Iodine-Catalyzed Highly Efficient Synthesis of 3-Alkylated/3-Alkenylated Indoles from 1,3-Dicarbonyl Compounds

Neetu Singh, Krishna Nand Singh*

Department of Chemistry, Faculty of Science, Banaras Hindu University, Varanasi 221005, India
Fax +91(542)2368127; E-mail: knsinghbhu@yahoo.co.in

Received: 26.05.2012; Accepted after revision: 10.06.2012

Abstract: Molecular iodine has been found to be an efficient and inexpensive catalyst for the synthesis of 3-alkylated/3-alkenylated indoles in excellent yields by using different indoles and 1,3-dicarbonyl compounds at room temperature.

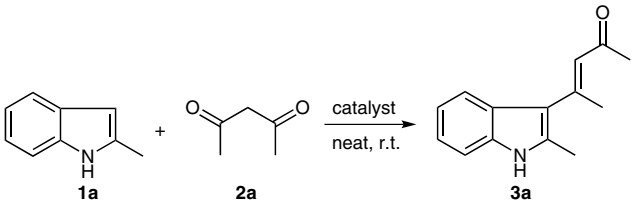
Key words: iodine, 3-alkenylated indoles, 1,3-dicarbonyl compounds, solvent-free, bis(indolyl)carbonyl compounds

The indole nucleus is a ubiquitous heterocycle in nature and represents a 'privileged' structural moiety with a broad spectrum of pharmaceutical and biological activities.[1] Among different substitution patterns, 3-substituted indoles are of special interest as important building blocks for the synthesis of therapeutic agents and display physiological properties such as anticancer, antimigraine, antidepressant, anti-inflammatory, antiestrogen, and antagonist activity.[2] The synthesis and selective functionalization of indoles at the C-3 position have been the focal point of active research over a prolonged period.[3] 3-Alkylated indoles are central compounds in pharmaceutical chemistry, and their direct synthesis involves the conjugate addition of indoles to α,β-unsaturated compounds in the presence of protic and Lewis acids.[4] While these methods for preparing 3-alkylated indoles are well established, there exist only a few reports for the alternative preparation of 3-alkenylated indoles using gold(III) chloride,[5] ionic liquid,[6] and iron(III) chloride.[7] These methods, however, suffer from one or other drawbacks, such as the use of strongly acidic conditions, moisture-sensitive catalysts, or expensive reagents. Therefore, there remains the demand for the development of a mild and efficient method for the preparation of 3-alkenylated indoles.

As molecular iodine (I_2) has received considerable attention as an inexpensive, easily available, and mild Lewis acid catalyst for various organic transformations,[8] it was thought worthwhile to explore the catalytic potential of I_2 and other unexplored catalysts for this particular conversion.

In view of the above and as a part of our ongoing program to develop viable protocols,[9] we report herein an iodine (10 mol%) catalyzed, mild, simple, and efficient procedure for the construction of 3-alkylated/3-alkenylated indoles at room temperature using different indoles and 1,3-dicarbonyl compounds (Scheme 1).

