Microwave-Promoted Michael Addition of Azaheterocycles to α,β-Unsaturated Esters and Acid under Solvent-Free Conditions

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Abstract: Regioselective Michael addition of *N*-9 adenine to ethyl acrylate under microwave activation in solid-liquid solvent-free phase-transfer catalysis using TBAB as catalyst and DABCO as base was extended to *tert*-butyl acrylate and acrylic acid. Under these conditions and in the presence of a catalytic amount of KOH, first Michael addition of indole and indolylmaleimide to acrylates is also reported.

Key words: microwave irradiation, Michael addition, azaheterocycles, phase-transfer catalysis, green chemistry

Alkylation of purines and indoles usually results in the formation of regioisomeric mixtures. Treatment of 6-substituted- and 2,6-disubstituted-purines with a base such as sodium hydride followed by addition of an alkylating agent normally produces both 7-and 9-alkylpurines,[1] except with 6-(heteroaryl)purine where regiospecific N-9-alkylation occured.[2] Therefore, functionalization at N-6 or C-8 positions of adenine and derivatives is usually performed with N-9-alkylated product to provide the desired compounds with better regioselectivities and yields.[3] Indole can also suffer from a lack of regioselectivity during N-1-alkylation with formation of the C-3 regiomeric product but can usually be controlled by reaction in basic medium.[4]

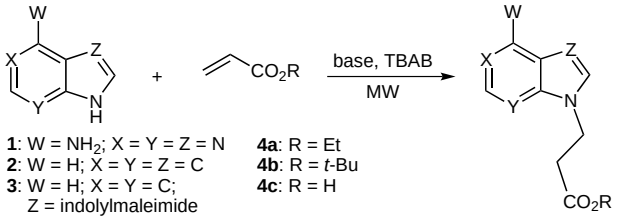
In the course of our ongoing work on ATP mimics, we were interested in functionalizing adenine **1** and alkylating the nitrogen atom of other azaheterocycles, such as indole **2** and bisindolylmaleimide **3** (Scheme 1).[5] Michael addition to α,β-unsaturated carbonyl compounds seems to be a mean of choice to get a short linker bearing a protected group that can be functionalized afterwards to introduce molecular diversity.

For this purpose, microwave irradiation allows performing reactions faster and in higher yields than in a conventional thermal method.[6] The phase-transfer catalyst tetrabutylammonium bromide (TBAB) is a highly microwave-absorbent material that is able to restitute heating around 100 °C in nonpolar reaction mixtures as well as to create a homogeneous medium in solvent-free reactions.

Microwave-assisted Michael addition of *N*-9 adenine **1** to α,β-unsaturated esters has been reported recently in solution[7,8] and under solvent-free conditions.[9,10] Some sterically hindered substituents in α,β-position of the Michael acceptors have been studied but with few alkoxy groups (Me, Et, *n*-Bu). *tert*-Butyl acrylate has only been reported to react with 6-chloropurine in water leading regioselectively to the N-9-alkylated product in 76% yield.[7]

We have been particularly interested in the regioselective addition of *N*-9 adenine **1** to **4a** described by Khalafi-Nezhad et al.[9] in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO), a catalytic amount of TBAB under microwave and solvent-free conditions, leading to compound **5a** in 72% yield. To the best of our knowledge, such conditions have never been described to N-1 position neither of indole **2** nor of bisindolylmaleimide **3** with Michael acceptors **4a**–**c**.

Herein, we report the results concerning the Michael addition assisted by microwave irradiation of azaheterocycles **1**–**3** to ethyl and *tert*-butyl acrylates (**4a**,**b**) and acrylic acid (**4c**) under solvent-free conditions leading to the corresponding derivatives in good yields depending on the presence of an additive base (Scheme 1).



Scheme 1

Performing conjugate addition of adenine **1** to **4a**, under the standard conditions reported by Khalafi-Nezhad,[9] led to the N-9-alkylated **5a** in 78% yield (Scheme 2 and Table 1, entry 1). Ethyl ester hydrolysis of **5a** was performed in HCl (3 N) to furnish the deprotected compound **5c**.

We were also interested in synthesizing functionalized ethenonucleobases for their fluorescent properties. *N*-1,*N*-6-Amino cyclization of adenine **5a** with chloroacetaldehyde in a sodium acetate buffer led to the alkylated etheno derivative **6a**[11] that went back to adenine **5c** during the previous acidic hydrolysis conditions of the ethyl ester.

