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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4883–4886

Observations on the copper(II) catalyzed reactions of enaminones and dimethyl diazomalonate

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Received 23 March 2007; revised 30 April 2007; accepted 10 May 2007
Available online 17 May 2007

Abstract—The $Cu(acac)_2$ catalyzed reactions of dimethyl diazomalonate with enaminones yielded 1,5-cyclization and α-CH insertion products. In the case of anilino derivatives (R^1 or $R^2 = Ph$), products resulting from an unusual insertion to the benzoyl ring dominated the reaction.
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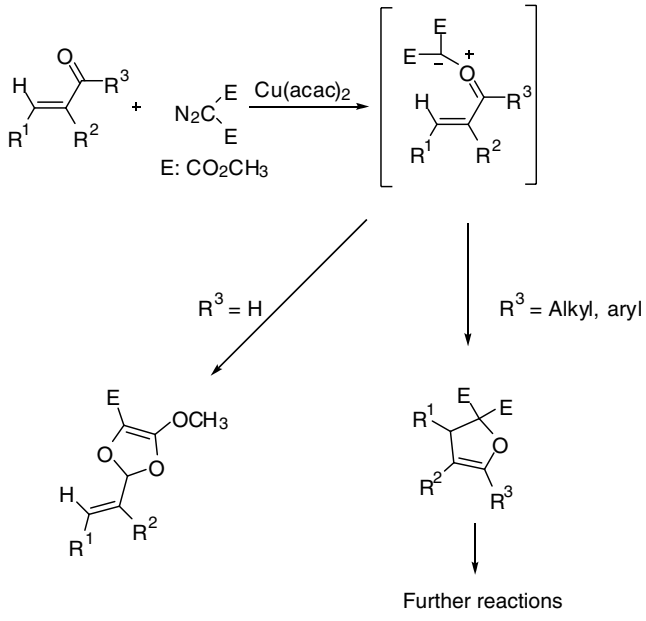
Inspired by the pioneering work of Spencer et al.,[1] our group has been studying the formal 1,5-electrocyclization reactions of carbonyl ylides derived from α,β-unsaturated carbonyl compounds and metallo-carbenoid species.[2] Cu(II) acetylacetonate induced decomposition of diacyl diazo compounds, such as dimethyl diazomalonate (dmdm), in the presence of α,β-unsaturated carbonyl compounds, such as α,β-unsaturated ketones and esters, were reported to yield mainly dihydrofuran derivatives. α,β-Enals, on the other hand, were found to yield dioxolanes, instead. For the reactions to proceed as described, it was reported that the unsaturated carbonyl compounds must be mono-substituted at their β-position and possess trans geometry. For the formation of dihydrofurans, the *s*-cis conformation is required. The products were reported to undergo further reactions (Scheme 1). Similar formal electrocyclizations were also reported by the Hamaguchi group.[3]

In all the investigations mentioned above, we employed α,β-unsaturated carbonyl compounds with alkyl or aryl groups as the β-substituent. As part of our ongoing studies, we wanted to see how a heteroatom, such as nitrogen, would affect the course of the reactions. This is analogous to the starting materials used by Spencer et al., who employed fixed cisoid β-alkoxy-α,β-unsaturated ketones in their reactions.[1]



Scheme 1. The reactions of α,β-unsaturated carbonyl compounds with dmdm.

A literature search revealed many reports on the reactions of β-amino-α,β-unsaturated compounds, that is, enaminones and diazo compounds,[4] but the most relevant study was that of Maas and Müller[5] who reported the formation of push–pull cyclopropanes and their rearrangement products using tertiary enaminones and diazoacetic esters under Cu(II) catalysis. Suprisingly, as noted by the authors, dihydrofuran formation was

Keywords: Enaminone; Carbonyl ylide; Diazo compound; Carbene.
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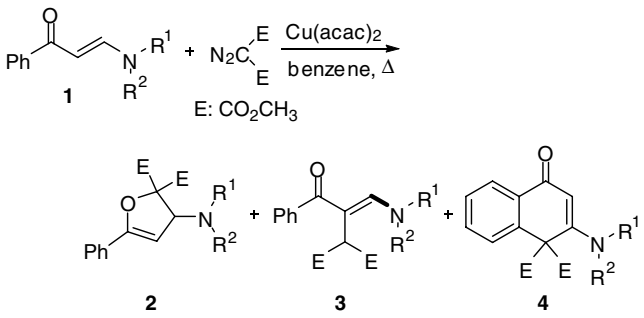
doi:10.1016/j.tetlet.2007.05.063



Scheme 2. The reactions of enaminones with dmdm.