Table 1 Optimization of Reaction Conditions for **3a**



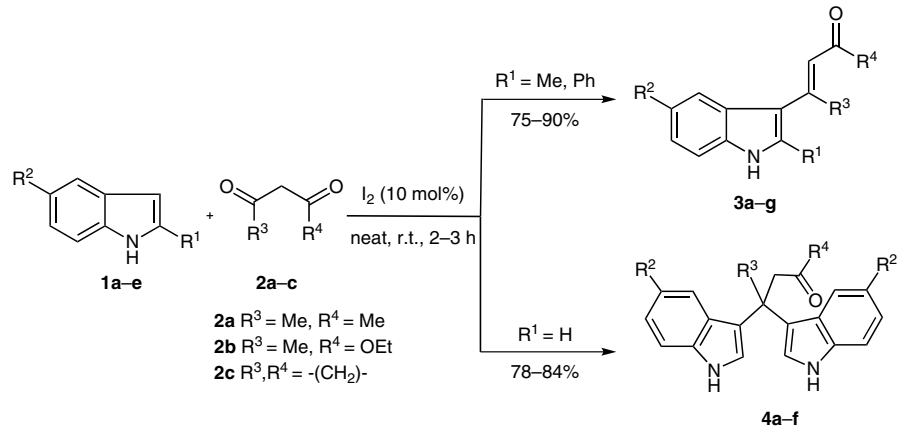
1a **2a** **3a**

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[a]
1	–	–	10	n.r.[b]
2	[bmim]BF_4 (10)	–	10	n.r.[b]
3	[bmim]PF_6 (10)	–	10	n.r.[b]
4	$ZnCl_2$ (10)	–	3	75
5	$MnCl_2·6H_2O$ (10)	–	3	60
6	$AlCl_3$ (10)	–	3	65
7	$NiCl_2·6H_2O$ (10)	–	3	70
8	$CuCl_2$ (10)	–	3	72
9	$LiClO_4$ (10)	–	3	50
10	$NH_2·SO_3H$ (10)	–	4	55
11	I_2 (10)	–	2	90
12	I_2 (10)	CH_2Cl_2	2	90
13	I_2 (10)	MeCN	2	78
14	I_2 (10)	THF	2	75
15	I_2 (10)	EtOH	2	78
16	I_2 (10)	MeOH	2	75
17	I_2 (5)	–	5	70
18	I_2 (15)	–	2	89
19	I_2 (20)	–	2	90

[a] Using an equimolar ratio of **1a** and **2a**.
[b] n.r. = no reaction.

In order to optimize the reaction conditions, the effect of different catalysts and solvents was investigated in detail for a typical reaction of 2-methyl indole (**1a**), and acetyl-

SYNLETT 2012, 23, 2116–2120
Advanced online publication: 03.08.2012
DOI: 10.1055/s-0032-1316684; Art ID: ST-2012-D0457-L



Scheme 1 C-3 Alkylation/alkenylation of indoles

acetone (**2a**). As solvent-free synthesis has gained much current interest, it was considered worthwhile to investigate the reaction under these conditions as well. The outcome is presented in Table 1 where it is evident that no conversion into the product was obtained in the absence of catalyst even after a prolonged reaction time of ten hours (Table 1, entry 1) and so a number of catalysts was then screened. Due to their intrinsic advantages as green catalysts, attempts were made to study the model reaction using some common ionic liquids such as [bmim]BF_4 and [bmim]PF_6, which resulted in no net reaction (Table 1, entries 2 and 3). However, many other catalysts such as $ZnCl_2$, $MnCl_2{\cdot}6H_2O$, $AlCl_3$, $NiCl_2{\cdot}6H_2O$, and $CuCl_2$ promoted the reaction to some extent (Table 1, entries 4–8); whereas catalysts such as lithium perchlorate and sulfamic acid provided relatively low product yields (Table 1, entries 9 and 10). Out of all the catalysts monitored, iodine was concluded to be the best at room temperature under solvent-free conditions to afford the product **3a** in 90% yield (Table 1, entry 11). In terms of catalyst concentration, 10 mol% of iodine was optimum for the effective completion of the reaction (Table 1, entry 11), as the reaction remained incomplete when 5 mol% of the catalyst were used (Table 1, entry 17). No further improvement was observed with 15 mol% or 20 mol% of iodine (Table 1, entries 18 and 19). In order to screen the effect of solvent, the model reaction was undertaken at room temperature using 10 mol% of iodine in different solvents (Table 1, entries 12–16). The best conversion was finally achieved either under solvent-free conditions or in dichloromethane at room temperature (Table 1, entries 11 and 12). To refrain from the use of dichloromethane, iodine (10 mol%) under solvent-free conditions at room temperature was chosen as the optimum condition and was subsequently applied to the reaction of 2-methylindole (**1a**), and 2-phenylindole (**1b**) with 1,3-dicarbonyl compounds such as acetylacetone (**2a**), ethyl acetoacetate (**2b**), and dimedone (**2c**) to afford a variety of 3-alkenylated indole derivatives **3a**–**g** in excellent yields with complete *E* selectivity (Table 2). It is worth mentioning that no side product was obtained under these conditions, albeit some of the reactions did not proceed smoothly under solvent-free conditions, thereby making the use of dichloromethane necessary to achieve desirable conversion (Table 2, entries 3, 6, and 7). It is interesting to note that when 2-unsubstituted indoles such as indole (**1c**), 5-bromoindole (**1d**), and 5-methoxyindole (**1e**), were reacted with 1,3-dicarbonyl compounds, we were confronted with the formation of bis(indolyl)carbonyl compounds **4a**–**f** (Table 2, entries 8–13) rather than the desired adducts.