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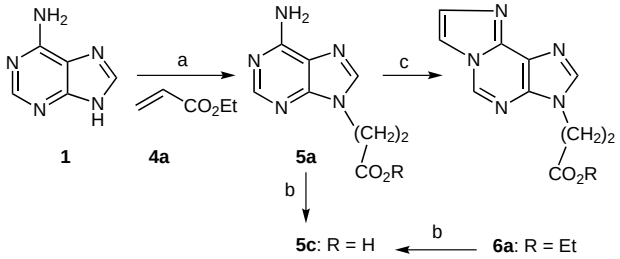
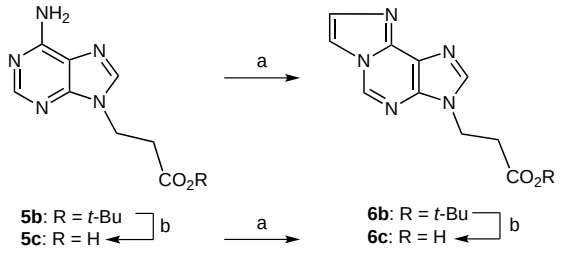


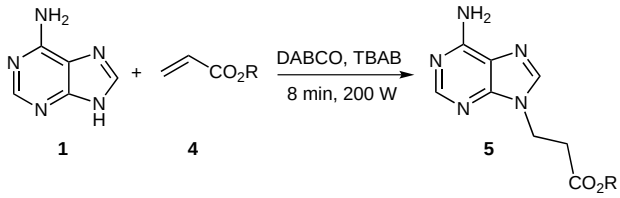
Scheme 2 *Reagents and conditions*: (a) DABCO, TBAB, 200 W, 8 min, 78%; (b) HCl (3 N), reflux, 4 h, 87%; (c) $ClCH_2CHO$, NaOAc, 45 °C, 48 h, 75%.



Scheme 3 *Reagents and conditions*: (a) $ClCH_2CHO$, NaOAc, 45 °C, 48 h, 68% from **5b** and 52% from **5c**; (b) TFA–CH_2Cl_2, r.t., 2 h, 87% from **5b**, and 80% from **6b**.

To overcome this disadvantage, we extended the above reaction to the anhydrous acid-sensitive protected and unprotected Michael acceptors **4b** and **4c**, respectively (Table 1, entries 2 and 3). Interestingly, under the same conditions, compounds **5b** and **5c** were obtained in quite comparable yields from **1** in a 15 mmol scale-up,[12–14] whereas reactions in a tenfold lesser quantity, yields dropped drastically to 17–26%, using a standard vessel. Hence, steric hindrance induced either by the bulky *tert*-butyl group or by the carboxylate salt showed no influence during the reaction, allowing the first preparation in one step of the useful synthon *N*-propanoic acid (**5c**). These encouraging results, added to the fact that ethyl acrylate **4a** has a particularly unpleasant smell, led us to work specifically with the Michael acceptors **4b** and **4c**.

Table 1 Michael Addition of Adenine **1** to Acrylates **4**



Entry	4	R	5	Yield (%)
1	**4a**	Et	**5a**	78[a] (26)[b]
2	**4b**	*t*-Bu	**5b**	71[a] (17)[b]
3[c]	**4c**	H	**5c**	72[a] (22)[b]

[a] Reaction conditions: **1** (15 mmol), molar ratio **1**/**4**/DABCO/TBAB = 1:1.5:1:0.2.
[b] Reactions performed with **1** (1.5 mmol).
[c] In this reaction a molar ratio of **1**/DABCO = 1:2 was used.

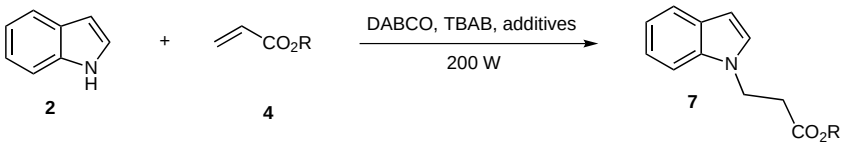
In order to check the relevance of using the *tert*-butylacrylate **4b** in comparison with the acrylic acid (**4c**) during the synthesis of compound **6c**, the alkylated compounds **5b** and **5c** were subjected to the amino cyclization in the conditions previously used for **5a** (Scheme 3) leading to the etheno derivatives **6b** and **6c**.[15] Compounds **5b** and **6b** were then subjected to anhydrous acidic conditions, leading to the corresponding acid derivatives **5c** and **6c** in good yields.

