Tetrahedron Letters 50 (2009) 4720–4723

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Photochemical cyclization of thioformanilides by chloranil: An approach to 2-substituted benzothiazoles

Valentina Rey, Silvia M. Soria-Castro, Juan E. Argüello, Alicia B. Peñéñory *

INFIQC, Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, 5000 Córdoba, Argentina

ARTICLE INFO

Article history:
Received 5 May 2009
Revised 4 June 2009
Accepted 4 June 2009
Available online 9 June 2009

ABSTRACT

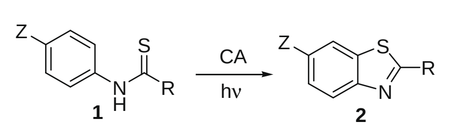
2-Substituted benzothiazoles were efficiently synthesized by radical cyclization of thioformanilides induced by chloranil under irradiation in 1,2-dichloroethane and toluene at 80 °C. Hydrogen atom abstraction from thiobenzamide by triplet chloranil was the key step of the mechanism, as confirmed by LFP experiments. The methodology developed is simple and afforded the easily isolated products from moderate to good yield.

Benzothiazole belongs to an important class of heterocyclic compounds and exhibits a wide range of biological properties as antitumor[1] and antituberculous agents,[2] LTD_4 receptor antagonists,[3] tracers for β-amyloid plaques in Alzheimeŕs disease,[4] calcium channel antagonists,[5] antitrypanosomal activity,[6] etc. Due to these biological activities, the synthesis of benzothiazole is an area of current interest. The classical method for the synthesis involves the condensation of *ortho*-amino thiophenols with substituted aldehydes, nitriles, carboxylic acids, acyl chlorides or esters.[7] This methodology, however, has a limited diversity of commercially available starting materials. Other alternatives to the synthesis of substituted benzothiazole include intramolecular radical nucleophilic substitutions ($S_{RN}1$),[8] Pd or copper-catalyzed[9] cyclization of *o*-halothioformanilides, and Bu_3SnH/AIBN-promoted cyclization of aryl radicals onto thioamides.[10] For the last three approaches, the synthesis of *ortho*-haloaryl amine precursors is the main difficulty observed. By far the most commonly employed procedure is the intramolecular cyclization of thioformanilides induced by potassium ferricyanide in a basic medium, known as Jacobsońs method.[11] In addition to electrochemical oxidations,[12] oxidants such as bromine, iodine,[13] hypervalent iodine such as Dess–Martin periodinane (DMP)[14] and phenyliodine(III) bis(trifluoroacetate) (PIFA),[15] ceric ammonium nitrate (CAN),[15] Mn(III) triacetate,[16] and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[17] have also been used.

As part of our ongoing research on the reactivity of sulfur radical cations generated by photoinduced electron transfer (PET) or chemical electron transfer (CET),[18] we were interested in the study of PET cyclization of thioformanilides (**1**) for the synthesis of benzothiazoles (**2**). For this study we have selected chloranil (CA) as sensitizer, which has been previously employed in PET reactions with sulfides and thiiranes.[18c,19] Thus, we report herein our results on the photoinduced oxidation reaction of thioamides **1** in the presence of CA as a convenient method for the synthesis of heterocycles **2** (Scheme 1).

N-Phenylbenzothioamide (**1a**, Z = H, Ar = Ph) was taken as a model compound to examine the cyclization reaction by CA under a variety of reaction conditions. Initially, we performed the reaction in the polar MeCN as solvent. Its results are summarized in Table 1. When a solution of **1a** with CA (1 equiv) was irradiated at λ_{max} = 365 nm at rt during 3 h of stirring, 38% of the benzothiazole **2a** was obtained. This reaction was almost suppressed with the addition of potassium *tert*-butoxide (1 equiv), working as a good electron donor. In the presence of only 0.5 equiv of CA and under irradiation, the yield of **2a** dropped to 26%. A similar result was found with an excess of CA (2 equiv) with the formation of **2a** in only 27% yield, together with *N*-phenylbenzamide (**3a**) (19% yield). Finally, when a mixture of **1a** and CA (1:1 ratio) was stirred for 3 h in the dark, only a trace of **2a** was observed, whereas **3a** was the main product from a dethioacetalization competitive polar pathway.

