Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201301051

Cascade Reactions: A Multicomponent Approach to Functionalized Indane Derivatives by a Tandem Palladium-Catalyzed Carbamoylation/Carbocylization Process

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Received: November 24, 2013; Revised: May 4, 2014; Published online: July 30, 2014

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201301051.

Abstract: A novel, multicomponent and stereoselective approach to functionalized indane derivatives is reported. It is based on a tandem process consisting of Pd-catalyzed oxidative carbamoylation of 2-(2-ethynylbenzyl)malonates with carbon monoxide, a secondary amine, and oxygen (with formation of a propiolamide intermediate), followed by carbocyclization, occurring through intramolecular addition of an *in situ* formed carbanion to the propiolamide moiety.

Keywords: carbamoylation; carbonylation; cascade reactions; indanes; multicomponent reactions; palladium

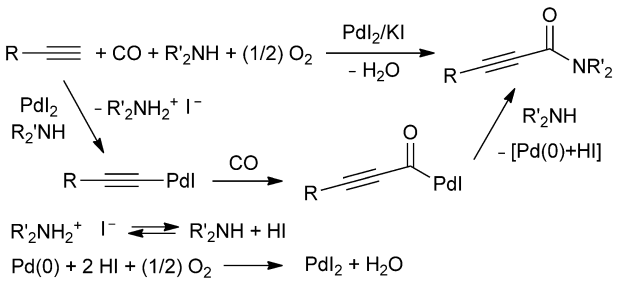
Introduction

"Cascade", "tandem", or "domino" reactions are processes in which two or more chemical transformations take place under identical conditions, with the product obtained in the first transformation becoming the substrate of the subsequent transformation(s), eventually leading to the final product.[1] These processes are of particular importance in synthesis, since they avoid the isolation and purification of the intermediate(s) and allow the formation in one step of the desired product starting from simple building blocks, with evident practical advantages, in terms of efficiency, selectivity, and atom, step and energy economy.[1–3]

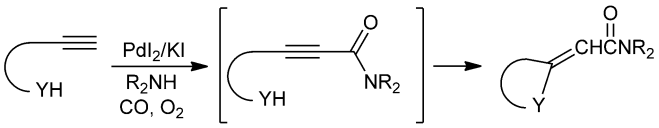
The PdI_2/KI-catalyzed oxidative carbamoylation of terminal alkynes, disclosed by our research group some years ago,[4] is a multicomponent reaction in which 1-alkynes, CO, a secondary amine, and oxygen react to selectively afford propiolamides, through the formation of an alkynylpalladium iodide species followed by carbon monoxide insertion and nucleophilic displacement by the amine. The active catalyst is the PdI_4^{2-} anion, formed *in situ* from the reaction between PdI_2 and an excess of iodide ligands. Scheme 1 shows the process, with anionic iodide ligands being omitted for clarity.

This kind of reactivity can be successfully exploited for the development of useful cascade reactions, when the alkyne substrate bears a suitably placed nucleophilic group.[5,6] In this case, in fact, the initially formed propiolamide intermediate can undergo a subsequent intramolecular conjugate addition with formation of a cyclic carbonylated derivative (Scheme 2).[5,6]

Although several applications of this concept have been described, leading to a variety of heterocyclic derivatives,[4,5] no example of a tandem triple bond carbamoylation–carbocyclization process has been reported so far. In this paper, we wish to report such a process, which allows the direct and multicomponent synthesis[7] of functionalized indanes **3** starting from readily available 2-(2-ethynylbenzyl)malonates

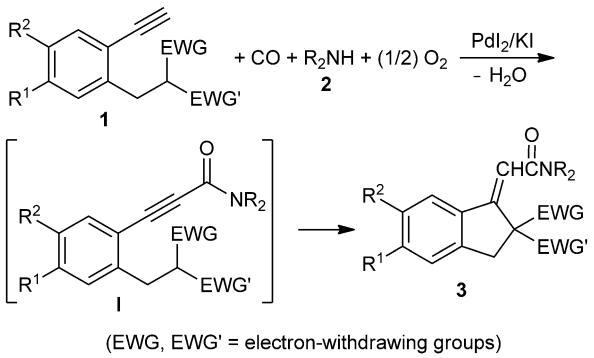


Scheme 1. PdI_2/KI-catalyzed oxidative carbamoylation of terminal alkynes.[4]



Scheme 2. Application of PdI_2-catalyzed oxidative carbamoylation of the terminal triple bond to the synthesis of carbonylated heterocycles. The oxidative carbonylation process is followed, *in situ*, by an intramolecular conjugate addition.[5,6]

and analogs (**1**), CO, O_2, and a secondary amine R_2NH (**2**), according to Scheme 3.

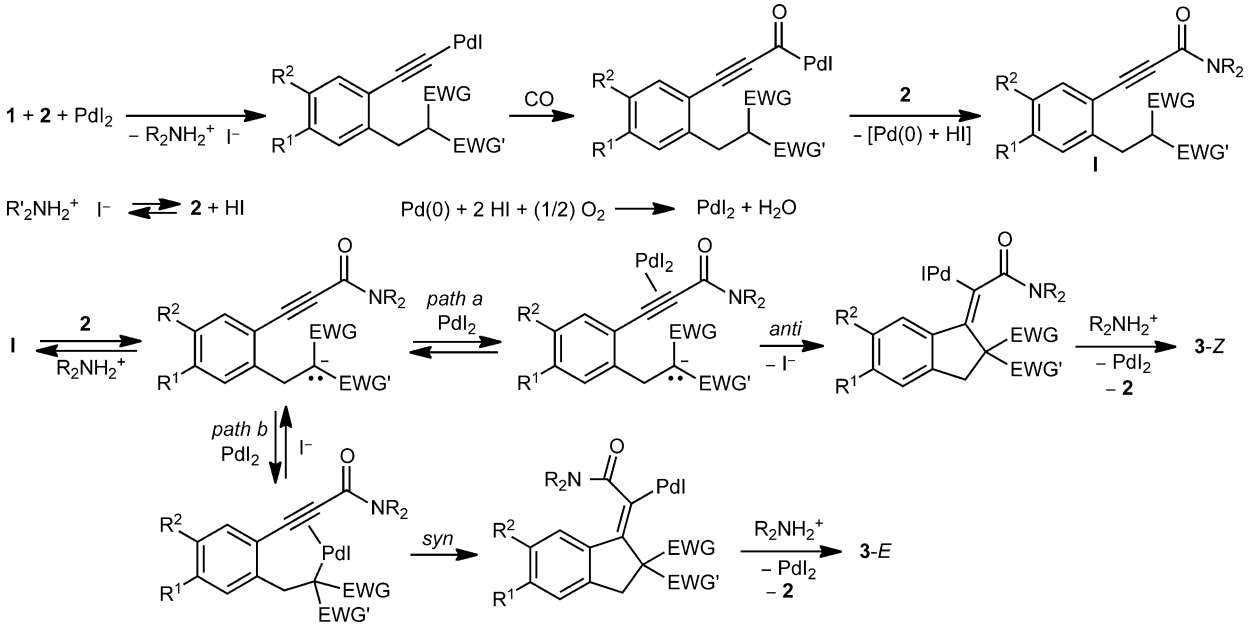


Scheme 3. This work: formation of carbonylated indane derivatives **3** by tandem oxidative carbamoylation of 2-(2-ethynylbenzyl)malonates and analogs **1**, to give propiolamide intermediates **I**, followed by carbocyclization.

Results and Discussion

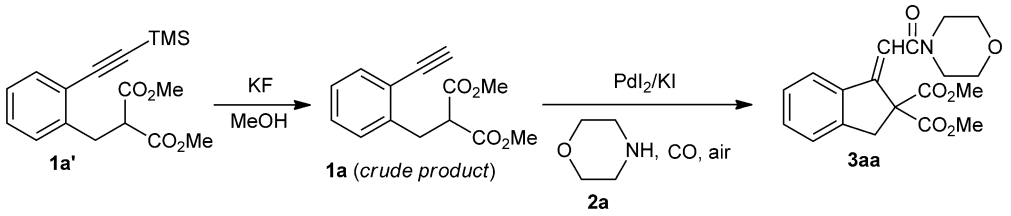
Our working hypothesis was based on the use of 2-(2-ethynylbenzyl)malonates and analogs (**1**), which, under the basic conditions employed to promote the triple bond oxidative carbamoylation leading to the propiolamide species **I**, could ensure a sufficient concentration of a carbanion intermediate to cause carbocyclization. The carbocyclization may be promoted by the electrophilic activation of the triple bond of **I** by PdI_2, as shown in Scheme 4. In path *a*, the intramolecular nucleophilic attack occurs in an *anti* fashion, with formation, after protonolysis, of the *Z* isomer of indane **3** (**3**-*Z*); in path *b*, palladation of the carbanion with simultaneous chelation by the triple bond takes place, followed by *syn* insertion and protonolysis, to give the *E* isomer of indane **3** (**3**-*E*).

