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Original TDAE strategy using α-halocarbonyl derivatives

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ABSTRACT

We report herein the selective C–C bond formation by the reaction of nitrobenzyl carbanions, formed via the TDAE strategy, with α-haloesters and α-haloamides. This reaction, extended in benzodioxole and dimethoxybenzene series provides new potentially CNS active agents.

1. Introduction

Benzodioxole and dimethoxybenzene moieties are present in the structure of a large number of biologically active compounds acting in various therapeutic domains: oncology with etoposide[1] and CNS pharmacology. Thus, paroxetine (Fig. 1) has become a commonly prescribed antidepressant[2] and piribedil is employed for its dopaminergic action against cognitive pathological deficit.[3] Furthermore, they represent protected forms of catechol moiety, scaffold of catecholamines and also included in the structure of entacapone.[4] This is used in the treatment of Parkinson's disease, as adjuvant to levodopa therapy. Otherwise, some 3-(3,4-dimethoxyphenyl)propanamide and 3-(benzodioxol-5-yl)propanamide scaffolds have recently revealed interesting analgesic and antipyretic properties.[5] Therefore, the development of new synthetic methodologies of benzodioxole and dimethoxybenzene derivatives appears quite important.

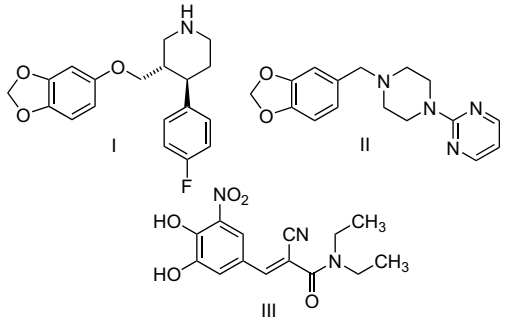

Figure 1. Structures of paroxetine (I), piribedil (II) and entacapone (III).

Tetrakis(dimethylamino)ethylene (TDAE) is an organic reducing agent,[6] which reacts with haloalkyl derivatives to generate an anion under mild conditions via two sequential transfer of one electron.[7] According to this strategy, we have recently developed several reactions between nitrobenzylic substrates and a series of carbonyl electrophiles such as aldehydes, ketones, α-ketoesters, α-ketolactams and ketomalonates leading to the corresponding alcohol adducts.[8]

Since the discovery of the TDAE reducing properties, haloalkyl derivatives, presenting an adequate reduction potential, have become the most common type of TDAE substrate, to produce a reacting carbanion. However, these carbanions are less reactive than the carbanions formed via the organometallic strategy, due to their stabilization by the $TDAE^{++}$ cation. Médebielle described the reaction with bromodifluoroalkyl substrates[9] while our team worked on *o*- and *p*-nitrobenzyl chlorides. Nishiyama presented the use of TDAE in the reductive debromination of 1,2-bis(bromoethyl)arenes or in the reductive dimerization of α-bromoesters.[10]

To explore the TDAE potentiality, we suggest the use of carbon halide bond-containing derivatives as electrophilic reagents, in order to realize a nucleophilic substitution. Thus, we have chosen some α-haloesters and α-haloamides, which are less reducible[11] than nitrobenzyl chlorides but sufficiently activated, under TDAE conditions, to undergo a nucleophilic substitution reaction. In addition, they present some worthwhile functionalized openings.

In continuation of our research program directed towards the development of original synthetic methods in medicinal chemistry[8,12] and the preparation of new potentially CNS active compounds,[13] we report herein the nucleophilic substitution by the nitrobenzylic anions (obtained by the TDAE strategy) of the halogen atom of α-haloesters and α-haloamides.

2. Preliminary study

Initially, we tempted a nucleophilic substitution reaction between the *p*-nitrobenzylic carbanion and ethyl 2-bromoacetate

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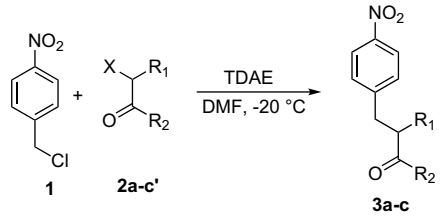
Table 1
Reaction of *p*-nitrobenzyl chloride with various α-halocarbonyl derivatives



Entry[a]	α-Halocarbonyl compounds	X	R_1	R_2	Yield[b] (%)
1	**2a**	Br	H	OC_2H_5	47
2	**2b**	Br	CH_3	OC_2H_5	Traces
3	**2c′**[c]	I	H	$N(C_2H_5)_2$	36

[a] Reaction conditions: 3 equiv of halocarbonyl compounds **2a**–**c**′, 1 equiv of **1** and 1 equiv of TDAE in anhydrous DMF were stirred at −20 °C for 1 h and then warmed up to 70 °C for 2 h, except with **2c**′, warmed up to rt for 3 h.
[b] % All yields refer to the chromatographically isolated pure products and are relative to chloride **1**.
[c] Compound **2c**′ was prepared by trans-halogenation of *N*,*N*-diethyl-2-chloroacetamide with NaI (3 equiv, 48 h in acetone).