The photoinduced reaction of **1a** with CA in 1,2-dichloroethane at rt afforded a similar yield of **2a** in relation to the reaction in MeCN. On the other hand, the formation of **2a** increased to 70% under solvent reflux (83.5 °C), and this reaction did not occur in the dark (Table 2, entries 1–3). According to the results obtained in MeCN, the **1a**/CA ratio of 1:1 gave the best yield of benzothiazole **2a**, whereas 0.5 or 2 equiv of CA decreased the yield of **2a** to 28% and 27%, respectively (Table 2, entries 4 and 5). In order to gain in-



Z = H, OMe; R = *t*-Bu, Ph, 4-C_6H_4-Y (Y = Me, *t*-Bu)

Scheme 1.

* Corresponding author. Tel.: +54 351 4334170; fax: +54 351 4333030.
E-mail address: penenory@fcq.unc.edu.ar (A.B. Peñéñory).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.06.020

Table 1
Photoinduced cyclization reaction of **1a** by CA in MeCN[a]

Entry	Ratio **1a**/CA	Product yield[b] (%)	
		2a	**3a**
1	1:1	38	5
2[c]	1:1	5	14
3	1:0.5	26	5
4	1:2	27	19
5[d]	1:1	<5	30

[a] All reactions run at rt, with 0.2 mmol of **1a** in MeCN (4 mL) under N_2 atmosphere. Irradiation time 3 h.
[b] Determined by GC using the internal standard method, error 5%.
[c] In the presence of *t*-BuOK (1 equiv).
[d] In the dark.

sight into the mechanism of this cyclization reaction, the effect of some additives was also studied, (Table 2). The addition of electron donors[20] better than thiobenzanilide **1a** (E_{ox} = 1.38 eV),[21] such as 1,2,3,5-tetramethoxybenzene (TMB, E_{ox} = 1.09 eV),[22] thiourea (E_{ox} = 0.117 eV),[23] and triethylamine (E_{ox} = 1.15 eV)[22] diminished or inhibited the formation of **2a** after 1 h under irradiation, in comparison with the reaction performed in the absence of any quencher (Table 2, entries 6–9). Furthermore, when the photoinduced reaction of **1a** with CA was carried out in the presence of 1 equivalent of 1,4-cyclohexadiene (1,4-C_6H_8) as hydrogen atom donor, inhibition of the cyclization reaction was observed (Table 2, entry 10).

Triplet chloranil (^{3}CA) is known to react nearly to the diffusion-controlled rate with a number of organic substrates,[24] and can be quenched by ET or hydrogen transfer reaction.[19] To evaluate the possibility of a one-electron oxidation pathway for this cyclization reaction, we examined the effect of the polarity of the solvent. Thus, the photoinduced reaction of **1a** with CA in toluene and benzene afforded 71% and 80% yields of **2a,** respectively, after 3 h at 80 °C. From these results, it can be observed that the isolated yields of **2a** increased as the polarity of the solvent decreased, unexpected for an ET process, which is more favorable in a polar solvent such as MeCN than in the non-polar benzene or toluene.

Therefore, in order to gain a better understanding of the reaction mechanism and the role of the photosensitizer, the triplet quenching of CA by **1a** was investigated by means of laser flash photolysis (LFP) at 355 nm. Figure 1 shows the decay traces obtained for the T-T absorption of CA in the presence of increasing amounts of **1a** in 1,2-dichloroethane as solvent. The triplet quenching rate constant (k_q) was determined as 6.1 × 10^9 M^{-1} s^{-1} (Fig. 1, inset). When MeCN was used as solvent, k_q was equal to

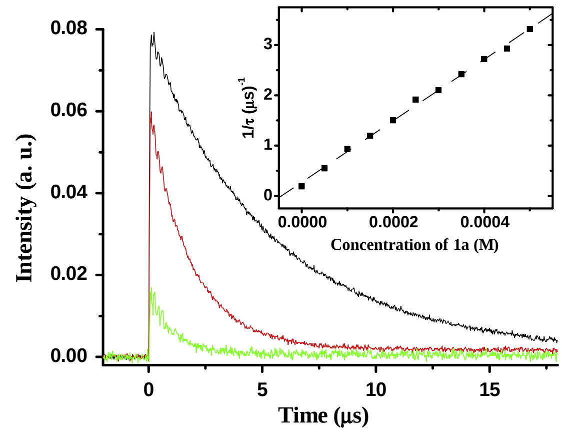


Figure 1. Decay traces of the T-T absorption of CA (1 mM) measured at 510 nm in the presence of increasing amounts of **1a**: 0 M (—), 0.05 mM (—), 0.1 mM (—). Inset: Plot of 1/τ against concentration of **1a** to obtain k_q in 1,2-dicholoroethane.