The first substrate we tested was dimethyl 2-(2-ethynylbenzyl)malonate **1a**, which was used as crude product deriving from deprotection of the corresponding TMS-protected precursor **1a′**.[8] Substrate **1a** was initially allowed to react in DME (substrate concentration = 0.2 mmol of **1a** per mL of DME) at 100 °C in the presence of PdI_2 (1 mol%), KI (10 mol%) and 2 equiv. of morpholine (**2a**), under 20 atm (at 25 °C) of a 4/1 mixture of CO and air. After 3 h, analysis of the reaction mixture revealed the formation of two carbonylation products, corresponding to the *E* and *Z* isomers of the desired dimethyl 1-(2-morpholino-2-oxoethyliden)indan-2,2-dicarboxylate (**3aa**-*E* and **3aa**-*Z*, respectively). The



Scheme 4. Cascade oxidative carbamoylation–carbocyclization leading to carbonylated indane derivatives **3**. The PdI_2-catalyzed oxidative carbamoylation of the triple bond of 2-(2-ethynylbenzyl)malonates and analogs **1** leads to propiolamide intermediates **I**, which then undergo carbocyclization to give **3**.

Table 1. PdI_2-catalyzed oxidative carbamoylation of 2-(2-ethynylbenzyl)malonate **1a** under different conditions.[a]



Entry	Solvent	**2a**:KI:PdI_2 molar ratio	Concentration of **1a**[b]	T [°C][c]	P_{CO} [atm]	P_{air} [atm]	Conversion of **1a** [%][c]	Yield of **3aa**-*E* [%][c]	Yield of **3aa**-*Z* [%][c]	Total yield [%][c]
1	DME	200:10:1	0.22	100	16	4	100	37	6	43
2	DME	200:10:1	0.22	80	16	4	100	33	7	40
3	DME	200:5:1	0.22	100	16	4	100	33	8	41
4	DME	200:20:1	0.22	100	16	4	100	32	7	39
5	DME	100:10:1	0.22	100	16	4	95	33	5	38
6	DME	200:10:1	0.10	100	16	4	100	42	8	50
7	DME	200:10:1	0.05	100	16	4	75	35	7	42
8	DME	200:10:1	0.22	100	32	8	100	45	11	56
9	dioxane	200:10:1	0.22	100	16	4	100	53	10	63
10	MeOH	200:10:1	0.22	100	16	4	100	41	23	64
11	MeCN	200:10:1	0.22	100	16	4	100	57	11	68
12	DMA	200:10:1	0.22	100	16	4	80	12	3	15

[a] All reactions were carried out in the presence of 1 mol% of PdI_2 in conjunction with an excess of KI for 3 h. Substrate **1a**, derived from desilylation of dimethyl 2-{2-[2-(trimethylsilyl)ethynyl]benzyl}malonate **1a′**, was used as the crude material, without further purification, in the carbonylation reaction.

[b] Given as mmol of crude **1a** per mL of solvent.

[c] Based on starting **1a′**, by GLC. The formation of unidentified heavy products (chromatographically immobile materials) accounted for the difference between substrate conversion and product yield in all cases.

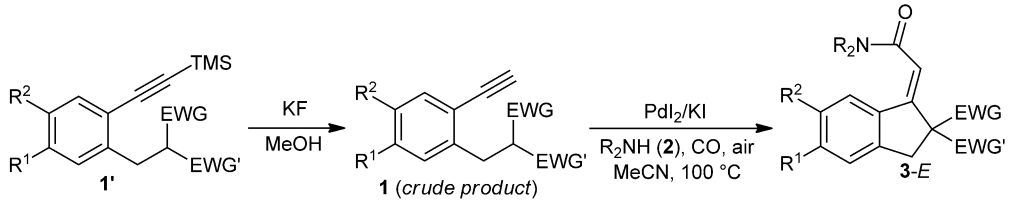
main product (37% isolated yield, Table 1, entry 1) turned out to be the *E* stereoisomer, which was fully characterized by spectroscopic techniques, including 2D COSY and NOESY NMR experiments.

In order to improve this initial result, we screened the reaction parameters to find the optimal conditions for the formation of **3aa**-*E*. The results obtained by changing the reaction temperature, **2a**:KI:PdI_2 molar ratio, substrate concentration, total pressure, and solvent are shown in Table 1, entries 2–12. The product yield was lower when working at 80 °C (entry 2) or with a KI/PdI_2 molar ratio of 5 or 20 rather that 10 (entries 3 and 4). A lower yield was also observed on using 1 equiv. of the amine **2a** rather than 2 equiv. (entry 5). On the other hand, an improvement in product yield was observed when the substrate concentration was lowered to 0.1 mmol of **1a** per mL of DME (entry 6) and the total pressure was raised to 40 atm (entry 8). Among the other solvents tested (dioxane, MeOH, MeCN, and DMA), acetonitrile provided the highest product yield (entry 11). On the basis of these results, the final optimized conditions corresponded to the use of MeCN as the solvent (substrate concentration = 0.1 mmol of **1a** per mL of MeCN), with a **1a**:**2a**:KI:PdI_2 molar ratio of 100:200:10:1, at 100 °C and under 40 atm of a 4:1 mixture CO and air. Under these conditions, after 3 h, carbonylated indane **3aa**-*E* was obtained in 65% isolated yield (based on starting dimethyl 2-{2-[2-(trimethylsilyl)ethynyl]benzyl}malonate **1a′**), together with only a 3% yield of **3aa**-*Z* (Table 2, entry 1).

To assess the generality of the method, we then applied the optimized conditions to other differently substituted substrates **1b–g**, bearing either π-donating or electron-withdrawing groups on the aromatic ring (such as a methoxy or nitro group, respectively) as well as different electron-withdrawing groups on the homobenzylic carbon. We also changed the nature of the amine, by testing the reactivity of other cyclic and acyclic secondary amines **2a–f**. The results obtained are shown in Table 2, entries 2–12. As can be seen, good yields of the corresponding carbonylated indanes were consistently obtained, even employing a hindered amine such as diisopropylamine **2f**. In some cases, better results in terms of product selectivity were observed by working at a lower substrate concentration (0.05 mmol per mL of solvent rather than 0.1, Table 2, entries 5, 7–9). The reaction consistently showed high diastereoselectivity, the *E* isomer being formed predominantly or exclusively.

Several pieces of experimental evidence support the proposed mechanism for the formation of prod-

Table 2. Stereoselective synthesis of functionalized indane derivatives **3** by tandem PdI_2-catalyzed oxidative carbamoylation of 2-(2-ethynylbenzyl)malonates and analogs (**1**)/carbocyclization.[a]



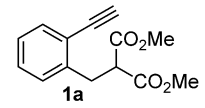
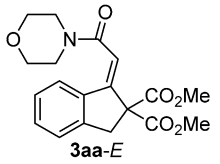
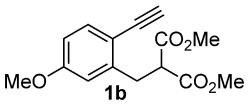
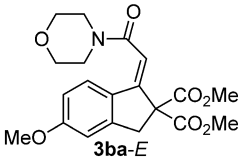
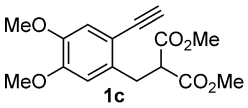
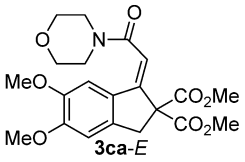
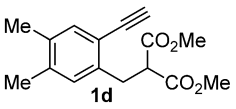
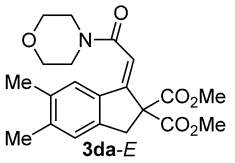
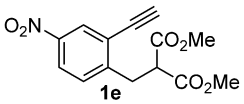
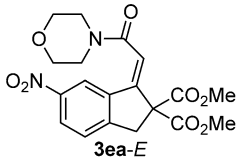
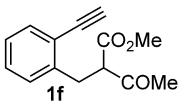
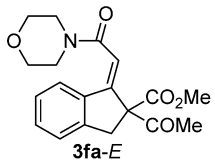
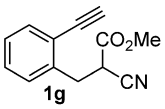
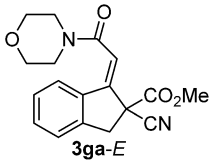
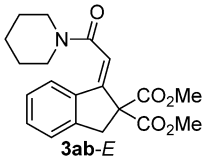
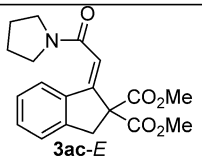
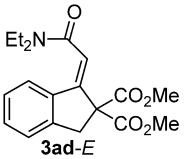
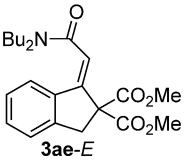
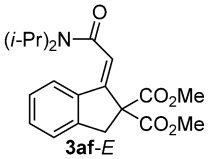
Entry	Substrate (**1**)	Concentration of **1**[b]	R_2NH	Time [h]	Product **3**-*E*	Yield [%][c] of **3**-*E*
1	 **1a**	0.10	 **2a**	3	 **3aa**-*E*	65[d]
2	 **1b**	0.10	**2a**	3	 **3ba**-*E*	63[e]
3	 **1c**	0.10	**2a**	3	 **3ca**-*E*	75
4	 **1d**	0.10	**2a**	3	 **3da**-*E*	63[f]
5	 **1e**	0.05	**2a**	5	 **3ea**-*E*	58
6	 **1f**	0.10	**2a**	3	 **3fa**-*E*	71
7	 **1g**	0.05	**2a**	5	 **3ga**-*E*	70
8	**1a**	0.05	 **2b**	5	 **3ab**-*E*	56