Table 2 Alkylation/Alkenylation of Indoles with 1,3-Dicarbonyl Compounds[9]

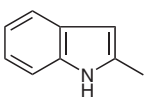
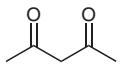
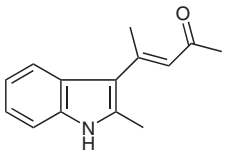
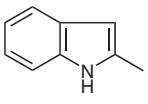
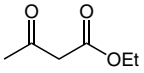
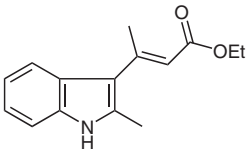
Entry	Indole	1,3-Dicarbonyl	Product	Time (h)	Yield (%)[a]
1	 **1a**	 **2a**	 **3a**	2	90
2	 **1a**	 **2b**	 **3b**	3	76

Table 2 Alkylation/Alkenylation of Indoles with 1,3-Dicarbonyl Compounds[9] (continued)

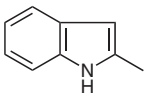
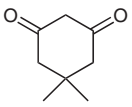
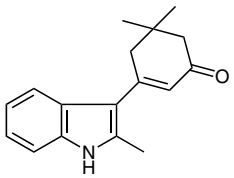
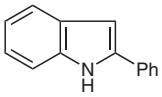
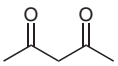
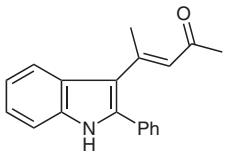
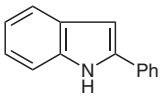
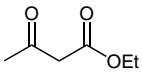
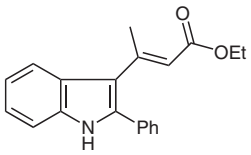
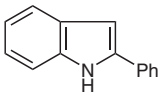
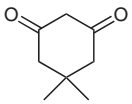
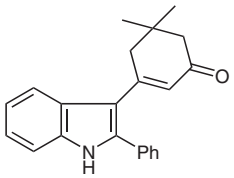
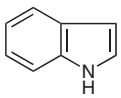
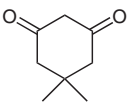
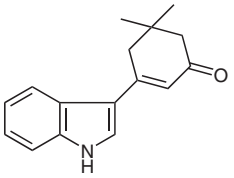
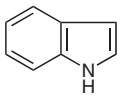
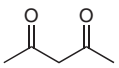
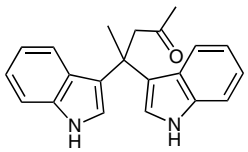
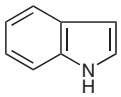
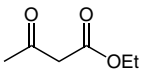
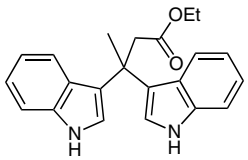
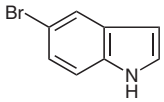
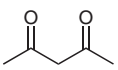
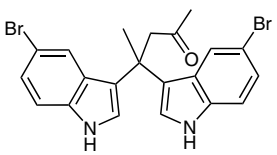
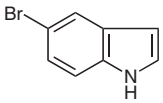
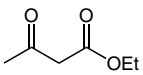
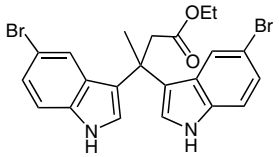
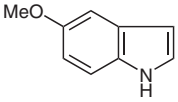
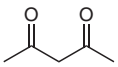
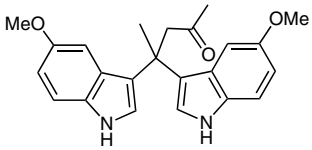
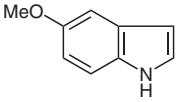
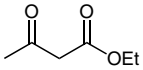
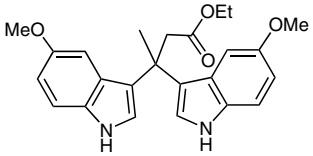
Entry	Indole	1,3-Dicarbonyl	Product	Time (h)	Yield (%)[a]
3	 **1a**	 **2c**	 **3c**	3	82[b]
4	 **1b**	 **2a**	 **3d**	2	80
5	 **1b**	 **2b**	 **3e**	3	78
6	 **1b**	 **2c**	 **3f**	2.5	81[b]
7	 **1c**	 **2c**	 **3g**	2	75[b]
8	 **1c**	 **2a**	 **4a**	2.5	80
9	 **1c**	 **2b**	 **4b**	3	83
10	 **1d**	 **2a**	 **4c**	3	80