Due to the variety and potent activity exhibited by indole derivatives, we then studied the microwave-assisted Michael addition of indole **2** to acrylates **4** (Table 2) since only one example has been reported in solution but with a C-3-substituted indole.[16] In conventional solution reaction, such Michael acceptors have proved to N-alkylated indole **2** in basic medium,[17] whereas Brønsted acid[18] and Lewis acid[19] catalysts promoted the C-3 alkylation. Interestingly, Michael addition of indole to ethyl 2-(diethylphosphoryl)acrylate in AcOH led to C-3-alkylated compounds and in basic medium to a mixture of both N- and C-3-alkylated products.[20] Under microwave irradiation, Michael addition of indole to β-nitrostyrene in water underwent in C-3 position,[21] whereas to alkyl halide N-alkylation occurred under phase-transfer catalysis.[22]

In the Khalafi-Nezhad's conditions[9] but with a slight excess of DABCO with respect to indole**2**, only 10% reacted with **4b** (Table 2, entry 1) leading regioselectively to **7b**. Indole **2** with a lower acidity than adenine would need a prolonged reaction time and/or a stronger base due to its lowest concentration of the anionic form in the reaction mixture. The presence of four equivalents of both KOH and K_2CO_3, a base mixture previously used with alkyl halide,[22] improved the conversion to 48% and significantly reduced the reaction time to 1.5 minutes until spark appeared (Table 2, entry 2). We could not conclude if the modest yield of compound **7b** was due to a lack of reactivity in this particular heterogeneous mixture or to aza-retro-Michael addition in thermal and basic conditions.[23] Using only KOH as additive base and lowering the amount to 0.4 equivalents dramatically enhance the formation of **7b** to 83% yield (Table 2, entry 3).[24,25] We assume that under microwave activation, TBAB first reacts with KOH to produce tetrabutylammonium hydroxide (TBAOH), as it was postulated in solution.[26] TBAOH seemed to be a highly microwave-absorbent material since the rise in temperature occurred much faster, reducing the reaction time and promoting the reaction in a more efficient manner.

These conditions applied to the ethyl ester **4a** furnished the alkylated indole **7a** but only in 56% yield, probably due to some saponification during the workup, since analytical control of the crude product showed only traces of the starting material **2** (Table 2, entry 4). In the presence of the acrylic acid (**4c**), although no alkylated product **7c**

Table 2 Michael Addition of Indole **2** to Acrylates **4**[a]



Entry	4	Additive (molar ratio)	Time (min)	7	R	Yield (%)
1	**4b**	none	10	**7b**	*t*-Bu	10
2	**4b**	KOH (4), K_2CO_3 (4)	1.5	**7b**	*t*-Bu	48
3	**4b**	KOH (0.4)	1	**7b**	*t*-Bu	83
4	**4a**	KOH (0.4)	1.5	**7a**	Et	56[c]
5[b]	**4c**	KOH (0.8)	1	**7c**	H	0

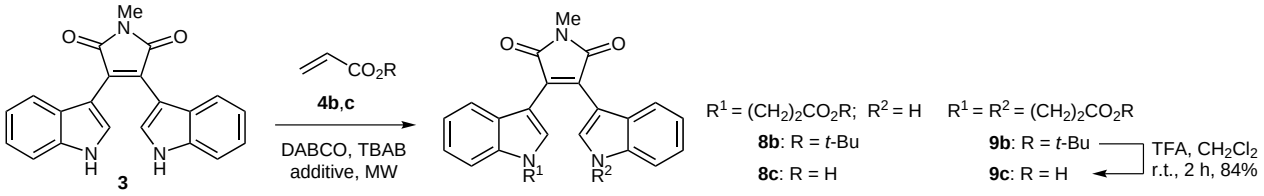
[a] Reaction conditions: **2** (15 mmol), molar ratio **2**/**4**/DABCO/TBAB = 1:1.5:1.2:0.2.
[b] In this reaction a molar ratio of **2**/DABCO = 1:2.4 was used.
[c] Unoptimized conditions.

has been isolated, Michael addition did occur, but was followed by in situ retro-Michael reaction under basic conditions and microwave activation (Table 2, entry 5), as already demonstrated to occur from adeninylpropionic acid under thermal and pressure conditions.[27]

We then applied the best conditions reported in Table 2 (entry 3) to Michael addition of adenine **1** to **4b**. In these basic conditions, the N-9-alkylated compound **5b** was obtained in 62% yield along with a mixture of byproducts resulting from nonregioselective and multialkylations. Although these minor byproducts were not independently isolated, mass spectra allowed identifying from mono- to penta-alkylated products. Indeed, positive ionization showed peaks corresponding to the mono- (264), di- (392), tri- (520), tetra- (648), and penta- (776) alkylated compounds, whereas detection by negative mode furnished peaks at 262, 390, and 518 indicating the presence of some unalkylated compounds at N-9 position.