Table 2. (Continued)

Entry	Substrate (**1**)	Concentration of **1**[b]	R_2NH	Time [h]	Product **3**-*E*	Yield [%][c] of **3**-*E*
9	**1a**	0.05	 **2c**	5	 **3ac**-*E*	57
10	**1a**	0.10	Et_2NH **2d**	3	 **3ad**-*E*	70
11	**1a**	0.10	Bu_2NH **2e**	3	 **3ae**-*E*	68[g]
12	**1a**	0.10	$(i\text{-Pr})_2NH$ **2f**	3	 **3af**-*E*	50

[a] All reactions were carried out in MeCN at 100 °C and under 40 atm (at 25 °C) of a 4:1 mixture of CO and air, in the presence of 1 mol% of PdI_2 in conjunction with an excess of KI (KI:PdI_2 molar ratio = 10). Substrates **1**, derived from desilylation of the corresponding TMS-protected precursors **1′**, were used as crude materials, without further purification, in the tandem reaction The **2**:**1** molar ratio was 2. Conversion of **1** was quantitative in all cases. The formation of unidentified heavy products (chromatographically immobile materials) accounted for the difference between substrate conversion and product yield in all cases.

[b] Given as mmol of crude **1** per mL of MeCN.

[c] Isolated yield based on starting **1′**.

[d] The reaction also led to the formation of small amounts of the *Z* isomer (3% GLC yield).

[e] The reaction also led to the formation of small amounts of the *Z* isomer (2% GLC yield).

[f] The reaction also led to the formation of small amounts of the *Z* isomer (6% GLC yield).

[g] The reaction also led to the formation of small amounts of the *Z* isomer (7% isolated yield).

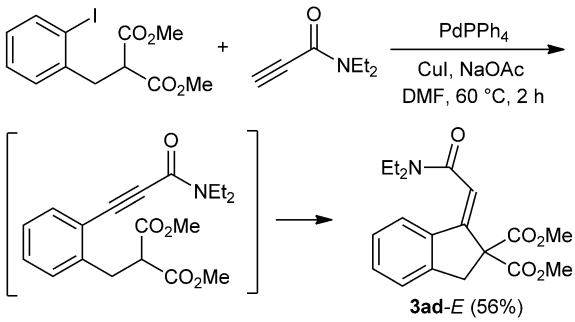
ucts **3** (Scheme 4). First of all, the reaction did not take place with substrates bearing an internal triple bond, since an alkynylpalladium intermediate could not be formed in this case. Also, no reaction occurred when a tertiary amine, such as triethylamine, was used instead of a secondary amine (partial decomposition of the substrate with the formation of a mixture of unidentified products was observed). Finally, formation of indane **3ad**-*E* in 56% yield was observed from the Sonogashira coupling between dimethyl 2-(2-iodobenzyl)malonate and *N*,*N*-diethylpropiolamide, carried out with $Pd(PPh_3)_4$ and CuI as catalysts and NaOAc as the base, as shown in Scheme 5. This latter result demonstrates that propiolamide **I** can indeed be the intermediate for the formation of indanes **3** under basic conditions and in the presence of palladium, according to the mechanism shown in Scheme 4.

Conclusions

In conclusion, we have reported a novel multicomponent carbonylative approach to functionalized indane derivatives **3** starting from simple and readily available substrates [2-(2-ethynylbenzyl)malonates and analogs (**1**), CO, a secondary amine (**2**), and O_2] (Scheme 3).

The cascade process leading to **3** occurs through the concatenation of two chemical transformations, the Pd-catalyzed oxidative carbamoylation of the triple bond of **1**, with formation of a propiolamide intermediate **I**, followed by carbocyclization (Scheme 4).

The process takes place under relatively mild conditions (MeCN as the solvent at 100 °C and under 40 atm of a 4:1 mixture of CO and air) and shows



Scheme 5. Formation of dimethyl (*E*)-1-(diethylcarbamoylmethylene)indane-2,2-dicarboxylate (**3ad**-*E*) by *in situ* cyclization of the propiolamide intermediate derived from Sonogashira coupling between *N*,*N*-diethylpropiolamide and dimethyl 2-(2-iodobenzyl)malonate.

high diastereoselectivity toward the formation of the *E* isomer. The products obtained belong to a particularly important class of carbocycles, which have shown several interesting pharmacological activities.[9,10]

Experimental Section

General Remarks

Solvent and chemicals were of reagent grade and were used without further purification. All reactions were analyzed by TLC on silica gel 60 F_{254} or on neutral alumina and by GLC using a gas chromatograph and capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase. Column chromatography was performed on silica gel 60 (70–230 mesh). Evaporation refers to the removal of solvent under reduced pressure.

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C on a Bruker DPX Avance 300 spectrometer or on a Bruker DPX Avance 500 spectrometer in $CDCl_3$ solutions at 300 or 500 MHz and 75 or 126 MHz, respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. IR spectra were taken with a JASCO FT-IR 4200 spectrometer. Mass spectra were obtained using a Shimadzu QP-2010 GC-MS apparatus at 70 eV ionization voltage. Microanalyses were carried out with a Carlo Erba Elemental Analyzer Mod. 1106.

Preparation of Substrate Precursors

Substrate precursors dimethyl 2-(2-iodobenzyl)malonate and methyl 2-(2-iodobenzyl)-3-oxobutyrate were prepared as reported in the literature.[11] Dimethyl 2-(2-iodo-4,5-dimethoxybenzyl)malonate, dimethyl 2-(2-iodo-4,5-dimethylbenzyl)malonate, dimethyl 2-(2-iodo-5-methoxybenzyl)malonate, dimethyl 2-(2-bromo-4-nitrobenzyl)malonate and methyl 2-cyano-3-(2-iodophenyl)propionate were prepared as described below.

General Procedure for the Preparation of Dimethyl 2-Halobenzylmalonates

The 2-halobenzyl bromide derivative (11 mmol) [2-iodobenzyl bromide (commercially available): 3.27 g; 2-iodo-4,5-dimethoxybenzyl bromide:[12] 3.93 g; 2-iodo-4,5-dimethylbenzyl bromide:[12] 3.57 g; 2-iodo-5-methoxybenzyl bromide:[12] 3.60 g; 2-bromo-4-nitrobenzyl bromide:[13] 3.24 g] was added under nitrogen to a stirred suspension of NaH (95% purity, 0.45 g, 15 mmol,) and dimethyl malonate (17 mmol, 2.25 g, 1.94 mL) in anhydrous THF (30 mL). The reaction mixture was allowed to reflux for 6 h under stirring. After cooling, the mixture was poured into 10% HCl (15 mL). The two phases were separated and the aqueous phase was extracted with ether (20 mL × 3). The collected organic phases were washed with brine to neutral pH, dried over $MgSO_4$ and evaporated to dryness. After filtration and evaporation of the solvent, products were purified by column chromatography on silica gel using the following mixtures as eluent: 8:2 hexane-acetone for the dimethyl 2-(2-iodo-4,5-dimethoxybenzyl)malonate, dimethyl 2-(2-iodo-4,5-dimethylbenzyl)-malonate and dimethyl 2-(2-iodo-5-methoxybenzyl)malonate; 95:5 hexane-AcOEt for dimethyl 2-(2-bromo-4-nitrobenzyl)malonate.

Dimethyl 2-(2-iodo-4,5-dimethoxybenzyl)malonate: Yield: 2.11 g, starting from 3.93 g of 1-bromomethyl-2-iodo-4,5-dimethoxybenzene (47%); colorless solid; mp 86–87 °C; IR (KBr): ν = 3001 (m), 2944 (m), 2846 (m), 1731 (s), 1596 (m), 1504 (m), 1353 (m), 1255 (m), 1218 (m), 1167 (m), 1032 (m), 949 (w), 869 (m), 793 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (s, 1H), 6.77 (s, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.81 (t, J = 7.8 Hz, 1H), 3.71 (s, 6H), 3.27 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0, 149.2, 148.5, 132.5, 121.9, 113.5, 88.1, 56.14, 55.97, 52.6, 51.9, 39.0; GC-MS (EI, 70 eV): m/z = 408 (45) [M$^+$], 345 (2), 307 (3), 281 (100), 277 (74), 250 (12), 221 (23), 207 (13), 191 (11), 150 (7), 105 (5), 77 (7); anal. calcd. for $C_{14}H_{17}IO_6$ (408.19): C 41.19, H 4.20, I 31.09; found: C 41.03, H 4.21, I 31.10.