1.7 × 10^{10} M^{-1} s^{-1}. It became clear that triplet quenching occurred at a near diffusion-controlled rate and no significant solvent effect was observed. While the triplet quenching of CA by **1a** in 1,2-dichloroethane resulted in the formation of a single band with absorption maximum at 430 nm, in MeCN a band with maximum ca. 450 nm was observed. The former corresponded to hydroquinone radical CAH· and the latter was assigned to chloranil radical anion ($CA^{\cdot-}$) (Fig. 2).[19,24] Furthermore, from the LFF experiments in MeCN, the absorption band assigned to $CA^{\cdot-}$ decays without any formation of a new transient.

Taking into consideration the steady-state and LFP experiments, a plausible mechanism for the CA-photosensitized cyclization reactions is outlined in Scheme 2. This involves the initial formation of the triplet chloranil followed by an hydrogen atom transfer from **1a** to ^{3}CA to afford thiyl radical **4** and hydroquinone radical CAH·, (pathway a, Scheme 2). The intramolecular addition of **4** onto the aromatic ring gives the intermediate substituted cyclohexadienyl radical **5**, which by hydrogen transfer to CAH· yields benzothiazole **2**. A similar homolytic aromatic substitution has also been proposed in the cyclization reaction in the presence of various oxidants.[11b,14,16,17] However, this is the first report where the mechanism is stated on the basis of experiments, and supported by proper characterization of the reactive intermediates by LFP. Another possibility of accounting for the formation of benzothiazole is ET from **1a** to ^{3}CA to generate the radical cation of thiobenzamide ($\mathbf{1a}^{\cdot+}$) and $CA^{\cdot-}$, (Scheme 2, pathway b), followed by

Table 2
Photoinduced cyclization reaction of **1a** by CA in 1,2-dichloroethane[a]

Entry	Conditions (**1a**/CA temp, time)	Compound added[b]	Product yield[c] (%)	
			2a	**3a**
1	1:1, rt, 3 h	—	44	<5
2	1:1, 83.5 °C,3 h	—	70	—
3[d]	1:1, 83.5 °C,3 h	—	<5	30
4	1:0.5, 83.5 °C,3 h	—	28	—
5	1:2, 83.5 °C,3 h	—	27	—
6	1:1, 83.5 °C,1 h	—	60	—
7	1:1, 83.5 °C,1 h	TMB	40	<5
8	1:1, 83.5 °C,1 h	Thiourea	35	<5
9	1:1, 83.5 °C,1 h	$N(CH_2CH_3)_3$	<5	[e]
10	1:1, 83.5 °C,3 h	1,4-C_6H_8	62	—

[a] All reactions run with 0.2 mmol of **1a** in 1,2-dichloroethane (4 mL) under N_2 atmosphere.
[b] One equivalent.
[c] Isolated yield.
[d] In the dark.
[e] Major product is benzamide.

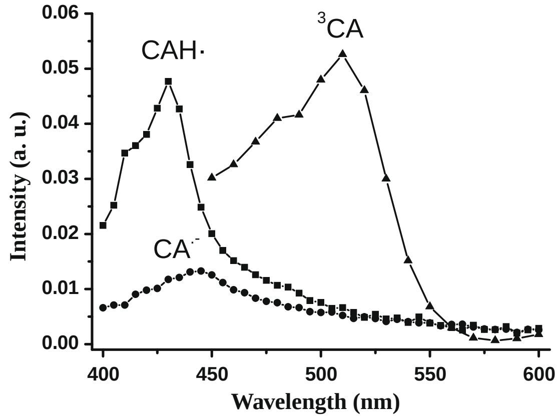
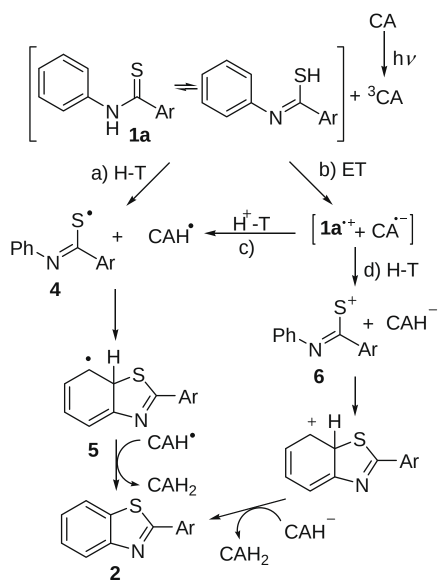


Figure 2. Transient absorption spectra obtained upon LFP (λ = 355 nm) of CA (1 mM), under argon: in the absence of quencher (▲) and in the presence of 1 mM of **1a** in 1,2-dichloroethane (■) and MeCN (●), Spectra recorded 2.5 μs after the laser pulse.