Under the standard conditions,[9] no reaction occurred between the Michael donor **3** and acrylate **4c** until one equivalent of TBAB was used in combination with 500 W microwave activation, leading to the substituted bisindolylmaleimides **8c** and **9c** (Table 3, entry 1). Likewise, the 2-(trimethylsilyl) ethoxymethyl (SEM) *NH*-bisindolylmaleimide[5] reacted under these conditions, but led predominantly to the unprotected compound **3**. Various attempts to regioselectively produce the monoalkylated **8b** failed, even in the presence of KOH (0.4 equiv, Table 3, entry 2). Nevertheless, under these conditions, the reaction took place with a catalytic amount of TBAB with 200 W power microwave activation, supporting our hypothesis of the formation of TBAOH.

Table 3 Michael Addition of Bisindolylmaleimide **3** to Acrylates **4b** and **4c**



Entry	MW power, time	Reagents (molar ratio)	8	Yield (%)	9	Yield (%)
1	500 W, 20 min	**4c** (3), TBAB (1), DABCO (5)[a]	**8c**	27	**9c**	37
2	200 W, 10 min	**4b** (1), TBAB (0.2), DABCO (1.2), KOH (0.4)[b]	**8b**	9	**9b**	25[c]
3	200 W, 10 min	**4b** (2.4), TBAB (0.2), DABCO (1.2), KOH (0.8)[b]	**8b**	0	**9b**	71

[a] Reactions performed with **3** (0.85 mmol).
[b] Reactions performed with **3** (5 mmol).
[c] Along with 60% of recovered starting material.

Thus, the resulting intermediate **8b** seems to be more reactive towards the alkylation than the starting material **3**. This result is quite different of what is usually observed in solution concerning monoprotection of symmetric bisindolylmaleimide. On the other hand, the bisalkylatedindolylmaleimide **9b** was obtained alone in 71% yield with an excess of Michael acceptor **4b** (Table 3, entry 3) and easily converted into **9c**.

We have shown that previously reported conjugate addition of adenine **1** to ethyl acrylate (**4a**) assisted by microwave activation can be extended to Michael acceptors, *tert*-butyl acrylate (**4b**), and acrylic acid (**4c**), as well as to other Michael donors, indole (**2**) and bisindolylmaleimide (**3**) in the presence of a catalytic amount of KOH, providing a regioselective access in good yields to the corresponding *N*-ethyl and *tert*-butylpropanoate and propanoic acid derivatives that can be further functionalized. In these environmentally friendly conditions, aza-Michael addition with acrylic acid had never been reported yet. Furthermore, *N*-ethyl and *tert*-butyl propanoate are also versatile protective groups of azaheterocycles since after ester hydrolysis, *N*-propanoic acid can easily undergo subsequent retro-Michael addition under basic conditions and thermal or microwave activation.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) (a) Estep, K. G.; Josef, K. A.; Bacon, E. R.; Carabateas, P. M.; Rumneyl, V. S.; Pilling, G. M.; Krafte, D. S.; Volberg, W. A.; Dillon, K.; Dugrenier, N.; Briggs, G. M.; Camiff, P. C.; Gorczyca, W. P.; Stankus, G. P.; Ezrid, A. M. *J. Med. Chem.* **1995**, *38*, 2582. (b) Guillarme, S.; Legoupy, S.; Bourgougnon, N.; Aubertin, A.-M.; Huet, F. *Tetrahedron* **2003**, *59*, 9635.

(2) (a) Zhong, M.; Robins, M. J. *J. Org. Chem.* **2006**, *71*, 8901. (b) Zhong, M.; Nowak, I.; Cannon, J. F.; Robins, M. J. *J. Org. Chem.* **2006**, *71*, 4216.

(3) Legraverend, M. *Tetrahedron* **2008**, *64*, 8585.

(4) Joule, J. A.; Mills, K.; Smith, G. F. *Heterocyclic Chemistry*, 3rd ed.; Chapman and Hall: London, **1995**, 516.

(5) Delarue-Cochin, S.; McCort-Tranchepain, I. *Org. Biomol. Chem.* **2009**, *7*, 706.