Dimethyl 2-(2-iodo-4,5-dimethylbenzyl)malonate: Yield: 2.52 g, starting from 3.57 g of 1-bromomethyl-2-iodo-4,5-dimethylbenzene (61%); yellow solid; mp 83–85 °C; IR (KBr): ν = 1730 (s), 1636 (m), 1434 (m), 1345 (m), 1233 (m), 1154 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (s, 1H), 6.97 (s, 1H), 3.82 (t, J = 7.8 Hz, 1H), 3.71 (s, 6H), 3.25 (d, J = 7.8 Hz, 2H), 2.16 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0, 140.2, 137.6, 137.3, 137.0, 131.6, 96.5, 52.5, 51.8, 38.7, 19.3, 18.8; GC-MS (EI, 70 eV): m/z = 376 (3) [M$^+$], 345 (2), 313 (8), 275 (3), 249 (100), 245 (17), 217 (5), 189 (27), 175 (8), 159 (8), 115 (13), 91 (8); anal. calcd. for $C_{14}H_{17}IO_4$ (376.19): C 44.70, H 4.55, I 33.73; found: C 44.86, H 4.56, I 33.64.

Dimethyl 2-(2-iodo-5-methoxybenzyl)malonate: Yield: 2.41 g, starting from 3.60 g of 1-bromomethyl-2-iodo-4-methoxybenzene (58%); colorless oil. IR (film): ν = 1736 (s), 1593 (m), 1469 (m), 1436 (m), 1343 (m), 1294 (m), 1238 (m), 1154 (m), 1042 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.7 Hz, 1H), 6.80 (d, J = 3.0 Hz, 1H), 6.53 (dd, J = 8.7, 3.0 Hz, 1H), 3.84 (t, J = 7.8 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 6H), 3.29 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 160.0, 141.2, 140.1, 116.5, 114.9, 88.7, 55.4, 52.6, 51.6, 39.5; GC-MS (EI, 70 eV): m/z = 378 (11) [M$^+$], 347 (2), 315 (7), 277 (3), 251 (100), 191 (17), 176 (8), 161

(12), 133 (5), 118 (4), 89 (6), 77 (5); anal. calcd. for $C_{13}H_{15}IO_5$ (378.16): C 41.29, H 4.00, I 33.56; found: C 41.40, H 4.39, I 33.62.

Dimethyl 2-(2-bromo-4-nitrobenzyl)malonate: Yield: 1.14 g, starting from 3.24 g of 2-bromo-1-bromomethyl-4-nitrobenzene (30%); yellow solid; mp 119–121 °C. IR (KBr): $\nu = 1746$ (s), 1522 (m), 1437 (m), 1352 (s), 1236 (m), 1158 (m), 1080 (w), 889 (m), 746 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.43$ (d, $J = 2.3$ Hz, 1H), 8.10 (dd, $J = 8.5$, 2.3 Hz, 1H), 7.46 (d, $J = 8.5$ Hz, 1H), 3.88 (t, $J = 7.7$ Hz, 1H), 3.74 (s, 6H), 3.44 (d, $J = 7.7$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.5$, 144.6, 132.0, 128.1, 124.8, 122.3, 52.9, 50.6, 35.0; GC-MS (EI, 70 eV): $m/z = 347$ (<0.5) [$(M+2)^+$], 345 (<0.5) [M^+], 266 (100), 206 (56), 160 (17), 102 (10), 89 (8); anal. calcd. for $C_{12}H_{12}BrNO_6$ (346.13): C 41.64, H 3.49, Br 23.08; found: C 41.60, H 3.48, Br 23.05.

Preparation of Methyl 2-Cyano-3-(2-iodophenyl)-propionate

To a suspension of NaH (12 mmol, 0.29 g) in anhydrous THF (20 mL) and HMPA (24 mmol, 4.2 mL) were sequentially added, under nitrogen at room temperature, methyl cyanoacetate (1.19 g, 12 mmol) dissolved in anhydrous THF (20 mL, 30 min) and 2-iodobenzyl bromide (3.56 g, 12 mmol). The resulting mixture was stirred at room temperature for 2 h. Saturated NH_4Cl (50 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The collected organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the product was purified by column chromatography on silica gel using, as eluent, 95:5 hexane-AcOEt; yield: 3.67 g, starting from 1.19 g of methyl cyanoacetate (97%); colorless solid; mp 80–81 °C. IR (KBr): $\nu = 2252$ (w), 1736 (s), 1449 (m), 1432 (m), 1266 (s), 1242 (m), 1023 (m), 900 (w), 747 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.86$ (d, $J = 7.8$ Hz, 1H), 7.43–7.31 (m, 2H), 7.06–6.96 (m, 1H), 3.94 (dd, $J = 9.9$, 6.0 Hz, 1H), 3.84 (s, 3H), 3.48 (distorted dd, $J = 13.9$, 6.0 Hz, 1H), 3.22 (distorted dd, $J = 13.9$, 9.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 165.7$, 139.9, 137.9, 131.0, 129.7, 128.9, 115.6, 100.0, 53.7, 40.5, 37.5; GC-MS (EI, 70 eV): $m/z = 315$ (10) [M^+], 217 (74), 188 (100), 156 (3), 145 (2), 129 (17), 102 (11), 90 (18), 77 (7); anal. calcd. for $C_{11}H_{10}INO_2$ (315.11): C 41.93, H 3.20, I 40.27, N 4.45; found: C 41.80, H 3.21, I 40.22, N 4.44.

Preparation of Substrates

Starting dimethyl 2-(2-trimethylsilanylethynylbenzyl)malonates **1a′–e′**, methyl 2-{2-[2-(trimethylsilyl)ethynyl]benzyl}-3-oxobutanoate **1f′** and methyl 2-cyano-3-(2-trimethylsilanylethynylphenyl)propionate **1g′** were prepared by Sonogashira coupling between the appropriate dimethyl 2-(2-halobenzyl)malonate, methyl 2-(2-iodobenzyl)-3-oxo-butyrate or methyl 2-cyano-3-(2-iodophenyl)propionate (prepared as described above) with ethynyltrimethylsilane, as described below.

General Procedure for 2-(2-Trimethylsilanylethynyl)-benzyl Ester Derivatives 1a′–1g′

To a stirred solution of the 2-halobenzyl ester derivative (8.06 mmol) [dimethyl 2-(2-iodobenzyl)malonate: 2.81 g; dimethyl 2-(2-iodo-4,5-dimethoxybenzyl)malonate: 3.29 g; dimethyl 2-(2-iodo-4,5-dimethylbenzyl)malonate: 3.03 g; dimethyl 2-(2-iodo-5-methoxybenzyl)malonate: 3.05 g; dimethyl 2-(2-bromo-4-nitrobenzyl)malonate: 2.79 g; methyl 2-(2-iodobenzyl)-3-oxobutyrate: 2.68 g; methyl 2-cyano-3-(2-iodophenyl)propionate: 2.54 g] and ethynyltrimethylsilane (9.67 mmol, 0.95 g), in NEt_3 (30 mL), was added under nitrogen $PdCl_2(PPh_3)_2$ (0.16 mmol, 113 mg). The mixture was stirred for 5 min, and then CuI (15.4 mg, 0.081 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The resulting ammonium salt was removed by filtration, the solvent was evaporated, and products were purified by column chromatography on silica gel, using the following mixtures as eluent: 95:5 hexane-AcOEt (for **1a′** and **1d′**); 8:2 hexane-acetone (for **1c′** and **1b′**); 9:1 hexane AcOEt (for **1e′**), 98:2 hexane-AcOEt (for **1f′** and **1g′**).

Dimethyl 2-(2-trimethylsilanylethynylbenzyl)malonate (1a′): Yield: 2.41 g, starting from 2.81 g of dimethyl 2-(2-iodobenzyl)malonate (94%); yellow oil. IR (film): $\nu = 2156$ (m), 1739 (s), 1483 (w), 1436 (m), 1251 (s), 1152 (m), 871 (s), 843 (s), 761 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.47–7.42 (m, 1H), 7.24–7.14 (m, 3H), 3.97 (t, $J = 7.7$ Hz, 1H), 3.69 (s, 6H), 3.37 (d, $J = 7.7$ Hz, 2H), 0.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.3$, 140.0, 132.5, 129.9, 128.6, 126.8, 122.8, 102.8, 99.4, 52.4, 51.8, 33.9, −0.2; GC-MS (EI, 70 eV): $m/z = 318$ (17) [M^+], 303 (50), 287 (5), 271 (9), 259 (27), 243 (14), 213 (9), 183 (16), 173 (70), 155 (98), 145 (27), 129 (27), 115 (36), 105 (27), 89 (95), 73 (32), 59 (100); anal. calcd for $C_{17}H_{22}O_4Si$ (318.44): C 64.12, H 6.96, Si 8.82; found: C 64.28, H 6.95, Si 8.83.