Scheme 2.

deprotonation to yield **4** and CAH$^{\cdot}$, or hydrogen transfer to afford a sulfur-centered cation **6** (pathway c or d, respectively, Scheme 2). Intramolecular electrophilic addition of **6** to the phenyl ring and deprotonation yield benzothiazole **2**. On the basis of the results obtained, an ET process is possible for the reaction conducted in the polar MeCN (pathway b + d), whereas the hydrogen atom transfer is the most feasible process when the reaction is performed in the non-polar benzene or toluene (pathway a). Both mechanisms can take place in 1,2-dichloroethane, (pathways a and b + c). However, the latter pathways are too fast to be observed in the available time window.

Thus, the photosensitizer CA behaves differently depending on the solvent employed. In non-polar solvent ^{3}CA acts as a hydrogen atom acceptor whereas in polar solvent it works as an electron oxidizing agent. Furthermore, these results reveal that hydrogen transfer (pathway a) is more effective for the synthesis of benzothiazoles.

To expand the scope of this procedure,[25] the photoinduced reactions of a variety of thioamides were explored, as illustrated in Table 3. The best yields of benzothiazoles were obtained in toluene at 80 °C after 3 h of irradiation, in comparison with its analogue reaction performed in 1,2-dichloroethane. For example, substrate **1f** afforded 58% yield of the corresponding benzothiazole in 1,2-dichloroethane and the performance of the reaction was improved to 80% yield when toluene was employed as solvent. This methodology is compatible with electron-donating groups (EDGs) on both phenyl moieties, whereas electron-withdrawing substituents (EWGs) on the anilide phenyl ring preclude the cyclization in 1,2-dichloroethane and in toluene. Finally, for **1b** (R = Me) dethioacetalization was the main pathway with the formation of *N*-phenyl-acetamide in both 1,2-dicholoroethane and toluene. On the other hand, substrate **1c** (R = *t*-Bu) afforded 10% yield of the benzothiazole derivative in 1,2-dicholoroethane, and 29% yield in toluene.

Table 3
Photoinduced cyclization reaction of **1** by CA in 1,2-dichloroethane (Method A) or toluene (Method B)[a]

Entry	1	Z	R	2 Yield[b] (%)	
				Method A[c]	Method B[d]
1	**1a**	H	Ph	70	71(80)[e](37)[f]
2	**1b**	H	Me	[g]	<5
3	**1c**	H	*t*-Bu	10[h]	29 (9)[f,i]
4	**1d**	NO_2	Ph	[g]	
5	**1e**	Cl	Ph	[g]	[g]
6	**1f**	OMe	Ph	58	80 (37)[f]
7	**1g**	OMe	4-MeC_6H_4	30	60 (30)[f]
8	**1h**	OMe	4-$tBuC_6H_4$	20	50

[a] All reactions run with 0.2 mmol of **1a** and CA (1 equiv) under N_2 atmosphere. Irradiation time 3 h.
[b] Isolated yield.
[c] In 1,2-dichloroethane under reflux (83.5 °C).
[d] In toluene at 80 °C.
[e] In benzene under reflux (80 °C).
[f] With DDQ instead of CA as sensitizer.
[g] Corresponding amide as the major product.
[h] Corresponding amide in 16% yield.
[i] Corresponding amide in 50% yield.