(6) (a) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (b) Caddick, S.; Fitzmaurice, R. *Tetrahedron* **2009**, *65*, 3325.

(7) Qu, G.-R.; Zhang, Z.-G.; Geng, M.-W.; Ran, X.; Zhao, L.; Guo, H.-M. *Synlett* **2007**, 721.

(8) Zare, A.; Hasaninejad, A.; Safinejad, R.; Moosavi, Zare. A. R.; Khalafi-Nezhad, A.; Beyzavi, M. H.; Miralai-Moredi, M.; Dehghani, E.; Kazerooni-Mojarrad, P. *ARKIVOC* **2008**, (*xvi*), 61.

(9) Khalafi-Nezhad, A.; Zarea, A.; Rad, M. N. S.; Mokhtari, B.; Parhami, A. *Synthesis* **2005**, 419.

(10) (a) Zare, A.; Hasaninejad, A.; Beyzavi, M. H.; Parhami, A.; Moosavi, Zare. A. R.; Khalafi-Nezhad, A.; Sharghi, H. *Can. J. Chem.* **2008**, *86*, 317. (b) Zare, A.; Hasaninejad, A.; Beyzavi, M. H.; MoosaviZare, A. R.; Safinejad, R.; Khalafi-Nezhad, A.; Asadi, F.; Baramaki, L.; Jomhori-Angali, S.; Ghaleh-Golobi, R. *Synth. Commun.* **2009**, *39*, 139.

(11) Borissow, C. N.; Black, S. J.; Paul, M.; Tovey, S. C.; Dedos, S. G.; Taylor, C. W.; Potter, B. V. L. *Org. Biomol. Chem.* **2005**, *3*, 245.

(12) Esposito, A.; Perino, M. G.; Taddei, M. *Eur. J. Org. Chem.* **1999**, 931.

(13) **Procedure for the Synthesis of 9-(2-*tert*-Butoxycarbonylethyl)adenine (5b)**
Adenine **1** (2.027 g, 15 mmol), DABCO(1.681 g, 15 mmol), TBAB (967 mg, 3 mmol) were ground until a homogeneous mass was obtained, then **4b** (3.27 mL, 22.5 mmol) was added. The reaction mixture was stirred using a dark magnetic bar for 30 min before irradiation at 200 W in a microwave oven. The reaction mixture was suspended in $CHCl_3$ (450 mL) and washed with H_2O (3 × 250 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give 2.81 g (71%) of **5b** as a white powder.

(14) **Spectral and Analytical Data of Compound 5b**
Mp 182–184 °C (lit.[12] 183–185 °C); R_f = 0.6 (CH_2Cl_2–MeOH = 9:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.14 (s, 1H, H-2), 8.09 (s, 1H, H-8), 7.16 (s, 2H, NH_2), 4.34 (t, *J* = 7.0 Hz, 2H, CH_2N), 2.85 (t, *J* = 7.0 Hz, 2H, CH_2CO), 1.31 (s, 9H, CH_3). ^{13}C NMR (500 MHz, DMSO): δ = 169.7 (CO), 155.9 (Cq-Ar), 152.3 (C-2), 149.4 (Cq-Ar), 140.9 (C-8), 118.7 (Cq-Ar), 80.4 (Cq-*t*-Bu), 39.0 (CH_2N), 34.9 (CH_2CO), 27.8 (CH_3). IR: ν = 3292 (NH_2), 1723 (CO) cm^{-1}. MS (ESI$^+$): *m/z* (%) = 264.0 (100) $[M+H]^+$. HRMS (ESI$^+$) calcd for $[C_{12}H_{17}N_5O_2+H]^+$: 264.1457; found: 264.1451.

(15) Karskela, T.; Lönnberg, H. *J. Org. Chem.* **2009**, *74*, 9446.

(16) Jennings, L. D.; Foreman, K. W.; Rush, T. S. III; Tsao, D. H. H.; Mosyak, L.; Kincaid, S. L.; Sukhdeo, M. N.; Sutherland, A. G.; Ding, W.; Kenny, C. H.; Sabus, C. L.; Liu, H.; Dushin, E. G.; Moghazeh, S. L.; Labthavikul, P.; Petersen, P. J.; Tuckman, M.; Ruzin, A. V. *Bioorg. Med. Chem.* **2004**, *12*, 5115.