Dimethyl 2-(5-methoxy-2-trimethylsilanylethynylbenzyl)-malonate (1b′): Yield: 1.91 g, starting from 3.05 g of dimethyl 2-(2-iodo-5-methoxybenzyl)malonate (68%); yellow oil. IR (film): $\nu = 2150$ (m), 1739 (s), 1605 (m), 1492 (m), 1436 (m), 1250 (s), 1159 (m), 1040 (m), 872 (m), 861 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.37$ (d, $J = 8.4$ Hz, 1H), 6.75 (distorted d, $J = 2.6$ Hz, 1H), 6.71 (distorted dd, $J = 8.4$, 2.6 Hz, 1H), 3.97 (t, $J = 7.7$ Hz, 1H), 3.77 (s, 2H), 3.70 (s, 6H), 3.33 (d, $J = 7.7$ Hz, 2H), 0.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.2$, 159.7, 141.9, 133.9, 115.6, 115.0, 112.5, 103.0, 97.6, 55.3, 52.4, 51.8, 34.1, −0.1; GC-MS (EI, 70 eV): $m/z = 348$ (100) [M^+], 333 (22), 317 (9), 301 (14), 289 (15), 285 (10), 273 (11), 243 (20), 213 (13), 203 (40), 185 (41), 159 (16), 145 (10), 128 (9), 89 (43); anal. calcd. for $C_{18}H_{24}O_5Si$ (348.47): C 62.04, H 6.94, Si 8.06; found: C 62.19, H 6.93, Si 8.07.

Dimethyl 2-(4,5-dimethoxy-2-trimethylsilanylethynylbenzyl)malonate (1c′): Yield: 2.93 g, starting from 3.29 g of dimethyl 2-(2-iodo-4,5-dimethoxybenzyl)malonate (96%); yellow oil. IR (film): $\nu = 2147$ (m), 1734 (s), 1603 (w), 1512 (m), 1439 (m), 1347 (m), 1222 (m), 1151 (m), 869 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.93$ (s, 1H), 6.72 (s, 1H), 3.93 (t, $J = 7.8$ Hz, 1H), 3.86 (s, 6H), 3.70 (s, 6H), 3.31 (d, $J = 7.8$ Hz, 2H), 0.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.3$, 149.4, 147.5, 133.7, 114.8, 114.6, 113.1, 103.1, 97.7, 56.0, 52.4, 52.1, 33.7, −0.1. GC-MS (EI, 70 eV): $m/z = 378$ (100) [M^+], 363 (7), 347 (6), 319 (6), 303 (5), 273 (5), 247 (55), 233 (30), 215 (28), 189 (16), 89 (15); anal. calcd. for $C_{19}H_{26}O_6Si$ (378.49): C 60.29, H 6.92, Si 7.42; found: C 60.11, H 6.93, Si 7.40.

Dimethyl 2-(4,5-dimethyl-2-trimethylsilanylethynylbenzyl)malonate (1d′): Yield: 2.35 g, starting from 3.03 g of di-

methyl 2-(2-iodo-4,5-dimethylbenzyl)malonate (84%); yellow oil. IR (film): $\nu = 2153$ (m), 1739 (s), 1436 (m), 1344 (w), 1250 (m), 1149 (m), 1031 (w), 862 (s), 760 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.21$ (s, 1H), 6.95 (s, 1H), 3.94 (t, $J = 7.7$ Hz, 1H), 3.69 (s, 6H), 3.29 (d, $J = 7.7$ Hz, 2H), 0.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.4$, 137.6, 137.4, 135.1, 133.5, 131.2, 120.0, 103.3, 98.1, 52.4, 52.0, 33.5, 19.7, 19.1, −0.1; GC-MS (EI, 70 eV): $m/z = 346$ (75) [M^+], 331 (40), 315 (9), 301 (12), 287 (34), 271 (19), 255 (5), 241 (21), 215 (14), 201 (98), 183 (100), 173 (17), 157 (28), 128 (14), 89 (37); anal. calcd. for $C_{19}H_{26}O_4Si$ (346.49): C 65.86, H 7.56, Si 8.11; found: C 65.70, H 7.55, Si 8.12.

Dimethyl 2-(4-nitro-2-trimethylsilanylethynylbenzyl)malonate (1e′): Yield: 2.28 g, starting from 2.79 g of dimethyl 2-(2-bromo-4-nitrobenzyl)malonate (78%); yellow oil. IR (film): $\nu = 2153$ (m), 1739 (s), 1526 (m), 1437 (m), 1352 (m), 1251 (m), 1155 (m), 1027 (w), 939 (w), 850 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.29$ (d, $J = 2.4$ Hz, 1H), 8.07 (dd, $J = 8.4$, 2.4 Hz, 1H), 7.42 (d, $J = 8.4$ Hz, 1H), 3.96 (t, $J = 7.6$ Hz, 1H), 3.72 (s, 6H), 3.44 (d, $J = 7.6$ Hz, 2H), 0.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.7$, 147.1, 146.9, 131.1, 127.4, 124.6, 123.1, 102.8, 100.2, 52.7, 51.2, 33.8, −0.4; GC-MS (EI, 70 eV): $m/z = 363$ (5) [M^+], 348 (100), 316 (26), 304 (34), 286 (14), 263 (3), 218 (37), 200 (20), 167 (10), 128 (9), 105 (9), 89 (67); anal. calcd. for $C_{17}H_{21}NO_6Si$ (363.44): C 56.18, H 5.82, Si 7.73; found: C 56.10, H 5.83, Si 7.72.

Methyl 2-{2-[2-(trimethylsilyl)ethynyl]benzyl}-3-oxobutanoate (1f′): Yield: 1.90 g, starting from 2.68 g of methyl 2-(2-iodobenzyl)-3-oxo-butyrate (78%); yellow oil, IR (film): $\nu =$ 2156 (m), 1739 (s), 1436 (m), 1299 (w), 1251 (m), 1152 (m), 872 (m), 842 (m), 761 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.44$ (m, 1H), 7.26–7.13 (m, 3H), 4.11–4.03 (m, 1H), 3.68 (s, 3H), 3.35 (distorted dd, $J = 13.5$, 6.9 Hz, 1H), 3.26 (distorted dd, $J = 13.5$, 7.9 Hz, 1H), 2.20 (s, 3H), 0.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 202.3$, 169.5, 140.4, 132.7, 129.9, 128.8, 126.7, 122.6, 103.2, 99.2, 59.5, 52.3, 33.1, 29.6, −0.1; GC-MS (EI, 70 eV): $m/z = 302$ (4) [M^+], 287 (83), 271 (11), 259 (45), 243 (34), 227 (51), 213 (34), 198 (10), 185 (32), 173 (50), 155 (86), 145 (24), 127 (27), 115 (21), 89 (100), 73 (92); anal. calcd. for $C_{17}H_{22}O_3Si$ (302.44): C 67.51, H 7.33, Si 9.29; found: C 67.40, H 7.35, Si 9.18.

Methyl 2-cyano-3-(2-trimethylsilanylethynylphenyl)propionate (1g′): Yield: 1.63 g, starting from 2.54 g of methyl 2-cyano-3-(2-iodophenyl)-propionate (71%); yellow oil. IR (film): $\nu = 2250$ (vw), 2156 (m), 1752 (s), 1483 (w), 1437 (m), 1251 (m), 874 (s), 760 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.53$–7.45 (m, 1H), 7.36–7.22 (m, 3H), 4.07 (dd, $J = 9.6$, 6.0 Hz, 1H), 3.81 (s, 3H), 3.58 (distorted dd, $J = 13.3$, 6.0 Hz, 1H), 3.18 (distorted dd, $J = 13.3$, 9.6 Hz, 1H), 0.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.1$, 137.6, 132.7, 130.1, 129.1, 127.8, 122.8, 116.0, 102.2, 100.4, 53.4, 37.7, 35.1, −0.2; GC-MS (EI, 70 eV): $m/z = 285$ (5) [M^+], 270 (100), 240 (90), 238 (37), 213 (26), 183 (13), 172 (42), 155 (10), 145 (18), 143 (16), 129 (12), 115 (15), 89 (67); anal. calcd. for $C_{16}H_{19}NO_2Si$ (285.41): C 67.33, H 6.71, N 4.91, Si 9.84; found: C 67.40, H 6.72, N 4.90, Si 9.82.

General Procedure for the Synthesis of Indanylidene Amide Derivatives 3-*E*

1st Step: general procedure for the deprotection of 2-(2-trimethylsilanylethynyl)benzyl ester derivatives 1a′–1g′ to give crude 2-(2-ethynylbenzyl)malonates and analogs 1a–1g: To a solution of the 2-(2-trimethylsilanylethynyl)benzyl ester derivatives **1′** (1.5 mmol) [**1a′**: 478 mg; **1b′**: 523 mg; **1c′**: 568 mg; **1d′**: 519 mg; **1e′**: 545 mg; **1f′**: 454 mg; **1g′**: 428 mg] in MeOH (12 mL) was added KF (305 mg, 5.3 mmol) at room temperature. The resulting mixture was stirred for 15 h at the same temperature, then water (30 mL) was added followed by Et_2O (30 mL). Phases were separated, and the organic phase was extracted with diethyl ether (30 mL × 2). The collected organic layers were dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, crude products **1a–1g** were used as such for the tandem carbonylation–carbocyclization step.

