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Predicting the reaction mechanism of nucleophilic substitutions at carbonyl and thiocarbonyl centres of esters and thioesters

Rodrigo Ormazábal-Toledo[a]*, Enrique A. Castro[b], José G. Santos[b], Daniela Millán[b], Alvaro Cañete[b], Renato Contreras[a] and Paola R. Campodónico[c]

In nucleophilic substitution reactions at carbonyl centres, there are two possible channels. The first one occurs when the attack of nucleophilic agents takes place simultaneously with the departure of the nucleofuge. This process is named as concerted. The second possibility is the formation of a reaction intermediate, typically a tetrahedral intermediate from which the nucleofuge departs after passing through a second transition state. This second mechanism is defined as stepwise. Whether a concerted or stepwise mechanism is to be expected for a given reaction depends on several factors. Among these determinants are the nucleophilicity of the attacking group, the leaving group ability of the nucleofuge, and the solvent, which affects both the stability of the intermediate or the transition states involved. The role of the electrophilic centre can however become an important factor that can determine the reaction mechanism. In this work we show that the group nucleophilic Fukui function model may be used to rationalize and to predict the reaction mechanism of the title compounds towards alicyclic amines. In general, when the electrophilic carbon centre is attached to the soft sulfur atom, the reaction mechanism is predicted to follow a stepwise route. When the electrophilic carbon atom is attached to a harder oxygen centre, the reaction mechanism is determined by chemical substitution at the nucleofuge moiety. Experimental verification for a set of four substrates is presented.

Supporting information may be found in the online version of this paper

Keywords: carbonyl derivatives; electron density reorganization; group Fukui function; kinetic measurements; reaction mechanisms

INTRODUCTION

The reaction mechanisms of carbonyl and thio derivatives with secondary alicyclic (SA) amine have been extensively studied.[1–26] These reactions have also received attention in the field of organic synthesis[27] and biological chemistry.[28] These processes can follow two reaction pathways: a concerted channel[17–19] or a stepwise route through a zwitterionic tetrahedral intermediate.[17–24] Along the concerted route, the nucleophilic attack at the electrophilic carbon of the C = X group (X = O, S) simultaneously occurs with the leaving group departure. On the other hand, along the stepwise mechanism[17–24] the interaction of the nucleophile with the electrophilic carbon at C = X moiety may lead to the formation of a tetrahedral intermediate, from which the leaving group detaches. The type of reaction pathways is determined by several factors that include, the electrophile–nucleophile pair,[25] the nature of the nucleophile,[24,26] the leaving group ability of the nucleofuge,[29–34] the permanent group electrofugality,[35,36] solvent effects[37,38] and the electrophilicity of the C = X group.[39,40] The latter is not yet completely understood and its effect on the reaction mechanism has been discussed on the basis of experimental evidence using a qualitative *push–pull effect* at the C = X group (see Scheme 1).[41,42]

In Scheme 1, the whole molecule is arbitrarily partitioned into three fragments that include the permanent group (PG) CH_3CH_2–Z (Z = O, S), the electrophilic centre (EC) C = X (X = O, S) and the leaving group (LG) Y–ϕ–$(NO_2)_n$; (Y = O, S and n = 0, 1, 2, 3). The total combination yields 32 substrates (see Tables 1 and 2).

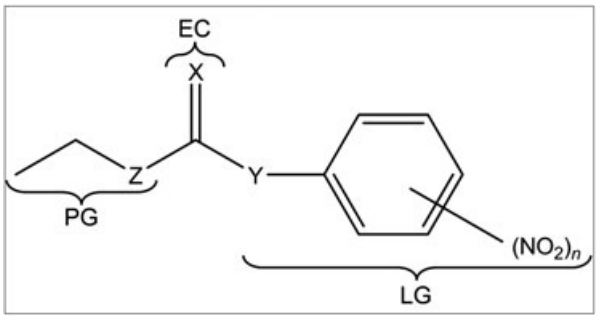
The present study begins with a theoretical analysis of these processes that focuses on the electron density reorganization within the substrates that results after varying the nature of the electrophilic centre and chemical substitution at the permanent and leaving groups. With this information at hand it becomes possible to anticipate the reaction mechanism (concerted or stepwise) that is expected for each combination. The theoretical analysis is first validated against known experimental data and then it is applied to predict the reaction mechanism of four substrates not experimentally