In a recent paper, the synthesis of benzothiazole by the cyclization of thioformanilides by DDQ was reported[17] and high yields (83–95% yield) in CH_2Cl_2 under laboratory light and without controlled atmosphere were reported.[26] In view of the similarity found between DDQ and CA, we tried DDQ with thioamides **1a**, **1f**, **1g,** and **1h** under different reaction conditions. We have performed diverse experiments with DDQ (1 equiv) in CH_2Cl_2 or $ClCH_2CH_2Cl$ under air or nitrogen atmosphere and at room temperature under laboratory light and under irradiation with medium pressure Hg lamps; and with different reactant concentrations (0.5 M and 0.05 M). The yields of benzothiazoles we have obtained were markedly inferior than those previously reported.[17] For example, the reactions between **1** (**1a**, **1f**, **1g**, and **1h** 0.05 M) and DDQ (1 equiv) in CH_2Cl_2 or $ClCH_2CH_2Cl$ at room temperature after 20 min of stirring under laboratory light afforded a mixture of the corresponding *N*-phenylbenzamide and benzothiazole as well as $DDQH_2$. One drawback of this methodology is the isolation of benzothiazole from the reaction mixture, which can only be improved by using a basic ion-exchange resin.[17b] In general, the isolated yields of the corresponding benzothiazole were modest (<33%). Additionally, the best result obtained for the reaction between **1a** and DDQ was that under photoinduced conditions in toluene at 80 °C, in which **1a** afforded a 37% isolated yield of the benzothiazole **2a** (Table 3, entry 1). On the other hand, the photochemical reaction of **1a** with CA in toluene at 80 °C gave 71% of the isolated benzothiazole **2a**. A similar behavior was observed with **1c**, **1f,** and **1g** (Table 3, entries 3, 6, and 7). The above results clearly show the advantage of the methodology developed here which implies the use of CA under irradiation in a non-polar solvent (Table 3).

In conclusion, for first time we have reported a photocyclization of thioformanilines induced by chloranil in toluene at 80 °C, to afford benzothiazole in moderate to good yields. The method is simple and the heterocycles are easily isolated from the reaction mixture.

Acknowledgments

This work was supported in part by Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Secretaría de Ciencia y Tecnología (SECyT)-Universidad Nacional de Córdoba (UNC), and Fondo para la Investigación Científica y Tecnológica (FONCyT). V.R. gratefully acknowledges receipt of a fellowship from CONICET. The authors thank Prof. S. Bertolotti for LFP facilities.

Supplementary data

Laser flash photolysis spectra of CA and **1b** in 1,2-dichloroethane, MeCN, and benzene, plot of 1/τ against concentration of **1a** to obtain k_q in MeCN (Figures S1, S2, S3, and S4). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.020.