2nd Step: general procedure for the tandem oxidative carbamoylation–carbocyclization of 1 to give functionalized indane derivatives 3-*E*: A 250-mL stainless steel autoclave was charged in the presence of air with PdI_2 (5.4 mg, 1.5×10^{-2} mmol), KI (24.9 mg, 1.5×10^{-1} mmol), anhydrous CH_3CN (15 mL or 30 mL, see Table 2), crude substrates **1a–g**, obtained as described above (formally corresponding to 1.5 mmol), and the amine **2** (**2a**: 261 mg; **2b**: 255 mg, **2c**: 213 mg; **2d**: 220 mg, **2e**: 388; **2f**: 304 mg; 3.0 mmol). The autoclave was sealed and, while the mixture was stirred, the autoclave was pressurized with CO (32 atm) and air (up to 40 atm). After being stirred at 100 °C for the required time (see Table 2), the autoclave was cooled, degassed and opened. The solvent was evaporated, and products **3**-*E* were purified by column chromatography on silica gel using the following mixtures as eluent: 7:3 hexane-acetone (**3aa**-*E*, **3ca**-*E*, **3da**-*E*), 8:2 hexane-acetone (**3ba**-*E*), 95:5 hexane-AcOEt (**3fa**-*E*, **3ga**-*E*), hexane (**3ad**-*E*), 7:3 hexane-AcOEt (**3ea**-*E*, **3ab**-*E*, **3ac**-*E*, **3ae**-*E*, **3af**-*E*). In some cases, small amounts of the corresponding *Z* isomers were detected by GLC-MS in the reaction crude, (see Table 2), even though most of them (with the exception of **3ae**-*Z*) could not be isolated in the pure state.

Dimethyl (*E*)-1-(2-morpholin-4-yl-2-oxoethylidene)indane-2,2-dicarboxylate (3aa-*E*): Yield: 350 mg, starting from 478 mg of dimethyl 2-(2-trimethylsilanylethynylbenzyl)malonate **1a′** (65%; Table 2, entry 1); yellow oil. IR (film): $\nu =$ 3018 (w), 1733 (s), 1622 (s), 1435 (m), 1242 (m), 1216 (m), 1114 (w), 1055 (w), 755 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.62$ (d, $J = 7.3$ Hz, 1H), 7.38–7.17 (m, 3H), 6.38 (s, 1H), 3.83–3.68 (m, 8H), 3.71 (s, 6H), 3.64–3.57 (m, 2H); 2D-NOESY data: the NOESY spectrum evidenced a strong interaction between the aromatic protons and the morpholine protons, in agreement with an *E* stereochemistry; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.3$, 166.5, 143.4, 142.8, 135.8, 130.1, 127.6, 124.9, 124.5, 120.3, 114.4, 67.0, 66.6, 63.7, 53.4, 46.5, 41.7, 39.3; GC-MS (EI, 70 eV): $m/z = 359$ (26) [M^+], 328 (1), 300 (22), 273 (94), 214 (16), 213 (100), 186 (17), 181 (13), 171 (14), 155 (25), 141 (12), 127 (35), 115 (13), 86 (12); anal. calcd. for $C_{19}H_{21}NO_6$ (359.37): C 63.50, H 5.89, N 3.90; found: C 63.41, H 5.90, N 3.91.

Dimethyl (*Z*)-1-(2-morpholin-4-yl-2-oxo-ethylidene)indane-2,2-dicarboxylate (3aa-*Z*): GLC yield *ca.* 3%, based on starting **1a′** (purity *ca.* 70%, by GLC-MS; Table 2, entry 1);

brown solid; mp 165–168 °C. IR (KBr): ν = 2862 (w), 1748 (s), 1646 (s), 1613 (w), 1433 (m), 1384 (m), 1272 (m), 1242 (w), 1112 (m), 1062 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.54 (d, 1H), 7.40–7.23 (m, 3H), 6.84 (s, 1H), 3.78–3.62 (m, 8H), 3.76 (s, 6H), 3.61–3.54 (m, 2H); GC-MS (EI, 70 eV): *m/z* = 359 (31) [M^+], 328 (3), 300 (15), 273 (94), 214 (16), 213 (100), 186 (13), 181 (13), 171 (16), 169 (11), 155 (24), 141 (11), 127 (39), 115 (13), 86 (11).

Dimethyl (*E*)-5-methoxy-1-(2-morpholin-4-yl-2-oxo-ethylidene)indane-2,2-dicarboxylate (3ba-*E*): Yield: 368 mg, starting from 523 mg of dimethyl 2-(4-methoxy-2-trimethylsilanylethynylbenzyl)malonate **1b′** (63%; Table 2, entry 2); yellow oil. IR (film): ν = 1733 (s), 1639 (s), 1493 (w), 1435 (s), 1255 (m), 1090 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 8.8 Hz, 1H), 6.82–6.73 (m, 3H), 6.23 (s, 1H), 3.85–3.58 (m, 10H), 3.81 (s, 3H), 3.78 (s, 6H); 2D-NOESY data: the NOESY spectrum evidenced a neat interaction between the aromatic protons and the morpholine protons, in agreement with an *E* stereochemistry; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 166.8, 161.6, 145.8, 143.0, 128.8, 126.0, 117.4, 114.6, 109.0, 67.1, 66.8, 64.4, 55.4, 53.3, 46.6, 41.7, 39.4; GC-MS (EI, 70 eV): *m/z* = 389 (28) [M^+], 330 (12), 303 (100), 276 (7), 243 (80), 216 (20), 211 (11), 201 (13), 185 (23), 157 (10), 142 (11), 114 (12); anal. calcd. for $C_{20}H_{23}NO_7$ (389.40): C 61.69, H 5.95, N 3.60; found: C, 61.54, H 5.93, N 3.61.

Dimethyl (*Z*)-5-methoxy-1-(2-morpholin-4-yl-2-oxo-ethylidene)indane-2,2-dicarboxylate (3ba-*Z*): GLC yield: *ca.* 2%, starting from **1b′** (Table 2, entry 2). The product was not pure enough to register IR, ^1H and ^{13}C NMR data; GC-MS (EI, 70 eV): *m/z* = 389 (26) [M^+], 330 (6), 303 (100), 276 (9), 243 (76), 216 (24), 211 (11), 201 (13), 185 (27), 157 (9), 114 (9).

Dimethyl (*E*)-5,6-dimethoxy-1-(2-morpholin-4-yl-2-oxo-ethylidene)indane-2,2-dicarboxylate (3ca-*E*): Yield: 472 mg, starting from 568 mg of dimethyl 2-(4,5-dimethoxy-2-trimethylsilanylethynylbenzyl)malonate **1c′** (75%; Table 2, entry 3); yellow oil. IR (film): ν = 3016 (m), 1735 (s), 1639 (s), 1503 (w), 1434 (m), 1347 (w), 1244 (s), 1115 (m), 754 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.28 (s, 1H), 6.74 (s, 1H), 6.23 (s, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.80–3.70 (m, 6H), 3.78 (s, 6H), 3.66–3.61 (m, 4H); 2D-NOESY data: the NOESY spectrum evidenced a strong interaction between the aromatic protons and the morpholine protons, in agreement with an *E* stereochemistry; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 166.7, 151.5, 148.9, 143.8, 137.1, 128.3, 117.2, 106.9, 106.6, 67.1, 66.8, 64.4, 55.9, 53.3, 46.6, 41.7, 39.3; GC-MS (EI, 70 eV): *m/z* = 419 (33) [M^+], 360 (13), 333 (67), 306 (11), 273 (100), 246 (25), 241 (22), 231 (12), 215 (17), 171 (13), 115 (9); anal. calcd. for $C_{21}H_{25}NO_8$ (419.43): C 60.14, H 6.01, N 3.34; found: C 60.28, H 6.03, N 3.33.