* *Correspondence to: Rodrigo Ormazábal-Toledo, Departamento de Química, Facultad de Ciencias, Universidad de Chile, Casilla 653, Santiago, Chile. E-mail: rormazabal@u.uchile.cl*

a *R. Ormazábal-Toledo, R. Contreras*
Departamento de Química, Facultad de Ciencias, Universidad de Chile, Casilla 653, Santiago, Chile

b *E. A. Castro, J. G. Santos, D. Millán, A. Cañete*
Facultad de Química, Pontificia Universidad Católica de Chile, Casilla 306, Santiago 6094411, Chile

c *P. R. Campodónico*
Instituto de Ciencias, Facultad de Medicina, Clínica Alemana Universidad del Desarrollo, código postal 771-0162, Santiago, Chile



Scheme 1. General partition of the molecules in the present study. PG, LG and EC stands for permanent group, leaving group and electrophilic centre, respectively

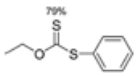
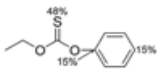
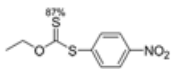
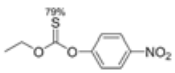
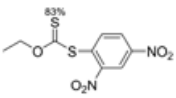
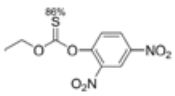
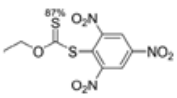
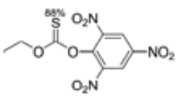
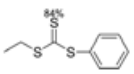
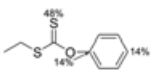
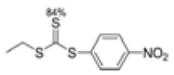
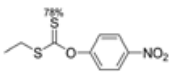
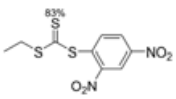
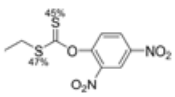
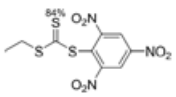
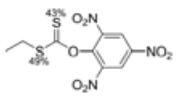
reported to date. These latter cases are verified here by performing experimental kinetic studies.

RESULTS AND DISCUSSION

For the series of thio-carbonyl (Table 1) and carbonyl (Table 2) derivatives,[7,16] we evaluated the group nucleophilic Fukui function of the three fragments EC, LG and PG in the molecule using the well-known model based on the condensed to atom nucleophilic Fukui function (FF).[29–32,35,36,43,44] The group nucleophilic Fukui function at region *Z* is easily implemented as follows:

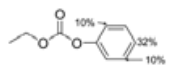
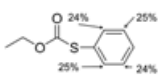
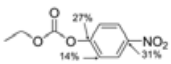
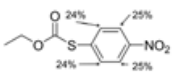
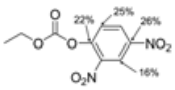
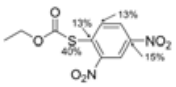
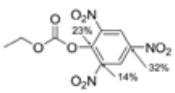
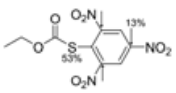
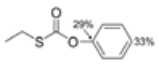
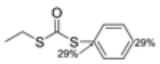
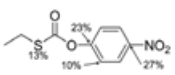
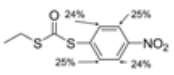
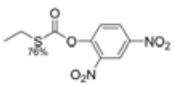
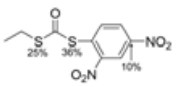
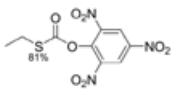
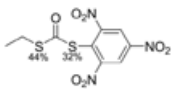
$$f_Z^- = \sum_{k \in Z} f_k^- \quad (1)$$

Table 1. Percentages of nucleophilic Fukui function on the fragments in thiocarbonyl derivatives and their reaction mechanisms[a]

