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LETTERS

A novel route to 6-substituted and 5,6-disubstituted 2-pyrones

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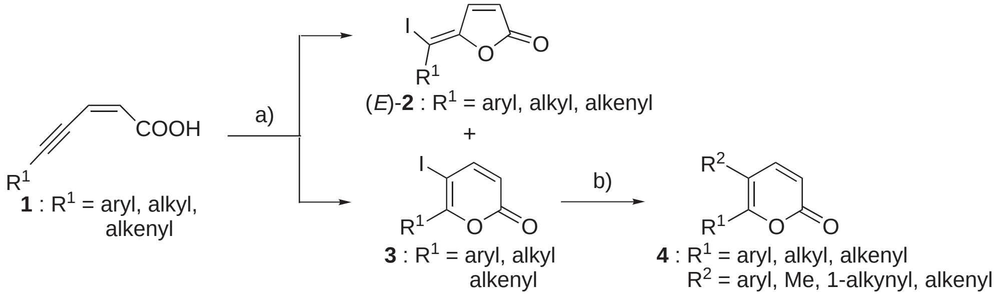
Abstract—6-Alkyl- and 6-(1-alkenyl)-5-iodo-2-pyrones, which are available as major products by reaction of the corresponding (*Z*)-2-en-4-ynoic acids with iodine and $NaHCO_3$ in CH_3CN, undergo insertion of activated zinc metal into their carbon–iodine bond to provide the corresponding 5-(iodozinc)-2-pyrones. Hydrolysis of these organometallics gives 6-substituted 2-pyrones in satisfactory yields including two natural products. On the other hand, the Pd-catalyzed reaction of the organozincs either with an activated alkenyl halide or with activated and deactivated (hetero)aryl halides provides 5,6-disubstituted 2-pyrones in fair to good yields. © 2001 Elsevier Science Ltd. All rights reserved.

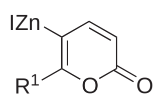
In recent years considerable efforts have been directed towards the synthesis of 2-pyrone derivatives either by traditional approaches[1] or by processes involving transition metal-catalyzed reactions.[2] In fact, 2-pyrones are useful synthetic intermediates[3] and occur as structural subunits in a wide variety of biologically active natural products.[4]

Recently, in the context of a research program aimed at the synthesis of natural and unnatural oxygen-containing heterocycles by approaches which involve transition metal-catalyzed reactions,[5] we developed a two-step protocol for the synthesis of 5,6-disubstituted 2-pyrones **4** (Scheme 1).[6]

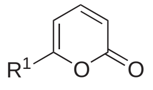
Even though the results of this procedure were satisfactory, we decided to search for a new alternative and practical synthetic route to unsymmetrically 5,6-disubstituted 2-pyrones, which was based on the use of compounds **3**, but did not involve the utilization and manipulation of toxic organotin compounds and their byproducts and was also amenable for the preparation 6-substituted 2-pyrones. Thus, we examined the possibility of converting iodides **3** into the corresponding 5-(iodozinc)-2-pyrones **5** and to use these organometallics in Pd-catalyzed reactions with electrophiles such as alkenyl and (hetero)aryl halides. On the other hand, hydrolysis of the metal–carbon bond of compounds **5** could allow a facile synthesis of 6-substituted 2-pyrones



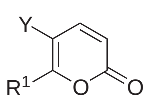
Scheme 1. (a) I_2 (3 equiv.), $NaHCO_3$ (3 equiv.), CH_3CN, 1.5 h, rt; (b) R^2-SnR_3, Pd cat.



5 : R^1 = aryl, alkyl, alkenyl



6 : R^1 = aryl, alkyl, alkenyl



7 : R^1 = alkyl, alkenyl
Y = (hetero)aryl, alkenyl

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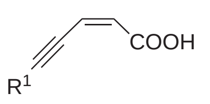
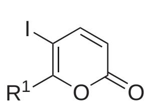
6 for which no general synthetic procedure has been reported so far in the literature.