Dimethyl (*E*)-5,6-dimethyl-1-(2-morpholin-4-yl-2-oxoethylidene)indane-2,2-dicarboxylate (3da-*E*): Yield: 366 mg, starting from 519 mg of dimethyl 2-(4,5-dimethyl-2-trimethylsilanylethynylbenzyl)malonate **1d′** (63%; Table 2, entry 4); yellow oil. IR (film): ν = 1737 (s), 1628 (s), 1435 (m), 1272 (m), 1198 (w), 1109 (m), 1059 (m), 976 (m), 885 (w), 806 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36 (s, 1H), 7.04 (s, 1H), 6.26 (s, 1H), 3.77 (s, 6H), 3.82–3.55 (m, 10H), 2.25 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 166.8, 143.0, 141.3, 139.5, 136.0, 133.8, 125.8, 125.2, 118.7, 67.1, 66.7, 64.1, 53.3, 46.5, 41.7, 39.1, 30.9, 20.2; GC-MS (EI, 70 eV): *m/z* = 387 (16) [M^+], 355 (1), 328 (14), 301 (58), 241 (100), 214 (13), 209 (18), 183 (18), 155 (13), 153 (12), 128 (6), 115 (8); anal. calcd. for $C_{21}H_{25}NO_6$ (387.43): C 65.10, H 6.50, N 3.62; found: C 65.01, H 6.48, N 3.61.

Dimethyl (*Z*)-5,6-dimethyl-1-(2-morpholin-4-yl-2-oxoethylidene)indane-2,2-dicarboxylate (3da-*Z*): GLC yield: *ca.* 6%, starting from **1d′** (Table 2, entry 4) The product was not pure enough to register IR, ^1H and ^{13}C NMR data; GC-MS (EI, 70 eV): *m/z* = 387 (23) [M^+], 355 (1), 328 (18), 301 (68), 241 (100), 214 (16), 209 (16), 183 (17), 155 (14), 153 (15), 128 (7), 115 (7).

Dimethyl (*E*)-1-(2-morpholin-4-yl-2-oxoethylidene)-6-nitroindane-2,2-dicarboxylate (3ea-*E*): Yield: 352 mg, starting from 545 mg of dimethyl 2-(4-nitro-2-trimethylsilanylethynylbenzyl)malonate **1e′** (58%; Table 2, entry 5); pale yellow solid; mp 177–179 °C. IR (KBr): ν = 1734 (s), 1623 (s), 1524 (m), 1434 (m), 1346 (m), 1264 (s), 1110 (m), 1066 (m), 755 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.55 (d, *J* = 1.9 Hz, 1H), 8.18 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 6.61 (s, 1H), 3.89–3.77 (m, 6H), 3.81 (s, 6H), 3.75–3.67 (m, 2H), 3.66–3.59 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5, 165.4, 150.0, 148.1, 140.7, 137.3, 125.6, 125.0, 123.7, 120.0, 67.1, 66.7, 64.0, 53.7, 46.6, 41.8, 39.2; GC-MS (EI, 70 eV): *m/z* = 404 (25) [M^+], 345 (24), 318 (100), 258 (59), 231 (11), 207 (18), 200 (17), 154 (14), 126 (18), 86 (33); anal. calcd. for $C_{19}H_{20}N_2O_8$ (404.37): C 56.43, H 4.99, N 6.93; found: C 56.53, H 4.98, N 6.95.

Methyl (*E*)-2-acetyl-1-(2-morpholin-4-yl-2-oxoethylidene)indane-2-carboxylate (3fa-*E*): Yield: 366 mg, starting from 454 mg of methyl 3-oxo-2-(2-trimethylsilanylethynylbenzyl)butyrate **1f′** (71%; Table 2, entry 6); yellow oil. IR (film): ν = 1714 (s), 1633 (s), 1434 (m), 1359 (w), 1238 (s), 1114 (m), 760 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.68–7.62 (m, 1H), 7.38–7.20 (m, 3H), 6.25 (s, 1H), 3.86–3.56 (m, 10H), 3.81 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.5, 170.7, 166.4, 143.3, 142.8, 136.2, 130.3, 127.7, 125.0, 124.8, 120.4, 70.6, 67.0, 66.7, 53.2, 46.6, 41.7, 38.1, 26.1; GC-MS (EI, 70 eV): *m/z* = 343 (absent) [M^+], 301 (64), 284 (1), 269 (14), 241 (8), 214 (100), 186 (96), 171 (18), 155 (64), 141 (5), 127 (48), 114 (12), 88 (25); anal. calcd. for $C_{19}H_{21}NO_5$ (347.37): C 66.46, H 6.16, N 4.08; found: C 66.29, H 6.17, N 4.09.

Methyl (*E*)-2-cyano-1-(2-morpholin-4-yl-2-oxoethylidene)indane-2-carboxylate (3ga-*E*): Yield: 343 mg, starting from 428 mg of methyl 2-cyano-3-(2-trimethylsilanylethynylphenyl)propionate **1g′** (70%; Table 2, entry 7); yellow oil. IR (film): ν = 2244 (w), 1742 (s), 1646 (vs), 1447 (m), 1273 (m), 1237 (m), 1214 (m), 1114 (m), 762 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 7.8 Hz, 1H), 7.43–7.24 (m, 3H), 6.51 (s, 1H), 3.90–3.68 (m, 4H), 3.84 (s, 3H), 3.68–3.48 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 164.8, 144.7, 143.0, 134.2, 131.3, 128.3, 125.6, 125.1, 118.8, 66.9, 66.7, 54.5, 51.6, 46.6, 41.9, 40.7; GC-MS (EI, 70 eV): *m/z* = 326 (26) [M^+], 311 (1), 295 (9), 267 (41), 241 (20), 240 (100), 228 (3), 214 (14), 196 (27), 180 (37), 155 (59), 153 (55), 127 (34), 86 (72); anal. calcd. for $C_{18}H_{18}N_2O_4$ (326.35): C 66.25, H 5.56, N 8.58; found: C 66.39, H 5.57, N 8.60.

Dimethyl (*E*)-1-(2-oxo-2-piperidin-1-ylethylidene)indane-2,2-dicarboxylate (3ab-*E*): Yield: 300 mg, starting from 478 mg of dimethyl 2-(2-trimethylsilanylethynylbenzyl)malonate **1a′** (56%; Table 2, entry 8); yellow solid; mp 104–

105 °C. IR (KBr): $\nu = 1736$ (s), 1618 (s), 1426 (s), 1280 (m), 1213 (m), 1152 (w), 1079 (m), 1024 (w), 953 (w), 897 (w), 850 (w), 785 (m), 763 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.61$ (d, $J = 7.8$ Hz, 1H), 7.30–7.23 (m, 2H), 7.23–7.17 (m, 1H), 6.41 (s, 1H), 3.78 (s, 6H), 3.74–3.66 (m, 4H), 3.65–3.59 (m, 2H), 1.70–1.56 (m, 4H), 1.53–1.44 (m, 2H); 2D-NOESY data: the NOESY spectrum evidenced neat interactions between the aromatic protons and the piperidine protons, and no nOe between the aromatic protons and the olefinic proton, in agreement with an *E* stereochemistry; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.5$, 166.2, 143.3, 142.1, 136.4, 129.8, 127.5, 125.0, 124.7, 121.6, 64.15, 53.1, 47.3 (br), 42.4 (br), 39.6, 26.5 (br), 25.7 (br), 24.8; GC-MS (EI, 70 eV): $m/z = 357$ (absent) $[M^+]$, 298 (18), 273 (63), 238 (19), 213 (100), 186 (24), 171 (16), 155 (30), 141 (13), 127 (39), 115 (13), 84 (58); anal. calcd. for $C_{20}H_{23}NO_5$ (357.40): C 67.21, H 6.49, N 3.92; found: C 67.17, H 6.48, N 3.92.

Dimethyl (*E*)-1-(2-oxo-2-pyrrolidin-1-yl-ethylidene)indane-2,2-dicarboxylate (3ac-*E*): Yield: 294 mg, starting from 478 mg of dimethyl 2-(2-trimethylsilanylethynylbenzyl)malonate **1a′** (57%; Table 2, entry 9); yellow oil. IR (film): $\nu = 1737$ (s), 1616 (s), 1435 (m), 1248 (m), 1097 (w), 1056 (w), 754 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.86$ (d, $J = 7.7$, 1H), 7.31–7.15 (m, 3H), 6.42 (s, 1H), 3.77 (s, 6H), 3.70 (s, 2H), 3.65–3.57 (m, 2H), 3.54–3.46 (m, 2H), 1.97–1.84 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.4$, 165.8, 143.6, 143.5, 136.3, 130.1, 127.5, 125.4, 124.6, 121.5, 64.3, 53.2, 47.1, 45.5, 39.5, 26.1, 24.5; GC-MS (EI, 70 eV): $m/z = 343$ (24) $[M^+]$, 312 (5), 284 (24), 273 (79), 252 (10), 229 (4), 213 (100), 186 (15), 181 (14), 171 (13), 155 (21), 141 (9), 127 (28), 70 (16); anal. calcd. for $C_{19}H_{21}NO_5$ (343.37): C 66.46, H 6.16, N 4.08; found: C 66.59, H 6.15, N 4.09.