Entry	Molecule[b]	EC	LG	PG	Exp[c]	Pred[d]	Entry	Molecule[b]	EC	LG	PG	Exp[c]	Pred[d]
1.1		81	17	2	S	S	3.1		50	49	1	S	S
1.2		89	9	2	S	S	3.2		83	15	2	S	S
1.3		86	12	2	S	S	3.3		91	7	2	S	S
1.4		90	8	2	S	S	3.4		93	5	2	-	S
2.1		85	9	6	—	S	4.1		50	47	3	—	S
2.2		86	8	6	—[e]	S	4.2		81	13	6	S[e]	S
2.3		85	9	7	—[e]	S	4.3		50	1	49	S[e]	S
2.4		86	8	7	—	S	4.4		47	1	52	—	S

[a]S, stepwise mechanism; C, concerted mechanism.
[b]The structures present the atoms on which the percentage of the nucleophilic Fukui function is greater than 10%.
[c]Experimental values from references.[4,5]
[d]Predicted values.
[e]Experimental validation based on kinetic study in this work.

Table 2. Percentages of nucleophilic Fukui function on the fragments in carbonyl derivatives and their reaction mechanisms[a]

Entry	Molecule[b]	EC	LG	PG	Exp[c]	Pred[d]	Entry	Molecule[b]	EC	LG	PG	Exp[c]	Pred[d]
5.1		1	99	0	—	S	7.1		0	100	0	S	S
5.2		1	98	0	S	S	7.2		0	100	0	S	S
5.3		1	99	0	C	C[f]	7.3		3	96	1	C	C
5.4		1	98	0	C	C[f]	7.4		3	95	1	C	C
6.1		1	99	0	—	S	8.1		5	93	2	—	S
6.2		1	88	11	S	S	8.2		0	99	0	S[e]	S
6.3		6	11	83	C	C	8.3		1	72	27	S[e]	S[f]
6.4		8	3	89	—	C	8.4		1	52	48	—	S[f]

[a]S, stepwise mechanism; C, concerted mechanism.
[b]The structures present the atoms on which the percentage of the nucleophilic Fukui function is greater than 10%.
[c]Experimental values from references.[6–8]
[d]Predicted values.
[e]Experimental validation based on kinetic study in this work.
[f]Borderline. See text for details.

where f_k^- is the condensed to atom nucleophilic FF. This may be easily obtained from a single point calculation at the minimum energy geometry of molecules, using a method described elsewhere.[43,44] The group nucleophilic FF formalism is a suitable model for this study because this regional index assesses well the change in electron density when the system changes the number of electrons (N) by chemical substitution. In other words, a global change in N (ΔN) results in a semi-local response at different sites or groups in the molecule.

For the C = S series (see families 1–4 in Table 1),[7,11] the major percentage in nucleophilic Fukui function is concentrated at the sulfur atom as compared with the C = O series (see families 5–8 in Table 2).[12–16] This result emphasizes the higher nucleophilicity of S atom versus O atom in these systems, a result probably traced to the higher polarizability of the C = S versus C = O bond. Note that this result may be used to quantitatively explain the *push effect* proposed in references.[41,42] The *pull effect* arises when the double bond of the C = X fragment is restored after the nucleophilic attack at the carbocation centre C. This latter process is easier for X = O.

On the other hand, for the C = O series (see families 5–8 in Table 2) the electronic charge is shifted towards the PG and LG groups because the C = O bond is polarized to a greater extent. Whether or not the mechanism is concerted or stepwise depends on the nature of the LG and PG groups.[29–31,35,36] In these series the regional nucleophilicity is condensed on the aromatic ring.[29–31] This distribution may be explained on the basis of resonant and inductive effects[45–47] induced by the presence of $-NO_2$ substituents at the LG. For instance, in compound **5.1** (which does not include NO_2 groups) the regional nucleophilicity is equally distributed on the aromatic moiety,

while in compound **5.2** the nucleophilic FF is localized at –*para* position. Note that in compounds **5.3** and **5.4** there is an additional inductive effect promoted by the incorporation of a second and third $–NO_2$ groups in *meta* and *ortho* positions.