We now wish to describe the synthesis of the organozincs **5** from iodides **3** and the use of these organometallics for the efficient preparation either of 6-alkyl- and 6-(1-alkenyl)-2-pyrones **6** including two natural products, or of 5,6-disubstituted 2-pyrones of general formula **7**, which are characterized by a (hetero)aryl or an alkenyl group in their 5-position. Moreover, we will report the preparation of a naturally-occurring 6-aryl-2-pyrone by Pd-catalyzed hydrogenolysis of the corresponding 6-aryl-5-iodo derivative.

Iodides **3a**–**d**, which we used as starting materials for the synthesis of compounds **6** and **7**, were prepared in 65, 65, 72 and 59% yields by reaction of carboxylic acids **1a**–**d**, respectively,[6] with 3.0 equiv. of iodine and 3.0 equiv. of $NaHCO_3$ in CH_3CN at 20°C for 1.5 h, followed by a $Na_2S_2O_3$ quench and purification of the resulting reaction mixtures by MPLC on silica gel.[6]



1a : $R^1 = C_5H_{11}$
1b : $R^1 = C_6H_{13}$
1c : $R^1 = (E)\text{-}C_3H_7\text{-}CH{=}CH$
1d : $R^1 = C_6H_5$



3a : $R^1 = C_5H_{11}$
3b : $R^1 = C_6H_{13}$
3c : $R^1 = (E)\text{-}C_3H_7\text{-}CH{=}CH$
3d : $R^1 = C_6H_5$

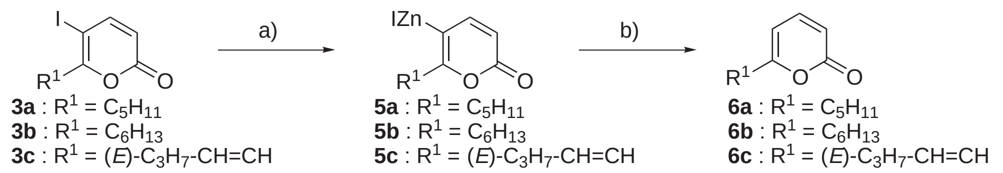
These iodides proved to undergo insertion of zinc metal into their carbon–iodine bond provided that the metal was first activated with 1,2-dibromoethane and then with Me_3SiCl.[7,8] In fact, GLC and GLC/MS analyses of the products, which were obtained by acidic hydrolysis of the reaction mixtures prepared by stirring THF solutions of compounds **3a**–**d** with 3–5 equiv. of activated zinc dust at 20°C for 3–3.5 h, showed that these iodides had been completely consumed. Moreover, in the case of the reaction mixtures which were obtained by treatment of 3 equiv. of zinc metal with **3a**–**c** followed by acidic hydrolysis, these GLC and GLC/MS analyses also showed the presence of a major product which was subsequently isolated and identified as the compound derived from hydrolysis of the organozinc iodides **5a**–**5c**, i.e. as **6a**–**6c**, respectively (Scheme 2).

Purification of these hydrolyzed reaction mixtures by MPLC on silica gel allowed the isolation of **6a**,[9a] **6b**[9a] and **6c**[9b] in 78, 88 and 52% yields, respectively.[10]

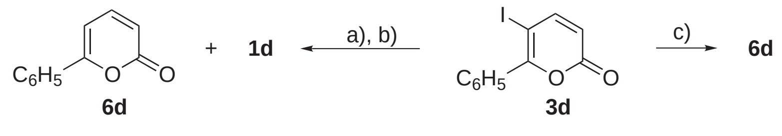
Compound **6a**, which possesses a characteristic coconut odour, is a fungal metabolite of *Trichoderma viride*[11] and has been shown to possess significant antifungal activity.[4d] Compound **6c** has been isolated from a strain of *Trichoderma viride*[9b] and has been shown to display antifungal properties similar to those of **6a**.[12]