(**2a**), ethyl 2-bromopropionate (**2b**) or *N*,*N*-diethyl-2-iodoacetamide (**2c**′) (Table 1). However, a high rate (37–44%) of the *p*-nitrobenzyl dimerization was observed explaining the poor to mild yields in compounds **3a**–**c**. These results are in accordance with those reported in our previous study.[8c]

3. Results and discussion

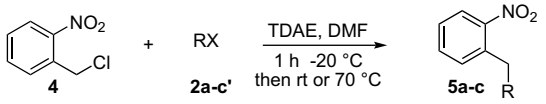
3.1. Optimization and limits

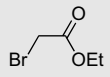
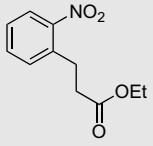
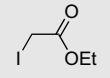
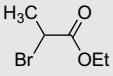
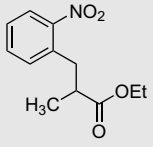
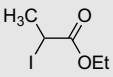
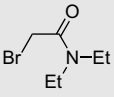
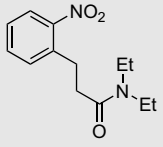
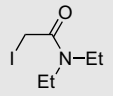
In order to explore this reactivity, the *o*-nitrobenzyl chloride, a less dimerizing substrate under TDAE conditions,[14] was used under the same reaction conditions. A high yield (92%) of substitution product **5a** was obtained by the reaction of *o*-nitrobenzyl chloride (**4**) with ethyl 2-bromoacetate (**2a**) in the presence of TDAE. This reaction was associated with dimer traces. In order to evaluate the scope and the limits of this reaction, a mechanistic study was carried out (Table 2).

The influence of the leaving halide atom has been studied. No reaction was observed with ethyl 2-chloroacetate and *N*,*N*-diethyl-2-chloroacetamide while good yields were obtained using the bromo and iodo derivatives **2a**, **2c** and **2c**′ (entries 1, 5 and 6). However, with ethyl iodoacetate (**2a**′) only a 50% yield was observed. This limited yield could be explained by secondary polymerization reactions, due to its lability under radical reaction conditions. The iodo esters usually produce polymers under radical reaction conditions.[15] These side reactions seem to limit the reaction yields to 50–55% with 2-iodoester (entries 2 and 4), but do not affect the α-iodoamides (entry 6), which are likely more stable under these conditions.

As concerns the influence of the substitution of the carbon–halide bond, we observed a decrease in yields with the ethyl 2-bromopropionate (34%) and no reaction was observed with ethyl

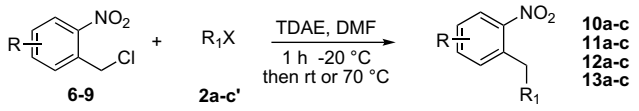
Table 2
Reaction of *o*-nitrobenzyl chloride with various halocarbonyl derivatives

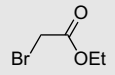
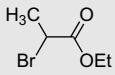
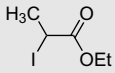
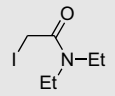


Entry[a]	α-Halocarbonyls		Conditions			Synthesized compound		Yield[c] (%)
1	**2a**		2 equiv	70 °C	2 h	**5a**		92
2	**2a**′		3 equiv	rt	3 h			50
3	**2b**		5 equiv	rt	48 h	**5b**		34
4	**2b**′[b]		3 equiv	rt	3 h			55
5	**2c**		3 equiv	70 °C	2 h	**5c**		52
6	**2c**′		3 equiv	rt	3 h			72

[a] All reactions were performed using 1 equiv (2 mmol) of TDAE in anhydrous DMF.
[b] Compounds **2b**′ and **2c**′ were prepared by trans-halogenation of ethyl 2-bromopropionate and *N*,*N*-diethyl-2-chloroacetamide with NaI (3 equiv, 48 h in acetone).
[c] % All yields refer to the chromatographically isolated pure products and are relative to chloride **4**.