Table 1. Product distribution from the reactions of enaminones with dmdm

Entry	R^1	R^2	Product distribution (yield, %)		
			2	**3**	**4**
a	Me	Me	1 (20%)	0.56 (14%)	—
b	–$(CH_2)_5$–		1 (28%)	0.23 (11%)	—
c	Me	Ph	1 (14%)	—	3.52 (42%)
d	Ph	Ph	1[a]	—	2.47 (40%)

[a] Product not isolated in pure state. Structural assignment based on ^{1}H NMR of an impure sample and GC–MS.

only detected in a few of the reactions in trace amounts. This was another reason for us to study the reactions of tertiary enaminones, this time with diazomalonates instead of diazoacetates.

Several β-amino-α,β-unsaturated ketones **1** were reacted with dmdm in boiling benzene in the presence of $Cu(acac)_2$ (Scheme 2) and the results are summarized in Table 1.

Contrary to the findings of Maas and Müller,[5] all the reactions gave significant amounts of dihydrofuran products **2**. With dimethylamino and piperidine as the β-amino groups, dihydrofurans were the main reaction products and this is the expected behaviour of diazomalonate in accordance with our previous findings.[2] α-CH insertion products **3** were also observed, although in lesser amounts. Whether they arose via ring opening of the initially formed cyclopropanes cannot be confirmed, because we were not able to detect any cyclopropane products from the reactions.

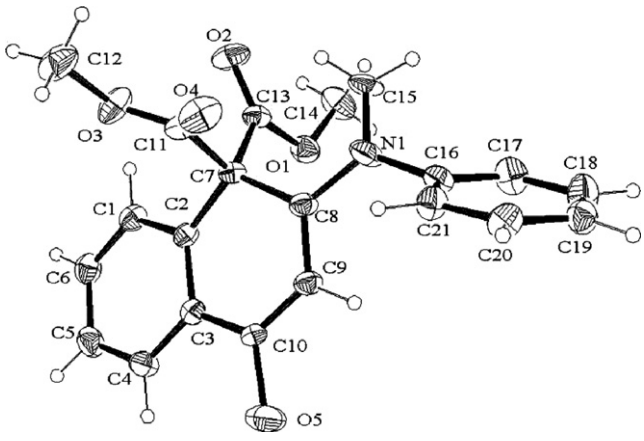


Figure 1. The structure of **4c**.

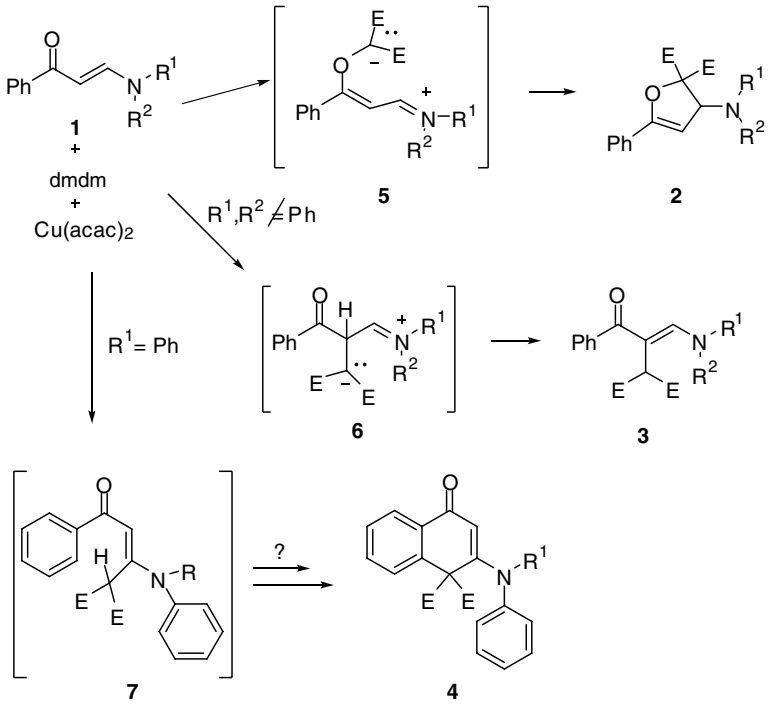
On the other hand, dihydrofuran **2c** was not the major product in the reaction of β-*N*-methylanilino acrylophenone (**1c**, $R^1 = Me$, $R^2 = Ph$). The ^{1}H NMR spectrum of major product **4c** showed a singlet at 7.16 ppm (1H) which was attributable to a vinylic hydrogen. The ester hydrogens were observed as a 6H singlet implying a planar symmetry, which was also confirmed by ^{13}C NMR spectroscopy. The molecular mass of **4c** was found to be 365, which shows that the loss of two hydrogens had occurred after the formal carbene-substrate addition reaction. The structure of **4c** was determined by crystallographic analysis of a single crystal (Fig. 1).[†] It is noteworthy that Son and Fu,[6] who recently worked with aromatic enones of acrylophenone, did not report the presence of such interactions with aromatic rings.