The *push–pull effect* at the C = X groups is finally reflected on the expected reaction mechanism. For instance, for the series 1–4, which correspond to an electrophilic centre with X = S, the corresponding reaction mechanisms are predicted to follow a stepwise channel.[7–11] This result may be traced to the strong stabilization of the tetrahedral intermediate; the *pull effect* polarizes the C = S bond thereby creating a more favourable carbocation centre, which facilitates the formation of a tetrahedral intermediate with the attacking amines.[7–11] Note that this effect is more pronounced for families 1 and 2,[7–9] where about 80% of nucleophilicity is concentrated at the sulfur atom directly attached to the carbonyl carbon centre. In these cases, the presence of a sulfur atom at the LG moiety increases its nucleophilicity thereby deactivating this fragment to act as a good nucleofuge. This is because a good leaving group is in general characterized by a high value of its group electrophilicity rather than its group nucleophilicity.[32]

For families 3[10,11] and 4 this effect is smaller. For instance for series 4, a significant amount of nucleophilic FF begins to concentrate at the S atom of the PG. Compounds **4.1** and **4.2** display similar patterns of concentration of nucleophilicity at the S atom of the EC centre, and the expected reactivity is similar to that shown by compounds **1.1**[7–9] and **1.2**,[7–9] and therefore, the reaction mechanism is consistently predicted as stepwise.[7–9] Compounds **4.3** and **4.4** on the other hand present significant distribution of nucleophilicity at the PG. A high nucleophilicity at the PG emphasizes its role as electrofuge in the reaction.[32] Note that both sulfur centres at the EC and PG cooperatively contribute to the stabilization of the carbocation, which leads to a significant stabilization of the tetrahedral intermediate, thus favouring a stepwise mechanism.[7–11] This prediction is subjected to testing by performing an experimental kinetic study that we discuss in the next section. For series 3, both the PG and LG bear an oxygen atom attached to the EC. For this series the picture is similar to that shown by series 1: the higher concentration in nucleophilic FF is again located at the sulfur atom of the EC moiety, and therefore the reaction mechanism is expected to follow a stepwise route.[7–9] In summary, compounds included in series 1–4 are systematically predicted to follow a stepwise reaction mechanism[7–11] while for compounds with X = O this result is not that general.[12–16]

We now proceed with the analysis of series 5–8.[12–16] In these series the effect is more complicated because there are several factors that contribute to the reaction mechanism. In series 6,[14] there are two patterns. Molecules **6.1** and **6.2**[14] are predicted to follow a stepwise route[14] because the nucleophilic FF is preferentially centred at the aromatic ring leading to a stabilization of the zwitterionic intermediate by a resonant factor. Compounds **6.3**[15] and **6.4** show an enhanced nucleophilicity at the S atom on the PG. Note that in this case there is no longer cooperative effects of the S atom at PG and the O atom at C = X. The concentration of nucleophilicity is clearly higher at the sulfur centre of the PG compared with compounds **4.3** and **4.4**, but this time the enhanced nucleophilicity at the S centre of the PG does not contribute to the stabilization of the intermediate, thereby favouring a concerted mechanism, in agreement with the experiment. Compounds **7.1**[15,16] and **7.2**[15,16] show a similar pattern to that displayed by compounds **6.1** and **6.2**[15] and therefore their mechanism may be classified as stepwise,[15,16] also in agreement with the experiment. For compounds **7.3**[15,16] and **7.4**,[15,16] on the other hand, the high nucleophilicity of the S atom at the LG suggests that the electron density flux will more likely be towards the LG rather to the oxygen atom at the EC group, thereby stabilizing the LG^- anion and the mechanism may probably follow a concerted route.[15,16] Compounds **8.1** and **8.2** show a similar pattern to that displayed by compounds **7.1**[15,16] and **7.2**[15,16] and therefore their reaction mechanism will more likely be stepwise. However, compounds **8.3** and **8.4** display an enhanced nucleophilicity at the sulfur centres vicinal to the EC group. This effect, if cooperative, will also contribute to the stabilization of the intermediate and their reaction mechanism may be classified as stepwise.

For the family of carbonates 5[12,13] (X = Y = Z = O) the picture is even more complex. For compounds **5.1** and **5.2**[12,13] the electronic analysis is similar to that displayed by compounds **8.1** and **8.2**, and therefore the expected reaction mechanisms would be stepwise. However, for compounds **5.3**[12,13] and **5.4**,[12,13] the distribution of group nucleophilicity is quite different to the other cases discussed above. Note that for these compounds, there is no significant regional nucleophilicity at the oxygen centres on the PG, LG and EC fragments. The entire nucleophilicity pattern is concentrated at the aromatic ring of the LG. For this reason there is no clear argument to cleanly classify the type of reaction mechanism based on the group nucleophilic FF for compounds **5.3** and **5.4**. Therefore, the corresponding mechanisms are predicted as borderline, albeit a concerted route could be feasible if nitro substitution leads to an enhancement of the nucleofugality of the corresponding LG.