Table 2 Alkylation/Alkenylation of Indoles with 1,3-Dicarbonyl Compounds[9] (continued)

Entry	Indole	1,3-Dicarbonyl	Product	Time (h)	Yield (%)[a]
11	 **1d**	 **2b**	 **4d**	2.5	78
12	 **1e**	 **2a**	 **4e**	2	82
13	 **1e**	 **2b**	 **4f**	3	84

[a] Isolated yield.
[b] Using CH_2Cl_2 as a solvent.

In conclusion, we have demonstrated the use of iodine as an efficient, inexpensive, and easy-to-handle catalyst for C-3 alkylation/alkenylation of various indoles with 1,3-dicarbonyl compounds at room temperature, for the most part under solvent-free conditions. Due to the mild and metal-free nature of the reaction, we believe that this process is a useful addition to the available synthetic methodologies.

Acknowledgment

We are grateful to the Council of Scientific and Industrial Research, New Delhi for financial assistance.

References and Notes

(1) (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, **1996**, 113. (b) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489. (c) Li, S.-M. *Nat. Prod. Rep.* **2010**, *27*, 57. (d) Lewis, S. E. *Tetrahedron* **2006**, *62*, 8655.

(2) (a) Rani, P.; SrivastavaV, K.; Kumar, A. *Eur. J. Med. Chem.* **2004**, 449. (b) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry*, 2nd ed., Vol. 2; Pergamon Press: New York, **1996**, 211. (c) Andreani, A.; Burnelli, S.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Varoli, L.; Landi, L.; Prata, C.; Berridge, M. V.; Grasso, C.; Fiebig, H.-H.; Kelter, G.; Burger, A. M.; Kunkel, M. W. *J. Med. Chem.* **2008**, *51*, 4563. (d) Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 175. (e) Hibino, S.; Chozi, T. *Nat. Prod. Rep.* **2001**, *18*, 66. (f) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1.

(3) (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (b) Bartoli, G.; Bencivennia, G.; Dalpozzob, R. *Chem. Soc. Rev.* **2010**, *39*, 4449.