The structure of **4c** implies that aromatic nucleophilic substitution occurs during the reaction, but would require carbene insertion to the β-CH bond which is unexpected (Scheme 3, intermediate **7**). One may speculate that such intermediates might form via ring opening of an initially formed cyclopropane (see, for example, the work of Maas[5]), but even this would most likely yield the α-CH insertion product of type **3**, which was actually observed in our reactions. More reliable proof would be required in order to confirm the presence of β-CH insertion products. Besides, the loss of hydrogen is not easily explained, either. Therefore, we cannot comment on the mechanism of the reaction at present. On the other hand, when anilino groups were present at the β-position, the unexpected aromatic insertion products **4c** and **4d** were the dominant products, whereas with aliphatic amino groups, no such products of type **4** were formed. α-CH insertion products were observed as the secondary products instead (Table 1).

Contrary to the literature data, our results show that significant amounts of dihydrofuran products can form in these reactions. In the case of aromatic amino groups, novel 3-anilino-4-oxo-1,4-dihydronaphthalene derivatives were the major products. Further studies on the formation of these novel products as well as the effects of catalyst changes on the product distribution are currently being conducted by our group.

Typical procedure[7] for the reaction of β- enaminones[8] with dmdm.[9] To a solution of **1** (1.5 equiv) in benzene (10 mL) was added $Cu(acac)_2$ (0.007 equiv), and the mixture was heated at reflux. A solution of dmdm (1 equiv) in benzene (4 mL) was added over 2.5 h under an N_2 atmosphere. When the IR spectrum of the reaction mixture indicated total consumption of dmdm (absence of the characteristic diazo band at 2130 cm^{-1}), the

[†] CCDC 641486 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif



Scheme 3. Possible routes leading to various products.

mixture was filtered, evaporated and purified by column chromatography or preparative TLC. The crude mixtures contained varying amounts of unidentified compounds (up to 20% by GC). The products[10] were characterized by NMR and MS.

Acknowledgement

This work was supported by *The Scientific and Technological Research Council of Turkey* (TUBITAK) (TBAG-105T418).