To test the predictive power of the model, we synthesized compounds **2.2**, **2.3**, **4.2**, **4.3**, **8.2** and **8.3** (see notes and Tables 1 and 2, respectively). We performed the kinetic measurements towards reaction with a series of SA amines. The Brønsted type-plots (*log* of rate coefficients vs. pK_a values) were analyzed for compounds **4.2**, **4.3**, **8.2** and **8.3** (see Figures S1 and S2). The Brønsted type-plots (statistically corrected) for compound **4.2** and **4.3** are linear with β values of 0.16 and 0.31, respectively. The values of the Brønsted slopes are in accordance with a stepwise mechanism where the first step is rate determining.[20–24]

The Brønsted type-plot (statistically corrected) for compound **8.2** is linear with a slope value $\beta = 0.9$, in accordance with a stepwise mechanism.[20–24] For compound **8.3** the Brønsted type-plot (statistically corrected) is curved with extreme β values of 0.1 and 0.8. The curved Brønsted plot is explained by a change in the rate-determining step, from the formation to the breakdown of $T^{\pm}$, as the amine becomes more basic.[1] Compounds **2.2** and **2.3** were synthesized; however, they did not react toward SA amines. This outcome is in accordance with the electronic structure of substrates 2: the high polarizability of the three sulfur atoms surrounding the electrophilic centre enhances the probability of obtaining an aromatic nucleophilic substitution product.

CONCLUDING REMARKS

In summary, the theoretical and experimental study on a series of 32 carbonyl and thio-carbonyl derivatives that undergo nucleophilic substitution reactions towards SA amines can be used to rationalize and to predict the reaction mechanism that is operative in each system. In general, when the electrophilic carbon centre is attached to the soft sulfur atom, the reaction mechanism is always

predicted to follow a stepwise route.[4] When the electrophilic carbon atom is attached to an oxygen atom, the reaction mechanism is determined by the electron density reorganization promoted by chemical substitution at the nucleofuge moiety.[12,16]

EXPERIMENTAL SECTION

Computational details

The 32 molecules compiled in Tables 1 and 2 were fully optimized at the Hartree–Fock (HF)/6-311G(d,p) and Becke, three-parameter, Lee–Yang–Parr (B3LYP)/6-311G(d,p) level of theory using the GAUSSIAN 03 suite of programs.[48] After the optimization procedure, frequency calculations were performed to confirm that the stationary points were true ground states (i.e. with no imaginary frequencies). Single point calculations on these optimized structures were carried out at the HF/6-311G(d,p) level of theory to obtain the population analysis and the group nucleophilic Fukui functions.[43,44] We have performed additional calculations by optimizing the structures at B3LYP/6-311G(d,p) level of theory and then we evaluated the FF using HF/6-311G(d,p) for the whole set of molecules. The HF approach has been reported to be the best method to evaluate the derivatives of the electron density with respect to the number of electrons (see reference [44]). Therein, it is shown that DFT methods for the FF calculations produce spurious negative values, especially when large basis sets, including polarization, functions are used.

Even though the calculation of nucleophilic FF were performed for compounds bearing an ethyl group on the permanent moiety the distribution of this semilocal index does not differ from the methyl derivative used in some kinetic measurements. The detailed calculation is included as supporting information.

Synthesis and characterization

Compounds **8.2** and **8.3**, were synthesized by the reaction of the corresponding benzenethiol with methyl chlorothiolformate, in dry THF, in the presence of triethylamine and N_2 atmosphere.[49,50] The analytical properties of these compounds are shown in the supporting information (Tables S1–S6). Compounds **2.2**, **2.3**, **4.2**, **4.3**, were synthesized by the reaction of the corresponding nitrobenzenethiol or nitrophenol derivative with CS_2, in acetone, in the presence of K_3PO_4. The synthesis details and analytical properties of these compounds are shown in the supporting information (Tables S1–S6). ^{1}H and ^{13}C NMR spectra were obtained, using tetramethylsilane as internal reference, and $CDCl_3$ and dimethyl sulfoxide (DMSO)-d_6 solutions. Electron Ionization-Mass Spectrometry (EI-MS) experiments were performed. The accurate mass measurements were performed at a resolution of 9000–10 000 (10% valley definition) by voltage scanning using perfluorokerosene. Column chromatography was performed on silica gel. All reagents used were of analytical reagent grade.