On the other hand, GLC/MS and ^{1}H NMR analyses of the reaction mixture which was obtained by acidic hydrolysis of the product derived from insertion of activated zinc metal into the carbon iodine bond of **3d**, showed the presence of two compounds in a ca. 22:78 molar ratio. They were identified as **6d** and **1d**, respectively (Scheme 3). It must also be noted that attempts to obtain **6d** selectively by a modification of this procedure, i.e. by using 5 equiv. of activated zinc dust or performing the insertion reaction in the presence of 1–3 equiv. of *N*,*N*,*N*′,*N*′-tetramethylenediamine, gave unsatisfactory results. Nevertheless, we succeeded in cleanly synthesizing naturally occurring **6d**,[13] using a protocol very similar to that previously employed to convert aryl triflates into the corresponding arenes.[14] In fact, treatment of **3d** with 2 equiv. of formic acid, 3 equiv. of Et_3N, 2 mol% $Pd(OAc)_2$ and 4 mol% PPh_3 in DMF at 60°C for 3 h gave **6d** in an 83% isolated yield (Scheme 3).

Finally, we found that, in contrast to that reported for the Pd-catalyzed reaction of 2-iodo-1-[2-(trimethylsilyl)ethoxymethyl]indole with the organozinc bromide derived from 5-bromo-2-pyrone, which proved to be low yielding,[3c] the reactions of the organozinc iodides **5a**–**c** with organic electrophiles such as alkenyl or (hetero)aryl halides in THF solution, in the presence of a catalyst precursor constituted of 2 mol% $Pd_2(dba)_3$ and 8 mol% PPh_3, gave the desired 5,6-disubstituted 2-pyrones **7** in fair to good yields. As shown in Table 1, where the results of some of these Pd-catalyzed cross-coupling reactions are summarized, compounds **5a** and **5b** could be reacted with typical activated alkenyl halides such as ethyl (*E*)-3-iodopropenoate (**8a**) (entry 1), with activated (hetero)aryl halides such as 2-bromo-

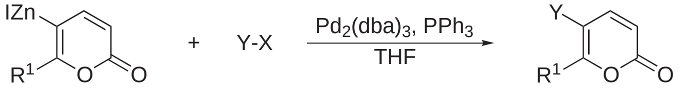


Scheme 2. (a) Activated zinc dust (3 equiv.), THF, rt, 3–3.5 h; (b) 5% HCl, 0°C.

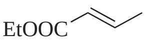
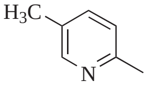
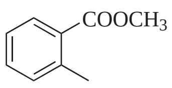
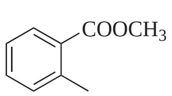
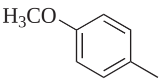
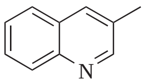
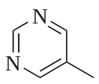


Scheme 3. (a) Activated zinc dust (3 equiv.), THF, rt, 3 h; (b) 5% HCl, 0°C; (c) Et_3N (3 equiv.), HCOOH (2 equiv.), $Pd(OAc)_2$ (2 mol%), PPh_3 (4 mol%), DMF, 60°C, 3 h.

Table 1. Palladium-catalyzed reactions of 5-(iodozinc)-2-pyrones **5** with organic electrophiles **8**[a]



5 **8** **7**

Entry	Organozinc iodide[b]			Electrophile			Reaction conditions		Product
	5	R^1	**8**	Y	X	**5**/**8** molar ratio	h/°C	**7**	Yield (%)
1	**5a**	C_5H_{11}	**8a**		I	1.20	18/20	**7a**	79
2	**5b**[c]	C_6H_{13}	**8b**		Br	0.71	39/20 then 5/70	**7b**	60
3[d]	**5b**[c]	C_6H_{13}	**8c**		Br	0.71	15/20 then 48/70[d]	**7c**	65
4	**5b**	C_6H_{13}	**8c**		Br	1.20	37/70	**7c**	33
5	**5b**	C_6H_{13}	**8d**		I	1.20	15/70	**7d**	68
6	**5b**[c]	C_6H_{13}	**8e**		Br	0.71	15/20 then 48/70	**7e**	64
7	**5a**	C_5H_{11}	**8f**		Br	1.20	44/20	**7f**	72

[a] Unless otherwise noted all the reactions were performed in the presence of 2 mol% $Pd_2(dba)_3$ and 8 mol% PPh_3.