References and notes

1. (a) Storm, L. D.; Spencer, T. A. *Tetrahedron Lett.* **1967**, 1865; (b) Spencer, T. A.; Villarica, R. M.; Storm, D. L.; Weaver, T. D.; Friary, R. J.; Posler, J. *J. Am. Chem. Soc.* **1967**, *89*, 5497; (c) Murayama, S. T.; Spencer, T. A. *Tetrahedron Lett.* **1969**, 4479.
2. (a) Anaç, O.; Daut, A. *Liebigs Ann. Recueil* **1997**, 1249; (b) Anaç, O.; Daut-Özdemir, A.; Sezer, Ö. *Helv. Chim. Acta* **2003**, *86*, 290; (c) Anaç, O.; Güngör, F. Ş.; Kahveci, Ç.; Cansever, M. Ş. *Helv. Chim. Acta* **2004**, *87*, 408; (d) Anaç, O.; Güngör, F. Ş.; Merey, G. *Helv. Chim. Acta* **2006**, *89*, 1231.
3. Hamaguchi, M.; Matsubara, H.; Nagai, T. *J. Org. Chem.* **2001**, *66*, 5395.
4. (a) Kascheres, C. M. *J. Braz. Chem. Soc.* **2003**, *14*, 945; (b) Eberlin, M. N.; Takahata, Y.; Kascheres, C. *J. Org. Chem.* **1990**, *55*, 5150; (c) Eberlin, M. N.; Kascheres, C. *J. Org. Chem.* **1988**, *53*, 2084; (d) Augusti, R.; Eberlin, M. N.; Kascheres, C. *J. Heterocycl. Chem.* **1995**, *32*, 1355.
5. Maas, G.; Müller, A. *Prakt. Chem.* **1998**, *340*, 315.
6. Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 1046.
7. Preparative TLC was performed on Merck Silica Gel 60 F254 plates and Merck aluminium oxide 90 active neutral (70–230 mesh ASTM). GC/MS: *Hewlett-Packard* instrument, with HP-1 capillary column (24 m) packed with cross-linked (phenylmethyl)siloxane; retention times t_R in min. Column temperature program: Isothermal at 100 °C for 5 min, heat to 290 °C with 20 °C/min and remain isothermal for 10 min.
8. Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277, *(E)-3-(Dimethylamino)-1-phenylprop-2-en-1-one* **1a**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.88 (disorted dd, *J*: 9.77 Hz, 2.54 Hz, 2H), 7.82 (d, *J*: 12.41 Hz, 1H), 7.44–7.34 (m, 3H), 5.70 (d, *J*: 12.36 Hz, 1H), 3.11 (br s, 3H), 2.91 (br s, 3H). t_R: 12.07. EI-MS: 175 (M^+, 49), 158 (100), 105 (21), 98 (64), 77 (21). *(E)-1-Phenyl-3-(piperidin-1-yl)prop-2-en-1-one* **1b**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.86 (dd, *J*: 7.64 Hz, 1.87 Hz, 2H), 7.76 (d, *J*: 12.49 Hz, 1H), 7.46–7.34 (m, 3H), 5.80 (d, *J*: 12.47 Hz, 1H), 3.34 (br s, 4H), 1.64 (br s, 6H). t_R: 14.18. EI-MS: 215 (M^+, 71), 198 (100), 186 (5), 172 (4), 138 (20), 110 (31), 105 (25), 91 (4), 77 (19). *(E)-1-Phenyl-3-(piperidin-1-yl)prop-2-en-1-one* **1c**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.22 (d, *J*: 12.68 Hz, 1H), 7.93 (dd, *J*: 7.69 Hz, 1.69, 2H), 7.49–7.34 (m, 5H), 7.22–7.13 (m, 3H), 6.09 (d, *J*: 12.68 Hz, 1H), 3.40 (s, 3H). t_R: 14.72. EI-MS: 237 (M^+, 55), 220 (92), 160 (52), 132 (100), 117 (27), 105 (28), 91 (12), 77 (36). *(E)-3-(Diphenylamino)-1-phenylprop-2-en-1-one* **1d**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.49 (d, *J*: 12.74 Hz, 1H), 7.77 (dd, *J*: 7.89 Hz, 1.5, 2H), 7.47–7.27 (m, 10H), 7.18 (d, *J*: 7.81 Hz, 3H), 6.02 (d, *J*: 12.78 Hz, 1H). t_R: 17.08. EI-MS: 299 (M^+, 65), 282 (20), 222 (48), 194 (100), 167 (18), 131 (4), 105 (32), 77 (39). $C_{21}H_{17}NO$ (299.37) Calcd: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.19; H, 5.69; N, 4.66.
9. Wulfman, D. S.; McGibboney, B. G.; Steffen, E. K.; Thinh, N. V.; McDaniel, R. S.; Peace, B. W. *Tetrahedron* **1976**, *32*, 1257.
10. *Spectroscopic data*: *Dimethyl 3-(dimethylamino)-5-phenylfuran-2,2(3H)dicarboxylate* **2a**: From preparative TLC (Al_2O_3, hexane/EtOAc 5:2). Yield 20%. ^{1}H NMR