Dimethyl (*E*)-1-(diethylcarbamoylmethylene)indane-2,2-dicarboxylate (3ad-*E*): Yield: 363 mg, starting from 478 mg of dimethyl 2-(2-trimethylsilanylethynylbenzyl)malonate **1a′** (70%; Table 2, entry 10); yellow oil. IR (film): $\nu = 1736$ (s), 1634 (s), 1465 (m), 1432 (m), 1257 (m), 1098 (m), 786 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.66$ (d, $J = 7.7$ Hz, 1H), 7.31–7.15 (m, 3H), 6.45 (s, 1H), 3.78 (s, 6H), 3.71 (s, 2H), 3.60–3.44 (m, 4H), 3.49 (q, $J = 7.1$ Hz, 2H), 1.25 (t, $J = 7.1$ Hz, 3H), 1.11 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.4$, 167.1, 143.3, 142.1, 136.2, 129.8, 127.4, 124.9, 124.7, 121.5, 64.0, 53.2, 42.7, 39.4, 14.3, 12.9; GC-MS (EI, 70 eV): $m/z = 345$ (17) $[M^+]$, 286 (19), 273 (60), 226 (6), 213 (100), 186 (22), 171 (12), 155 (23), 141 (10), 127 (28), 115 (10), 100 (5), 72 (39); anal. calcd. for $C_{19}H_{23}NO_5$ (345.39): C 66.07, H 6.71, N 4.06; found: C 66.25, H 6.73, N 4.06.

Dimethyl (*E*)-1-(dibutylcarbamoylmethylene)indane-2,2-dicarboxylate (3ae-*E*): Yield: 410 mg, starting from 478 mg of dimethyl 2-(2-trimethylsilanylethynylbenzyl)malonate **1a′** (68%; Table 2, entry 11); colorless oil. IR (film): $\nu = 2957$ (m), 1736 (s), 1629 (m), 1464 (w), 1432 (m), 1247 (s), 1097 (w), 1055 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.70$–7.64 (m, 1H), 7.30–7.14 (m, 3H), 6.44 (s, 1H), 3.77 (s, 6H), 3.70 (s, 2H), 3.51–3.37 (m, 4H), 1.71–1.58 (m, 2H), 1.55–1.20 (m, 6H), 0.98 (t, $J = 7.2$, 3H), 0.86 (t, $J = 7.2$, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.4$, 167.4, 143.2, 142.1, 136.2, 129.8, 127.4, 125.0, 124.6, 121.6, 64.0, 53.2, 48.2, 44.7, 39.5, 31.0, 29.7, 20.4, 19.9, 13.9, 13.8; GC-MS (EI, 70 eV): $m/z = 401$ (absent) $[M^+]$, 344 (12), 342 (29), 310 (41), 274 (18), 273 (100), 214 (21), 213 (97), 186 (26), 181 (14), 171 (16), 155 (27), 141 (12), 128 (65), 127 (26), 115 (10), 86 (11); anal. calcd. for $C_{23}H_{31}NO_5$ (401.50): C 68.80, H 7.78, N 3.49; found: C 68.68, H 7.76, N, 3.50.

Dimethyl (*Z*)-1-(dibutylcarbamoylmethylene)indane-2,2-dicarboxylate (3ae-*Z*): Yield: 42 mg, starting from 478 mg of dimethyl 2-(2-trimethylsilanylethynylbenzyl)malonate **1a′** (7%; Table 2, entry 11); yellow oil. IR (film): $\nu = 1738$ (s), 1633 (s), 1591 (m), 1531 (w), 1460 (m), 1433 (m), 1378 (w), 1253 (s), 1098 (w), 784 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.60$–7.53 (m, 1H), 7.37–7.22 (m, 3H), 6.87 (s, 1H), 3.72 (s, 6H), 3.67 (s, 2H), 3.43–3.31 (m, 4H), 1.72–1.59 (m, 2H), 1.59–1.45 (m, 2H), 1.45–1.23 (m, 4H), 0.98 (t, $J = 7.3$ Hz, 3H), 0.86 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.1$, 166.0, 150.9, 143.2, 139.8, 130.4, 127.5, 125.1, 121.1, 113.7, 63.1, 52.6, 48.3 (br), 46.0 (br), 43.5, 31.8 (br), 30.2 (br), 20.3, 13.9; GC-MS (EI, 70 eV): $m/z = 401$ (absent) $[M^+]$, 342 (24), 310 (43), 300 (3), 273 (96), 254 (7), 229 (5), 213 (100), 186 (22), 181 (14), 171 (15), 155 (25), 141 (11), 128 (52), 115 (10); anal. calcd. for $C_{23}H_{31}NO_5$ (401.50): C 68.80, H 7.78, N 3.49; found: C 68.68, H 7.76, N 3.50.

Dimethyl (*E*)-1-(diisopropylcarbamoylmethylene)indan-2,2-dicarboxylate (3af-*E*): Yield: 280 mg, starting from 478 mg of dimethyl 2-(2-trimethylsilanylethynylbenzyl)malonate **1a′** (50%; Table 2, entry 12); yellow solid; mp 105–107 °C. IR (KBr): $\nu = 1737$ (s), 1623 (s), 1438 (m), 1371 (w), 1324 (m), 1255 (m), 1170 (w), 1098 (w), 1045 (m), 757 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 7.7$ Hz, 1H), 7.34–7.13 (m, 3H), 6.40 (s br, 1H), 4.46 (heptuplet, $J = 6.7$ Hz, 1H), 3.82–3.57 (m, 3H), 3.77 (s, 6H), 1.55 (d, $J = 6.7$ Hz, 6H), 1.15 (d, $J = 6.7$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.5$, 167.1, 143.0, 140.7, 136.5, 129.6, 127.2, 124.73, 124.68, 123.2, 63.8, 53.1, 50.0, 45.7, 39.5, 21.1, 20.5; GC-MS (EI, 70 eV): $m/z = 373$ (absent) $[M^+]$, 342 (5), 314 (6), 273 (95), 228 (7), 213 (100), 186 (27), 171 (16), 155 (26), 141 (12), 127 (32), 115 (14), 100 (76); anal. calcd. for $C_{23}H_{31}NO_5$ (401.50): C 68.80, H 7.78, N 3.49; found: C 68.94, H 7.77, N 3.50.

Sonogashira Coupling Between *N,N*-Diethylpropiolamide and Dimethyl 2-(2-Iodobenzyl)malonate to Give Dimethyl (*E*)-1-(Diethylcarbamoylmethylene)-indane-2,2-dicarboxylate (3ad-*E*) (Scheme 5)

1st Step: preparation of *N,N*-diethylpropiolamide: To a cooled (−20 °C), stirred solution of propiolic acid (1.0 g, 15 mmol) in anhydrous CH_2Cl_2 were added, under nitrogen, dicyclohexylcarbodiimide (3.1 g, 15 mmol) and diethylamine (1.1 g, 15 mmol). The mixture was allowed to warm up to room temperature and stirred for 15 h. The mixture was then filtered through a short pad of silica gel, which was washed with CH_2Cl_2. After concentration under vacuum, the resulting oil was purified by column chromatography on silica gel, using 8:2 hexane/Et_2O as eluent, to give pure *N,N*-diethylpropiolamide; yield: 0.83 g (44%); yellow oil. IR (film): $\nu = 2978$ (m), 2874 (w), 2101 (m), 1628 (s), 1432 (m), 1276 (m), 1150 (w), 741 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.61$ (q, $J = 7.1$ Hz, 2H, NCH_2), 3.43 (q, $J = 7.1$ Hz, 2H, NCH_2), 3.09 (s, 1H, ≡CH), 1.23 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 1.15 (t, $J = 7.1$ Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 152.9$, 77.7, 77.5, 43.6, 39.5, 14.4, 12.8; GC-MS (EI, 70 eV): $m/z = 125$ (8) $[M^+]$, 97 (88), 82 (90), 69 (51), 67 (100), 56 (58), 54 (64); anal. calcd. for $C_7H_{11}NO$

(125.17): C 67.17, H 8.86, N 11.19; found: C 67.03, H 8.87, N 11.17.

2nd Step: Sonogashira coupling between *N,N*-diethylpropiolamide and dimethyl 2-(2-iodobenzyl)malonate leading to 3ad-*E*: *N,N*-Diethylpropiolamide (125 mg; 1.0 mmol), was added under nitrogen to a stirred solution of dimethyl 2-(2-iodobenzyl)malonate (400 mg, 1.1 mmol), CuI (9.5 mg, 0.05 mmol), NaOAc (246 mg, 3.0 mmol) and $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) in anhydrous DMF (10 mL). The reaction mixture was stirred for 2 h at 60 °C. After cooling, the mixture was diluted with AcOEt (50 mL) followed by water (50 mL). Phases were separated, and the organic phase was washed with water (50 mL) and then dried over Na_2SO_4. After filtration and evaporation of the solvent, the product was purified by column chromatography on silica gel, using as eluent 6:4 hexane-AcOEt, to give pure dimethyl (*E*)-1-(diethylcarbamoylmethylene)indane-2,2-dicarboxylate (**3ad-*E***); yield: 194 mg (56%).

Acknowledgements

Thanks are due to the European Commission, FSE (Fondo Sociale Europeo) and Calabria Region for a fellowship grant to R.M.

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