[b] Unless otherwise noted the organozinc iodides were prepared by treatment of iodides **3** with 3 equiv. of activated zinc dust in THF.

[c] This organozinc derivative was prepared by reaction of **3b** with 5 equiv. of activated zinc dust in THF.

[d] This reaction was performed for 15 h at 20°C and for 24 h at 70°C in the presence of $Pd_2(dba)_3$ (2 mol%) and PPh_3 (8 mol%). After this period $Pd_2(dba)_3$ (2 mol%) and PPh_3 (8 mol%) were added and the reaction mixture was stirred at 70°C for 24 h.

5-methylpyridine (**8b**), methyl 2-bromobenzoate (**8c**), 3-bromoquinoline (**8e**) and 5-bromopyrimidine (**8f**) (entries 2–6), as well as with a typical deactivated aryl halide such as 4-iodoanisole (**8d**) (entry 7).[15] Table 1 also shows that, when **5b** was coupled with **8c** using the experimental conditions employed for the synthesis of compounds **7a**, **7d** and **7f**, i.e. preparing **5b** by treatment of **3b** with 3 equiv. of activated zinc dust and using a **5b**/**8c** molar ratio of 1.20, the yield of the desired cross-coupled product **7c** was rather low (entry 4).

Nevertheless, we found that this yield could be significantly improved when this coupling reaction was performed using a **5b**/**8c** molar ratio of 0.71; **5b** was prepared by treatment of **3b** with 5 equiv. of activated zinc dust (entry 3). On the basis of this result, we thought it right to prepare compounds **7b** and **7e** using a protocol very similar to that employed in entry 3 (entries 2 and 6, respectively).

In conclusion, we have shown that easily available 6-substituted 5-(iodozinc)-2-pyrones **5** are synthetically useful organometallic reagents. In fact, they can be conveniently employed for the efficient and selective preparation either of 6-substituted 2-pyrones, which include some natural products, or a large variety of unsymmetrically 5,6-disubstituted 2-pyrones of general formula **7**. The synthesis of compounds **7** from the organozinc iodides **5** complements a procedure recently developed in our laboratory.[6]