(17) (a) Robarge, M. J.; Bom, D. C.; Tumey, L. N.; Varga, N.; Gleason, E.; Silver, D.; Song, J.; Murphy, S. M.; Ekema, G.; Doucette, C.; Hanniford, D.; Palmer, M.; Pawlowski, G.; Danzig, J.; Loftus, M.; Hunady, K.; Sherf, B. A.; Mays, R. W.; Stricker-Krongrad, A.; Brunden, K. R.; Harrington, J. J.; Bennani, Y. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1749. (b) Yeom, C.-E.; Kim, M. J.; Kim, B. M. *Tetrahedron* **2007**, *63*, 904. (c) Ferlin, M. G.; Bortolozzi, R.; Brun, P.; Castagliuolo, I.; Hamel, E.; Basso, G.; Viola, G. *ChemMedChem* **2010**, *5*, 1373. (d) Hou, X.; Hemit, H.; Yong, J.; Nie, L.; Aisa, H. A. *Synth. Commun.* **2010**, *40*, 973; and references cited therein.

(18) Cooper, L. C.; Chicchi, G. G.; Dinnell, K.; Elliott, J. M.; Hollingworth, G. J.; Kurtz, M. M.; Locker, K. L.; Morrison, D.; Shaw, D. E.; Tsao, K.-L.; Watt, A. P.; Williams, A. R.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1233.

(19) (a) Mohammadpoor-Baltork, I.; Memarian, H. R.; Khosropour, A. R.; Nikoofar, K. *Heterocycles* **2006**, *68*, 1837. (b) Kumar, V.; Kaur, S.; Kumar, S. *Tetrahedron Lett.* **2006**, *47*, 7001.

(20) Couthon-Gourvès, H.; Simon, G.; Haelters, J.-P.; Corbel, B. *Synthesis* **2006**, 81.

(21) De Rosa, M.; Soriente, A. *Tetrahedron* **2010**, *66*, 2981.

(22) Bogdal, D.; Pielichowski, J.; Jaskot, K. *Heterocycles* **1997**, *45*, 715.

(23) Boncel, S. A.; Mączka, M.; Walczak, K. Z. *Tetrahedron* **2010**, *66*, 8450.

(24) **Optimized Procedure for the Synthesis of 1-(2-*tert*-Butoxycarbonylethyl)indole (7b)**
Indole **2** (1.77 g, 15 mmol), DABCO (1.681 g, 15 mmol), TBAB (967 mg, 3 mmol) were ground until a homogeneous mass was obtained, then **4b** (3.27 mL, 22.5 mmol) was added. The reaction mixture was stirred using a dark magnetic bar for 30 min. KOH (337 mg, 6 mmol) was added, and the mixture was stirred for further 2 min just before irradiation at 200 W in a microwave oven. The reaction mixture was suspended in CH_2Cl_2 (200 mL), washed with H_2O (3 × 200 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (cyclohexane–EtOAc = 99:1) to give 3.06 g (83%) of **7b** as a brown oil.

(25) **Spectral and Analytical Data of Compound 7b**
^{1}H NMR (500 MHz, DMSO): δ = 7.56 (d, *J* = 8.0 Hz, 1 H, H-7), 7.50 (d, *J* = 8.2 Hz, 1 H, H-4), 7.35 (d, *J* = 3.2 Hz, 1 H, H-2), 7.14 (t, *J* = 8.0 Hz, 1 H, H-6), 7.02 (t, *J* = 8.2 Hz, H-5), 6.42 (d, *J* = 3.2 Hz, 1 H, H-3), 4.40 (t, *J* = 6.7 Hz, 2 H, CH_2N), 2.74 (t, *J* = 6.7 Hz, 2 H, CH_2CO), 1.32 (s, 9 H, CH_3). ^{13}C NMR (500 MHz, $CDCl_3$): δ = 170.2 (CO), 135.7, 128.7 (Cq-Ar), 127.8 (C-4), 121.4 (C-5), 120.9 (C-7), 119.3 (C-6), 109.1 (C-2), 101.3 (C-3), 80.7 (Cq-*t*-Bu), 41.7 (CH_2N), 36.0 (CH_2CO), 27.8 (CH_3). IR: ν = 1726 (CO) cm^{-1}. MS (ESI$^+$): m/z (%) = 246.1 (100) $[M+H]^+$. HRMS (ESI$^+$): *m/z* calcd for $[C_{15}H_{19}N_5O_2 + H]^+$: 246.1489; found: 246.1488.

(26) Wang, M.-L.; Liu, B.-L. *J. Chin. Inst. Chem. Eng.* **2007**, *38*, 85.

(27) Lira, E. P.; Huffman, C. W. *J. Chem. Soc.* **1966**, 2188.