(250 MHz, $CDCl_3$): δ 7.65 (dd, $J = 7.74$ Hz, 3.15 Hz, 2H, *ortho* C_{Ar}–H), 7.38–7.33 (m, 3H, Ar-H), 5.50 (d, *J*: 2.86 Hz, 1H, H–C(4)), 4.77 (d, *J*: 2.83 Hz, 1H, H–C(3)), 3.82 (s, 3H, CO_2CH_3), 3.78 (s, 3H, CO_2CH_3), 2.32 (s, 6H, $N(CH_3)_2$). ^{13}C NMR (60 MHz, $CDCl_3$): δ 167.3 (C=O), 165.5 (C=O), 155.3 (C(5)), 128.5, 128.3, 127.6, 124.9 (all C_{Ar}), 93.2 (C(4)), 91.4 (C(2)), 72.4 (C(3)), 52.3 (CO_2CH_3), 51.7 (CO_2CH_3), 41.5 (N–CH_3), 38.4 (N–CH_3). t_R: 12.90. EI-MS: 305 (M^+, 32), 304 (46), 290 (10), 274 (7), 261 (51), 246 (45), 217 (70), 202 (70), 171 (40), 158 (100), 144 (16), 115 (53), 105 (9), 77 (16), 59 (10). $C_{16}H_{19}NO_5$ (305.33) Calcd: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.05; H, 6.14; N, 4.55. *Dimethyl 5-phenyl-3-(piperidin-1-yl)furan-2,2(3H)-dicarboxylate* **2b**: From column chromatography (Al_2O_3, hexane/EtOAc 5:1). Yield 28%. ^1H NMR (250 MHz, $CDCl_3$): δ 7.64 (dd, *J*: 7.78 Hz, 1.90 Hz, 2H, *ortho* C_{Ar}–H), 7.37–7.33 (m, 3H, other Ar-H), 5.52 (d, *J*: 2.82 Hz, 1H, H–C(4)), 4.73 (d, *J*: 2.81 Hz, 1H, H–C(3)), 3.82 (s, 3H, CO_2CH_3), 3.78 (s, 3H, CO_2CH_3), 2.64–2.55 (m, 4H, N–$(CH_2)_2$), 1.44–1.26 (m, 6H). ^{13}C NMR (60 MHz, $CDCl_3$): δ 162.8 (C=O), 133.4, 130.0, 128.6, 128.4 (all C_{Ar}), 102.5 (C(4)), 92.8 (C(2)), 88.6 (C(3)), 50.8 (CO_2CH_3), 44.6 (piperidine, C2′, C6′), 29.7 (piperidine, C3′, C5′), 22.5 (piperidine, C4′). t_R: 14.49. EI-MS: 345 (M^+, 13), 344 (20), 286 (100), 261 (29), 217 (31), 185 (34), 129 (11), 115 (18), 84 (7), 59 (4). $C_{19}H_{23}NO_5$ (345.39) Calcd: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.12; H, 6.63; N, 4.10. *Dimethyl 3-(methyl(phenyl)amino)-5-phenylfuran-2,2(3H)-dicarboxylate* **2c**: From column chromatography (Al_2O_3, hexane/EtOAc 5:1). Yield 14%. ^1H NMR (250 MHz, $CDCl_3$): δ 7.73 (dd, *J*: 5.4 Hz, 1.9 Hz, 2H), 7.41 (dd, *J*: 5.03 Hz, 1.78 Hz, 3H), 7.30 (td, ^3J: 7.08 Hz and 8.52 Hz, ^4J: 1.88 Hz, 1.38 Hz, 0.92 Hz, 2H), 7.00 (d, *J*: 8.05 Hz, 2H), 6.80 (t, *J*: 7.18 Hz, 1H) (aromatics), 6.12 (d, *J*: 3.13 Hz, 1H, H–C(3)), 5.43 (d, *J*: 3.02 Hz, 1H, H–C(4)), 3.88 (s, 3H, CO_2CH_3), 3.52 (s, 3H, CO_2CH_3), 2.77 (s, 3H, NCH_3). ^{13}C NMR (60 MHz, $CDCl_3$): δ 168.1 (C=O), 166.0 (C=O), 156.8 (C(5)), 149.2, 129.7, 129.1,129.0, 128.5, 126.1, 117.8, 113.5 (all C_{Ar}), 95.6 (C(4)), 91.4 (C(2)), 69.7 (C(3)), 53.6 (CO_2CH_3), 52.6 (CO_2CH_3), 32.8 (NCH_3). t_R: 15.70. EI-MS: 367 (M^+, 9), 261 (100), 217 (64), 202 (40), 185 (7), 171 (22), 158 (8), 129 (8), 115 (19), 105 (6), 77 (14), 59 (5). $C_{21}H_{21}NO_5$ (367.40) Calcd: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.58; H, 5.70; N, 3.50. *(E)-Dimethyl 2-(1-(dimethylamino)-3-oxo-3-phenylprop-1-en-2-yl)malonate* **3a**: From preparative TLC (Al_2O_3, hexane/EtOAc 5:2). Yield 14%. ^1H NMR (250 MHz, $CDCl_3$): δ 7.94 (d, *J*: 6.92 Hz, 2H, *ortho* C_{Ar}–H), 7.57–7.42 (m, 3H, Ar-H), 7.35 (s, 1H, C=CH), 3.81 (s, 6H, $CH(CO_2CH_3)_2$), 3.64 (s, 1H, $CH(CO_2CH_3)_2$), 2.44 (s, 6H, $N(CH_3)_2$). t_R: 13.53. EI-MS: M^+ unobserved, 246 (M−COOMe, 100), 187 (40), 172 (4), 158 (4), 115 (6), 105 (18), 77 (11), 72 (15). $C_{16}H_{19}NO_5$ (305.33) Calcd: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.30; H, 6.39; N, 4.29. *(E)-Dimethyl 2-(3-oxo-3-phenyl-1-(piperidin-1-yl)prop-1-en-2-yl)malonate* **3b**: From column chromatography (Al_2O_3, hexane/EtOAc 5:1). Yield 11%. ^1H NMR (250 MHz, $CDCl_3$): δ 7.94 (dd, *J*: 7.72 Hz, 1.60 Hz, 2H, *ortho* C_{Ar}–H), 7.58–7.44 (m, 3H, Ar-H), 7.39 (s, 1H, C=CH), 3.78 (s, 6H, $CH(CO_2CH_3)_2$), 3.76 (s, 1H, $CH(CO_2CH_3)_2$), 2.63–2.59 (m, 4H, N–$(CH_2)_2$), 1.31–1.26 (m, 6H). t_R: 14.87. EI-MS: M^+ unobserved, 344 ($M-H^+$, 1), 286 (100), 227 (13), 198 (4), 148 (3), 105 (14), 77 (6). $C_{19}H_{23}NO_5$ (345.39) Calcd: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.81; H, 6.50; N, 4.24. *Dimethyl 3-(methyl(phenyl)amino)-4-oxonaphthalene-1,1(4H)-dicarboxylate* **4c**: Crystallized from the reaction mixture. Also obtained in varying amounts from column fractions. Yield 42%. Mp: 262–265 °C (decomposition) ^1H NMR (250 MHz, $CDCl_3$): δ 7.59 (dd, *J*: 7.42 Hz, 1.62 Hz, 2H), 7.54 (dd, *J*: 7.83 Hz, 1.40 Hz, 1H), 7.47–7.29 (m, 4H) (all aromatics), 7.16 (s, 1H, H–C(2)), 7.13 (dd, *J*: 7.78 Hz, 0.87 Hz, 1H, Ar-H), 6.94 (dd, *J*: 8.24 Hz, 0.63 Hz, 1H, H–C(8)), 3.74 (s, 6H, CO_2CH_3), 3.31 (s, 3H, NCH_3). ^{13}C NMR (60 MHz, $CDCl_3$): 193.2 (C=O), 170.5 (C=O), 146.8 (C(2)), 139.6, 136.3, 130.4, 130.3, 129.0, 128.5, 128.4, 124.0, 121.1, 113.2 (all C_{Ar}), 59.5 (C(1)), 53.1 (CO_2CH_3), 39.8 (NCH_3). t_R: 17.80. EI-MS: 365 (M^+, 1), 306 (100), 278 (3), 262 (2), 246 (4), 234 (3), 218 (4), 143 (4), 102 (2), 77 (3). $C_{21}H_{19}NO_5$ (365.38) Calcd: C, 69.03; H, 5.24; N, 3.83. Found: C, 69.10; H, 5.32; N, 3.85. *Dimethyl 3-(diphenylamino)-4-oxonaphthalene-1,1(4H)-dicarboxylate* **4d**: From column chromatography (Al_2O_3, hexane/EtOAc 5:1). Yield 40%. ^1H NMR (250 MHz, $CDCl_3$): δ 7.63–7.55 (m, 3H, Ar-H), 7.51–7.40 (m, 5H, Ar-H), 7.37 (s, 1H, C=CH), 7.34–7.26 (m, 4H, Ar-H), 7.16–7.10 (m, 2H, Ar-H), 3.79 (s, 6H, $C(CO_2CH_3)_2$). ^{13}C NMR (60 MHz, $CDCl_3$): 146.7, 143.9, 132.0, 131.6, 130.0, 129.6, 129.0, 127.4, 127.0, 126.3, 116.5 (all C_{Ar}), 102.4, 56.8 (C(1)), 52.4 (CO_2CH_3). t_R: 21.41. EI-MS: 427 (M^+, 1), 368 (100), 207 (8), 105 (3), 77 (5). $C_{26}H_{21}NO_5$ (427.45) Calcd: C, 73.06; H, 4.95; N, 3.28. Found: C, 72.92; H, 4.42; N, 3.02.