Compound 2.2: yield, 85%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.55 (s, 3H); 7.28 (d, 2H, J = 9.1 Hz); 8.13 (d, 2H, J = 9.1 Hz); ^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm): 14.4; 123.9; 124.5; 125.0; 126.3; 149.0; 205.1. HRMS (EI$^+$) *m/z* $C_8H_7NO_2S_3$ Calcd. 244.96389, found 244.96310

Compound 2.3: yield, 75%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.62 (s, 3H); 7.54 (d, 1H, J = 9.0 Hz); 8.40 (dd, 1H, J_1 = 9.0, J_2 = 2.5 Hz); 9.11 (d, 1H, J = 2.5 Hz). ^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm): 16.44; 121.7; 126.3; 127.7; 143.7; 144.5;162.1; 187.1; HRMS (EI$^+$) *m/z* $C_8H_6N_2O_4S_3$ Calcd. 289.94897, found 289.94639.

Compound 4.2: ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.15 (s, 3H); 6.9 (d, 2H, J = 9.31 Hz); 8.1 (d, 2H, J = 9.4 Hz).^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm): 14.4; 123.1; 124.5; 144.0, 157.19, 192.06. HRMS (EI$^+$) *m/z* $C_8H_7NO_3S_2$ Calcd. 228.98673, found 228.98589.

Compound 4.3: ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.55 (s, 3H); 6.33 (d, 1H, J = 9.77 Hz); 7.74 (dd, 1H, J_1 = 3.2, J_2 = 9.78 Hz); 8.6 (d, 1H, J = 3.2 Hz);. ^{13}C-NMR (400 MHz, DMSO-d_6) δ (ppm): 16.6; 122.6; 126.3; 128.8; 144.6; 147.5; 163; 193. HRMS (EI$^+$) *m/z* $C_8H_6N_2O_5S_2$ Calcd. 273.97181, found 273.97364.

Compound 8.2: ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 2.47 (s, 3H); 7.69 (d, 2H, J = 9.0 Hz); 8.26 (d, 2H, J = 9.0 Hz). ^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm): 13.7, 124.1, 135.2, 135.3, 135.6, 207; HRMS (EI$^+$) *m/z* $C_8H_7NO_3S_2$ Calcd. 228.98673, found 228.98589.

Compound 8.3: ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.52 (s, 3H); 8.08 (d, 1H, J = 8.7 Hz); 8.45 (dd, 1H, J_1 = 8.7, J_2 = 2,4 Hz); 8.89 (d, 1H, J = 2.4 Hz). ^{13}C-NMR (400 MHz, DMSO-d6) δ (ppm): 13.90; 120.6; 126.6; 132.3; 137.1; 147.5; 147.7; 213.3; HRMS (EI$^+$) *m/z* $C_8H_6N_2O_5S_2$ Calcd. 273.97181, found 273.97126

Kinetic measurements

The kinetics of the reactions were analyzed through a diode array spectrophotometer in water, at 25.0 ± 0.1 °C and an ionic strength of 0.2 M (maintained with KCl). The reactions were followed at the 300–500 nm wavelength range. All reactions were studied under at least a 10-fold amine excess over the substrate, with the initial concentration of the latter being 2.5 × 10^{-5} M. For the reactions of 4.2, 4.3, 8.2 and 8.3, pseudo-first-order rate coefficients (k_{obsd}) were found throughout, the kinetics being measured for at least four half-lives at 400 nm, following 4-nitro and 2,4-dinitro phenoxide or thiophenoxide anions formation.

Product studies

These assays were carried out using UV–Vis spectrophotometry, by comparison of the spectra at the end of the reactions with those corresponding to authentic samples.

SUPPORTING INFORMATION

Supporting Information may be found in the online version of this article.

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