(4) (a) Reddy, A. V.; Ravinder, K.; Niranjan Reddy, V. L.; Gound, T. V.; Ravikanth, V.; Venkateswarlu, Y. *Synth. Commun.* **2003**, *33*, 3687. (b) Chen, D.; Yu, L.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 4467. (c) Sharma, G. V. M.; Reddy, J. J.; Lakshmi, P. S.; Krishna, P. R. *Tetrahedron Lett.* **2004**, *45*, 7729. (d) Kumar, A. V.; Rao, K. R. *Tetrahedron Lett.* **2011**, *52*, 5188. (e) Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700. (f) Bartoli, G.; Bartolacci, M.; Bosco, M.; Foglia, G.; Giuliani, A.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2003**, *68*, 4594. (g) Rajabi, F.; Razavia, S.; Luque, R. *Green Chem.* **2010**, *12*, 786. (h) Hou, X.; Hemit, H.; Yong, J.; Nie, L.; Aisa, H. A. *Synth. Commun.* **2010**, *40*, 973. (i) Ekbote, S. S.; Panda, A. G.; Malhari, D.; Bhor, M. D.; Bhanage, B. M. *Catal. Commun.* **2009**, *10*, 1569. (j) King, H. D.; Meng, Z.; Denhart, D.; Mattson, R.; Kimura, R.; Wu, D.; Gao, Q.; Macor, J. E. *Org. Lett.* **2005**, *7*, 3437.

(5) (a) Arcadi, A.; Alfonsi, M.; Bianchi, G.; D'Anniballe, G.; Marinelli, F. *Adv. Synth. Catal.* **2006**, *348*, 331.

(6) (a) Santra, S.; Majee, A.; Hajra, A. *Tetrahedron Lett.* **2011**, *52*, 3825. (b) Rad-Moghadam, K.; Sharifi-Kiasaraie, M. *Tetrahedron* **2009**, *65*, 8816.

(7) Yadav, J. S.; Reddy, B. V. S.; Praneeth, K. *Tetrahedron Lett.* **2008**, *49*, 199.

(8) (a) Kumar, K. P.; Satyanarayana, S.; Reddy, P. L.; Narasimhulu, G.; Ravirala, N.; Reddy, B. V. S. *Tetrahedron Lett.* **2012**, *53*, 1738. (b) Gao, S.; Tzeng, T.; Sastry, M. N. V.; Chu, C.; Liu, J.; Lin, C.; Yao, C. *Tetrahedron Lett.* **2006**, *47*, 1889. (c) Varala, R.; Nuvula, S.; Adapa, S. R. *J. Org. Chem.* **2006**, *71*, 8283. (d) More, S. V.; Sastry, M. N. V.; Wang, C. C.; Yao, C. F. *Tetrahedron Lett.* **2005**, *46*, 6345. (e) Li, X.; Mao, Z.; Wang, Y.; Chen, W.; Lin, X. *Tetrahedron* **2011**, *67*, 3858. (f) Reddy, B. V. S.; Grewal, H. *Tetrahedron Lett.* **2011**, *52*, 761. (g) Kavala, V.; Lin, C.; Kuo, C.-W.; Fang, H.; Yao, C.-F. *Tetrahedron* **2012**, *68*, 1321. (h) Datta, B.; Madhusudana Reddy, M. B.; Pasha,

M. A. *Synth. Commun.* **2011**, *41*, 2331. (i) Verma, A. K.; Aggarwal, T.; Rustagia, V.; Larock, R. C. *Chem. Commun.* **2010**, *46*, 4064. (j) Lamar, A. A.; Nicholas, K. M. *J. Org. Chem.* **2010**, *75*, 7644. (k) Togo, H.; Iida, S. *Synlett* **2006**, 2159.

(9) (a) Raghuvanshi, D. S.; Singh, K. N. *Synlett* **2011**, 373. (b) Singh, N.; Singh, S. K.; Khanna, R. S.; Singh, K. N. *Tetrahedron Lett.* **2011**, *52*, 2419. (c) Raghuvanshi, D. S.; Singh, K. N. *Tetrahedron Lett.* **2011**, *52*, 5702. (d) Kumari, K.; Raghuvanshi, D. S.; Jouikov, V.; Singh, K. N. *Tetrahedron Lett.* **2012**, *53*, 1130. (e) Allam, B. K.; Singh, K. N. *Tetrahedron Lett.* **2011**, *52*, 5851

General Experimental Procedure for the 3-Alkenylation/3-Alkylation of Indoles (Table 2)

A mixture of indole (1 mmol), 1,3-dicarbonyl compound (1 mmol) and I_2 (10 mol%) was taken in a round-bottom flask and stirred at r.t. for the appropriate time (Table 2). After the completion of reaction as indicated by TLC, a sat. aq solution of $Na_2S_2O_3$ (2 × 5 mL) was added, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic phases were dried over anhyd Na_2SO_4, filtered, and evaporated under reduced pressure to furnish the crude product which was purified by column chromatography.