Acknowledgements

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References

1. (a) Kvita, V.; Fischer, W. *Chimia* **1992**, *46*, 457–468; (b) Kotretsou, S. I.; Georgiadis, M. P. *Org. Prep. Proced. Int.* **2000**, *32*, 161–167; (c) Stanovnik, B. *J. Heterocyclic Chem.* **1999**, *36*, 1581–1593; (d) Kepe, V.; Polanc, S.; Kocevar, M. *Heterocycles* **1998**, *48*, 671–678.
2. (a) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770–8779; (b) Kalinin, V. N.; Shilova, O. S.; Okladnoy, D. S.; Schmidhammer, H. *Mendeleev Commun.* **1996**, 9–10; (c) Tsuda, T.; Morikawa, S.; Saegusa, T. *J. Chem. Soc., Chem. Commun.* **1989**, 9–10; (d) Liebeskind, L. S.; Wang, J. *Tetrahedron* **1993**, *49*, 5461–5470; (e) Cerezo, S.; Moreno-Mañas, M.; Pleixats, R. *Tetrahedron Lett.* **1998**, *54*, 7813–7818.
3. (a) Afarinkia, K.; Posner, G. H. *Tetrahedron Lett.* **1992**, *33*, 7839–7842; (b) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. *J. Org. Chem.* **1999**, *64*, 690–691; (c) Danieli, B.; Lesma, G.; Martinelli, M.; Passarella, D.; Peretto, I.; Silvani, A. *Tetrahedron* **1998**, *54*, 14081–14088; (d) Chen, C.-H.; Liao, C.-C. *Org. Lett.* **2000**, *2*, 2049–2052.
4. (a) Barrero, A. F.; Oltra, J. E.; Herrador, M. M.; Sanchez, J. F.; Quilez, J. F.; Rojas, F. J.; Reyes, J. F. *Tetrahedron* **1993**, *49*, 141–150; (b) Schlingmann, G.; Milne, L.; Carter, G. T. *Tetrahedron* **1998**, *54*, 13013–13022; (c) Shi, X.; Leal, W. S.; Liu, Z.; Schrader, E.; Meinwald, J. *Tetrahedron Lett.* **1995**, *36*, 71–74; (d) Gehrt, A.; Erkel, G.; Anke, T.; Sterner, O. *Z. Naturforsch.* **1997**, *53c*, 89–92; (e) Claydon, N.; Asllan, M.; Hanson, J. R.; Avent, A. G. *Trans. Br. Mycol. Soc.* **1987**, *88*, 503–513.
5. (a) Rossi, R.; Bellina, F.; Catanese, A.; Mannina, L.; Valensin, D. *Tetrahedron* **2000**, *56*, 479–487; (b) Bellina, F.; Ciucci, D.; Vergamini, P.; Rossi, R. *Tetrahedron* **2000**, *56*, 2533–2545; (c) Rossi, R.; Bellina, F.; Biagetti, M; Catanese, A.; Mannina, L. *Tetrahedron Lett.* **2000**, *41*, 5281–5286; (d) Rossi, R.; Bellina, F.; Raugei, E. *Synlett* **2000**, 1749–1752; (e) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron: Asymmetry* **1999**, *10*, 1163–1172; (f) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 7799–7802; (g) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 7599–7602; (h) Rossi, R.; Bellina, F.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 3017–3020.
6. Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron*, in press.
7. Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2392–2394.
8. A similar reaction has been recently employed for the synthesis of the organozinc bromide corresponding to 5-bromo-2-pyrone: Ref. 3c.
9. The spectral properties of **6a**–**c** were in agreement with those previously reported. See: (a) Pittet, A. O.; Klaiber, E. M. *J. Agric. Food Chem.* **1975**, *23*, 1189–1195 (for **6a** and **6b**); (b) Moss, M. O.; Jackson, R. M.; Rogers, D. *Phytochemistry* **1975**, *14*, 2706–2708 (for **6c**).
10. Compounds **6a**–**c** were prepared according to the following procedure. A mixture of zinc dust (Aldrich, 325 mesh, 1.21 g, 18.48 mmol) and THF (5 ml) containing 1,2-dibromoethane (0.123 g, 0.65 mmol) was stirred under argon at 65°C for 1 min and then it was allowed to cool to 20°C. Chlorotrimethylsilane (0.66 ml, 0.52 mmol) was added and after 20 min at 20°C a solution of a 5-iodo-2-pyrone **3** (6.16 mmol) in THF (15 ml) was added dropwise. The mixture was stirred at 20°C for 3–3.5 h and then it was allowed to settle. The clear solution of the organozinc derivative **5** so obtained was transferred via syringe to a new reaction flask, hydrolyzed at 0°C with 5% HCl and extracted with Et$_2$O. The dried organic extract was concentrated under reduced pressure and the residue was purified by MPLC on silica gel to give the desired compound **6**.
11. Collins, R. P.; Halim, A. F. *J. Agr. Food Chem.* **1972**, *20*, 437–438.
12. Dickinson, J. M. *Nat. Prod. Rep.* **1993**, *00*, 71–98.
13. Dean, F. M. *Naturally-Occurring Oxygen Ring Compounds*; Butterworth: London, 1963; pp. 82–134.
14. Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541–5544.
15. All new compounds were obtained in analytically pure form. Selected spectral properties of compounds **7a**–**f** are as follows. Compound **7a**: mp 35°C. MS, m/z (%): 264 (8), 219 (11), 162 (100), 137 (41), 121 (98), 107 (36), 93 (38). IR (KBr): 1750, 1719, 1638, 1551, 1304, 1181, 834 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 7.59 (1H, d, $J=15.7$ Hz), 7.53 (1H, d, $J=9.8$ Hz), 6.26 (1H, d, $J=9.8$ Hz), 6.15 (1H, d, $J=15.7$ Hz), 4.26 (2H, q, $J=7.5$ Hz), 2.70 (3H, t, $J=7.8$ Hz), 1.72 (2H, t, $J=7.8$ Hz), 1.38–1.29 (3H, m), 1.33 (3H, t, $J=7.5$ Hz), 0.90 ppm (3H, t, $J=7.0$ Hz). Compound **7b**: MS, m/z (%): 271 (7), 215 (22), 214 (29), 201 (100), 186 (25), 158 (18), 130 (23). IR (film): 1736, 1633, 1551, 1487, 1067, 1014, 823 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 8.49 (1H, d, $J=2.6$ Hz), 7.59–7.53 (1H, m), 7.56 (1H, d, $J=9.6$ Hz), 7.21 (1H, d, $J=8.4$ Hz), 6.25 (1H, d, $J=9.6$ Hz), 2.66 (2H, t, $J=7.7$ Hz), 2.39 (3H, s), 1.80–1.64 (2H, m), 1.32–1.18 (6H, m), 0.85 ppm (3H, t, $J=6.6$ Hz). Compound **7c**: MS, m/z (%): 314 (7), 225 (18), 212 (100), 184 (27), 115 (29), 43 (41), 41 (22). IR (film): 1725, 1637, 1549, 1290, 1260, 1087, 768 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 8.04 (1H, dd, $J=7.3$ and 1.9 Hz), 7.59 (1H, ddd, $J=7.5$, 7.5 and 1.7 Hz), 7.49 (1H, ddd, $J=7.5$, 7.5 and 1.7 Hz), 7.23 (1H, dd, $J=7.7$ and 1.5 Hz), 7.18 (1H, d, $J=9.6$ Hz), 6.19 (1H, d, $J=9.6$ Hz), 3.78 (3H, s), 2.26 (2H, t, $J=7.5$ Hz), 1.68–1.50 (2H, m), 1.30–1.10 (6H, m), 0.81 ppm (3H, t, $J=6.6$ Hz). Compound **7d**: MS, m/z (%): 286 (35), 215 (13), 187 (39), 145 (100), 115 (15), 102 (31). IR (film): 1735, 1632, 1610, 1544, 1513, 1248, 825 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 7.28 (1H, d, $J=9.4$ Hz), 7.15 (2H, d, $J=8.8$ Hz), 6.95 (2H, d, $J=8.8$ Hz), 6.21 (1H, d, $J=9.4$ Hz), 3.85 (3H, s), 2.49 (2H, t, $J=7.7$ Hz), 1.75–1.20 (8H, m), 0.84 ppm (3H, t, $J=6.6$ Hz). Compound **7e**: MS, m/z

