the *Z*/*E* ratio of **3a** did not affect formation of the desired product. The molecular structure of **6a** was confirmed by X-ray crystallographic analysis (Figure 1 and see the Supporting Information).[19] This methodology was also successfully applied to the reactions of **3b**, **3c**, **3g–i**, and **3k**, producing the desired products **6b–g** in yields ranging from 64 to 84% (Table 3, entries 2–7). Surprisingly, the treatment of **3d–f**, which do not have a protecting group on the nitrogen atom, with guanidine nitrate under the same reaction conditions only gave the deacetylation products **7a–c**

Table 3: Synthesis of meridianin derivatives from **3**.[a]



Entry	**3** or **6**	R^1 (R^3 = H)	R^2	R^4	Product	Yield [%][b]
1	**3a**	Me	Me	H	**6a**	71
2	**3b**	Me	Bn	H	**6b**	68
3	**3c**	Me	allyl	H	**6c**	64
4	**3g**	Me	Bn	Br	**6d**	84
5	**3h**	4-$MeOC_6H_4$	Me	H	**6e**	63
6	**3i**	4-$MeOC_6H_4$	Bn	H	**6f**	65
7	**3k**	4-$MeOC_6H_4$	Bn	Br	**6g**	80
8	**6b**	Me	H	H	**8a**	76
9	**6d**	Me	H	Br	**8b**	81
10	**6f**	4-$MeOC_6H_4$	H	H	**8c**	78
11	**6g**	4-$MeOC_6H_4$	H	Br	**8d**	83

[a] Reaction conditions for synthesis of **6**: **3** (0.25 mmol), guanidine nitrate (0.5 mmol), KOH (1.5 mmol), EtOH (5 mL), reflux, 22 h. Conditions for synthesis of **8**: **6** (0.25 mmol) *t*BuOK (1.75 mmol), DMSO (1 mL), O_2 (1 atm), RT, 3–4 h. [b] Yield of isolated product. DMSO = dimethyl sulfoxide.



[Eq. (4)], which suggests that the N-protected ketene monothioacetals of type **3** should be used for synthesis of meridianin derivatives. Debenzylation of the *N*-benzyl protected meridianin compounds **6b**, **6d**, **6f**, and **6g** with *t*BuOK/DMSO under an atmosphere of oxygen[18] afforded N-deprotected meridianin derivatives **8a–d** in yields ranging from 76 to 83% (Table 3, entries 8–11).

In summary, metal-free direct alkenylation of indoles was realized by using acid-mediated substitution reactions of α-oxo ketene dithioacetals with indoles, selectively affording β-indolyl mono- and disubstitituted α,β-unsaturated carbonyl compounds. Condensation of these indolyl/ketene monothioacetals and guanidine nitrate successfully led to meridianin derivatives.

Experimental Section

A general procedure for the synthesis of compounds **3**. Synthesis of (*Z*/*E*)-4-(ethylthio)-4-(1-methyl-1*H*-indol-3-yl)but-3-en-2-one ((*Z*/*E*)-**3a**): TFA (0.75 mL, 10.0 mmol) was added to a stirred solution of **1a** (95.0 mg, 0.5 mmol) and **2a** (65.5 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) and then the mixture was refluxed for 30 min until **2a** was completely consumed as determined by TLC methods. Water (20 mL) was then added to the reaction mixture and extracted using CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (10 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (petroleum ether (30–60 °C)/diethyl ether 3:1, v/v) to give **3a** as a yellow solid (109 mg, 84%, *Z*/*E* 9:1 by ^1H NMR determination in [D_6]DMSO). Single yellow crystals of pure (*Z*)-**3a** were obtained from recrystallization in petroleum ether (30–60 °C)/diethyl ether (3:1, v/v) at room temperature for 15 days.

A general procedure for synthesis of meridianin derivatives **6**. Synthesis of **6a**: A mixture of **3a** (65 mg, 0.25 mmol), guanidine nitrate (61 mg, 0.5 mmol), and KOH (84 mg, 1.5 mmol) in EtOH (5 mL) was refluxed for 22 h until **3a** was completely consumed as determined by TLC monitoring. The mixture was cooled to ambient temperature, and 15 mL CH_2Cl_2 was added, and the reactions mixture was then filtered. The volatiles in the filtrate were evaporated under reduced pressure and the resultant residue was purified by silica gel column chromatography (petroleum ether (30–60 °C)/diethyl ether 3:1, v/v) to afford **6a** as a white solid (42 mg, 71%).

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[19] CCDC 719584 ((*Z*)-**3a**), 719583 (**4g**), and 719585 (**6a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