Spectral Data of some Representative Products

(*E*)-Ethyl-3-(2-methyl-1*H*-3-indolyl)-2-butenoate (3b)

IR (KBr): 3411, 2933, 1718 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.99 (br s, 1 H), 7.65 (d, 1 H, *J* = 7.5 Hz), 7.29–7.25 (m, 1 H), 7.17–7.09 (m, 2 H), 5.92 (s, 1 H), 4.25 (q, 2 H, *J* = 7.2 Hz), 2.66 (s, 3 H), 2.51 (s, 3 H), 1.35 (t, 3 H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 152.0, 135.0, 132.7, 127.0, 121.7, 120.3, 119.5, 117.1, 116.8, 110.4, 59.5, 20.4, 14.4,13.4. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.99; H, 7.06; N, 5.68.

Ethyl 3,3-Bis(1*H*-3-indolyl)butanoate (4b)

IR (KBr): 3406, 3351, 3056, 2938, 1724 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.95 (br s, 2 H), 7.35–7.28 (m, 4 H), 7.10–7.03 (m, 4 H), 6.88 (t, 2 H, *J* = 7.5 Hz), 3.86 (q, 2 H, *J* = 7.2 Hz), 3.37 (s, 2 H), 2.08 (s, 3 H), 0.86 (t, 3 H, *J* = 7.2 Hz). Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.21; H, 6.25; N, 8.01.

4,4-Bis(5-bromo-1*H*-3-indolyl)pentan-2-one (4c)

IR: 3342, 3321, 2966, 1680 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.08 (br s, 2 H), 7.37 (m, 2 H), 7.20–7.13 (m, 6 H), 3.42 (s, 2 H), 1.95 (s, 3 H), 1.60 (s, 3 H). Anal. Calcd for $C_{21}H_{18}Br_2N_2O$: C, 53.19; H, 3.83; N, 5.91. Found: C, 53.11; H, 3.70; N, 5.84.

Ethyl 3,3-Bis(5-bromo-1*H*-3-indolyl)butanoate (4d)

IR (KBr): 3423, 3360, 2976, 1713 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.06 (br s, 2 H), 7.37 (m, 2 H), 7.20–7.14 (m, 6 H), 3.89 (q, 2 H, *J* = 7.2 Hz), 3.28 (s, 2 H), 2.02 (s, 3 H), 0.91 (t, 3 H, *J* = 7.2 Hz). Anal. Calcd for $C_{22}H_{20}Br_2N_2O_2$: C, 52.41; H, 4.00; N, 5.56. Found: C, 53.33; H, 4.05; N, 5.51.

4,4-Bis(5-methoxy-1*H*-3-indolyl)pentan-2-one (4e)

IR (KBr): 3408, 3360, 2934, 1695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.90 (br s, 2 H), 7.22–7.07 (m, 4 H), 6.76–6.73 (m, 4 H), 3.61 (s, 6 H), 3.46 (s, 2 H), 1.95 (s, 3 H), 1.57 (s, 3 H). Anal. Calcd for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43; N, 7.44. Found: C, 73.22; H, 6.43; N, 7.35.

Ethyl 3,3-Bis(5-methoxy-1*H*-3-indolyl)butanoate (4f)

IR (KBr): 3409, 3365, 2978, 1719 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.87(br s, 2 H), 7.19–7.10 (m, 4 H), 6.74–6.71 (m, 4 H), 3.89 (q, 2 H, *J* = 7.2 Hz), 3.61 (s, 6 H), 3.33 (s, 2 H), 2.04 (s, 3 H), 0.90 (t, 3 H, *J* = 7.2 Hz). Anal. Calcd for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.83; H, 6.28; N, 6.78.