(%): 307 (43), 237 (24), 222 (26), 208 (57), 167 (38), 166 (100), 140 (20), 43 (24). IR (film): 1736, 1634, 1545, 1464, 1031, 949, 824 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 8.81 (1H, d, $J=2.2$ Hz), 8.15 (1H, d, $J=8.1$ Hz), 8.04 (1H, d, $J=2.2$ Hz), 7.86 (1H, d, $J=8.1$ Hz), 7.79 (1H, ddd, $J=8.1$, 8.1 and 1.7 Hz), 7.62 (1H, dd, $J=7.6$ and 7.6 Hz), 7.38 (1H, d, $J=9.5$ Hz), 6.32 (1H, d, $J=9.5$ Hz), 2.54 (2H, t, $J=7.7$ Hz), 1.75–1.65 (2H, m), 1.29–1.20 (6H, m), 0.81 ppm (3H, t, $J=6.6$ Hz). Compound **7f**: mp 79–81°C. MS, m/z (%): 244 (11), 188 (14), 173 (19), 160 (32), 159 (62), 117 (100), 63 (45). IR (KBr): 1726, 1628, 1540, 1310, 990, 837, 727 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 9.25 (1H, s), 8.68 (2H, s), 7.26 (1H, d, $J=9.6$ Hz), 6.32 (1H, d, $J=9.6$ Hz), 2.48 (2H, t, $J=7.8$ Hz), 1.79–1.60 (2H, m), 1.35–1.15 (4H, m), 0.88 ppm (3H, m).