References and notes

1. (a) Bradshaw, T. D.; Westwell, A. D. *Curr. Med. Chem.* **2004**, *11*, 1009–1021; (b) Hutchinson, I.; Bradshaw, T. D.; Matthews, C. S.; Stevens, M. F. G.; Westwell, A. D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 471–474; (c) Yohsida, M.; Hayakawa, I.; Hayashi, N.; Agatsuma, T.; Oda, Y.; Tanzawa, F.; Iwasaki, S.; Koyama, K.; Furukawa, H.; Kurakata, S.; Sugano, Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3328–3332.
2. Palmer, P. J.; Trigg, R. B.; Warrington, J. V. *J. Med. Chem.* **1971**, *14*, 248–251.
3. Lau, C. K.; Dufresne, C.; Gareau, Y.; Zamboni, R.; Labelle, M.; Young, R. N.; Metters, K. M.; Rochette, C.; Sawyer, N.; Slipetz, D. M.; Charette, L.; Jones, T.; McAuliffe, M.; McFarlane, C.; Ford-Hutchinson, A. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1615–1620.
4. (a) Zheng, M.-Q.; Yin, D.-Z.; Qiao, J.-P.; Zhang, L.; Wang, Y.-X. *J. Fluorine Chem.* **2008**, *129*, 210–216; (b) Serdons, K.; Verduyckt, T.; Vanderghinste, D.; Cleynhens, J.; Borghgraef, P.; Vermaelen, P.; Terwinghe, C.; Van Leuven, F.; Van Laere, K.; Kung, H.; Bormans, G.; Verbruggen, A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 602–605.
5. Lara, B.; Gandía, L.; Torres, A.; Olivares, R.; Martínez-Sierra, R.; García, A. G.; López, M. G. *Eur. J. Pharmacol.* **1997**, *325*, 109–119.
6. Neres, J.; Brewer, M. L.; Ratier, L.; Botti, H.; Buschiazzo, A.; Edwards, P. N.; Mortenson, P. N.; Charlton, M. H.; Alzari, P. M.; Frasch, A. C.; Bryce, R. A.; Douglas, K. T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 557–583.
7. (a) Pratap, U. R.; Mali, J. R.; Jawale, D. V.; Mane, R. A. *Tetrahedron Lett.* **2009**, *50*, 1352–1354; (b) Bahrami, K.; Khodaeci, M. M.; Naali, F. *J. Org. Chem.* **2008**, *73*, 6835–6837; (c) Lim, H.-J.; Myung, D.; Lee, I. Y. C.; Jung, M. H. *J. Comb. Chem.* **2008**, *10*, 501–503; (d) Chakraborti, A. K.; Rudrawar, S.; Kaur, G.; Sharma, L. *Synlett* **2004**, 1533–1536.
8. (a) Bowman, W. R.; Heaney, H.; Smith, P. H. G. *Tetrahedron Lett.* **1982**, *23*, 5093–5096; (b) Jayanthi, G.; Muthusamy, S.; Paramasivam, R.; Ramakrishnam, V. T.; Ramasamy, N. K.; Ramamurthy, P. *J. Org. Chem.* **1997**, *62*, 5766–5770.
9. (a) Benedí, C.; Bravo, F.; Uriz, P.; Fernández, E.; Claver, C.; Castillón, S. *Tetrahedron Lett.* **2003**, *44*, 6073–6077; (b) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802–1808; (c) Wang, J.; Peng, F.; Jiang, J.; Lu, Z.; Wang, L.; Bai, J.; Pan, Y. *Tetrahedron Lett.* **2008**, *49*, 467–470.
10. Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119–10128.
11. (a) Shi, D.-F.; Bradshaw, T. D.; Wrigley, S.; McCall, C. *J. Med. Chem.* **1996**, *39*, 3375–3384; (b) Downer, N. K.; Jackson, Y. A. *Org. Biomol. Chem.* **2004**, *2*, 3039–3043.
12. Tabakovic, I.; Trkovnik, M.; Batusic, M.; Tabakovic, K. *Synthesis* **1979**, 590–592.
13. (a) Moghaddam, F. M.; Boeini, H. Z. *Synlett* **2005**, 1612–1614; (b) Downer-Riley, N. K.; Jackson, Y. A. *Tetrahedron* **2007**, *63*, 10276–10281.
14. Bose, D. S.; Idrees, M. *J. Org. Chem.* **2006**, *71*, 8261–8263.
15. Downer-Riley, N. K.; Jackson, Y. A. *Tetrahedron* **2008**, *64*, 4345–4347.
16. Mu, X.-J.; Zou, J.-P.; Zeng, R.-S.; Wu, J.-C. *Tetrahedron Lett.* **2005**, *46*, 4345–4347.
17. (a) Bose, D. S.; Idrees, M. *Tetrahedron Lett.* **2007**, *48*, 669–672; (b) Bose, D. S.; Idrees, M.; Srikanth, B. *Synthesis* **2007**, 819–823.
18. (a) Adam, W.; Argüello, J. E.; Peñéñory, A. B. *J. Org. Chem.* **1998**, *63*, 3905–3910; (b) Peñéñory, A. B.; Puiatti, M.; Argüello, J. E. *Eur. J. Org. Chem.* **2005**, 122–144; (c) Puiatti, M.; Argüello, J. E.; Peñéñory, A. B. *Eur. J. Org. Chem.* **2006**, 4528–4536.
19. Del Giacco, T.; Elisei, F.; Lanzalunga, O. *Phys. Chem. Chem. Phys.* **2000**, *2*, 1701–1708.
20. Oxidation potential versus SCE are given.
21. Waisser, K.; Polasek, M.; Nemec, I.; Exner, O. *J. Phys. Org. Chem.* **2000**, *13*, 127–132.
22. Murov, S. L.; Carmichael, I.; Hug, G. L. *Handbook of Photochemistry*; Marcell Dekker: New York, 1993.
23. Bordwell, F. G.; Ji, G.-Z. *J. Am. Chem. Soc.* **1991**, *113*, 8398–8401.
24. Izquierdo, M. A.; Miranda, M. A. *Eur. J. Org. Chem.* **2004**, 1424–1431.
25. *Representative experimental procedure*: The reactions were carried out in a 10 mL three-necked Schlenk tube, equipped with a nitrogen gas inlet, a condenser, and a magnetic stirrer. The tube was dried under vacuum, filled with nitrogen, and then charged with dried 1,2-dichloroethane or toluene (Method A or B, respectively) (4.0 mL). Thioanilide **1a** (0.2 mmol) and CA (0.2 mmol) were added to the degassed solvent under nitrogen and irradiated for 3 h with a medium pressure Hg lamp emitting maximally at 365 nm at the temperature indicated. After analyzing the reaction mixture by GC and GC–MS, the solvent was evaporated and benzothiazole was isolated by radial or column chromatography. The identity of all the products was confirmed by ^{1}H and ^{13}C NMR and MS spectrometry. All the benzothiazole compounds are known and their data are in good agreement with those reported.
26. The concentration of the reactant in Ref. 17a,b is not given.