Table 3
Reaction of various *o*-nitrobenzyl chloride derivatives with compounds **2a–c**



Entry	TDAE substrate	R	α-Halocarbonyl derivatives	Substitution product	Yield[d] (%)
1	**6**	4-Cl	**2a** 	**10a**	23[a]
2	**7**	5-CH_3		**11a**	78[a]
3	**8**	4,5-$(OCH_3)_2$		**12a**	68[a]
4	**9**	4,5-OCH_2O		**13a**	85[a]
5	**6**	4-Cl	**2b** 	**10b**	Traces[b]
6	**7**	5-CH_3		**11b**	46[b]
7	**8**	4,5-$(OCH_3)_2$	**2b′** 	**12b**	50[c]
8	**9**	4,5-OCH_2O		**13b**	53[c]
9	**6**	4-Cl	**2c′** 	**10c**	18[c]
10	**7**	5-CH_3		**11c**	83[c]
11	**8**	4,5-$(OCH_3)_2$		**12c**	72[c]
12	**9**	4,5-OCH_2O		**13c**	82[c]

[a] Reaction conditions: 2 equiv of **2a**, 1 equiv of **6–9** and 1 equiv of TDAE in anhydrous DMF were stirred at −20 °C for 1 h and then warmed up to 70 °C for 2 h.
[b] Reaction conditions: 5 equiv of **2b**, 1 equiv of **6–9** and 1 equiv of TDAE in anhydrous DMF were stirred at −20 °C for 1 h and then warmed up to rt for 48 h.
[c] Reaction conditions: 3 equiv of **2b′** and **2c′**, 1 equiv of **6–9** and 1 equiv of TDAE in anhydrous DMF were stirred at −20 °C for 1 h and then warmed up to rt for 3 h.
[d] % All yields refer to the chromatographically isolated pure products and are relative to chloride **6–9**.

2-bromoisobutyrate. This difference of reactivity could be explained by the steric hindrance and electronic effect of alkyl groups. The use of iodo ester **2b′** improved to a moderate 55% yield of **5b**.

Moreover, the influence of the carbon–halide bond position was studied. No reaction was observed with the ethyl 3-bromopropionate.

Finally to optimize this reactivity, we modified some parameters such as reaction time, temperature and amount of α-halocarbonyl derivative. After monitoring by TLC, optimized conditions were defined for each halocarbonyl derivative: the reaction temperature of bromo derivatives (**2a** and **2c**) was 70 °C and rt for iodo derivatives (**2b′** and **2c′**). The optimal conditions were found to be 3 h and 3 equiv of the halo compound except for **2a** (2 h, 2 equiv).

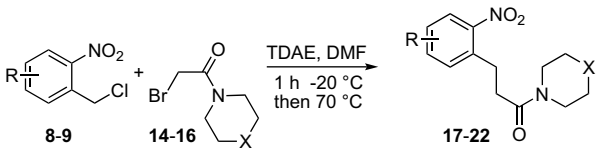
All these experimental data (dimer formation, influence of the leaving halide atom, …) led us to suggest a nucleophilic substitution mechanism for the reaction of the nitrobenzyl carbanion, formed from TDAE, with α-halocarbonyl derivatives.

3.2. Generalization to various *o*-nitrobenzyl chloride derivatives

To generalize the TDAE reactivity on α-haloesters and amides, using their respective optimized protocol, we conducted a study using various *o*-nitrobenzyl chloride derivatives (Table 3) such as 4-chloro-2-nitrobenzyl chloride (**6**), 5-methyl-2-nitrobenzyl chloride (**7**), 4,5-dimethoxy-2-nitrobenzyl chloride (**8**) and 6-nitropiperonyl chloride (**9**).

According to our previous study,[12f] the lowest reactivity was observed with the 4-chloro-2-nitrobenzyl chloride (**6**): traces to 23%. This poor reactivity could be explained by the unstability of the radical intermediate. Other chloride derivatives gave fair to good yields (46–85%).

Table 4
Reaction of 4,5-dimethoxy-2-nitrobenzyl chloride and 6-nitropiperonyl chloride with various α-bromoacetamide



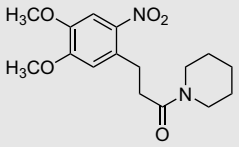
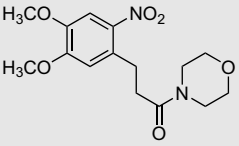
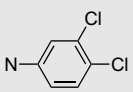
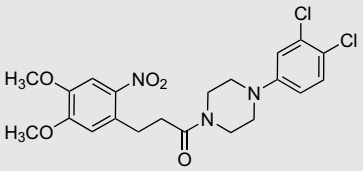
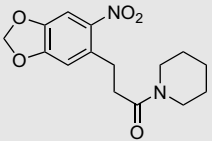
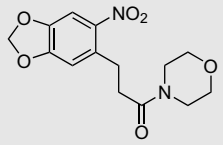
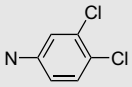
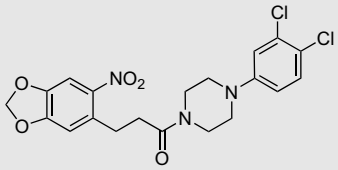
Entry[a]	TDAE substrate	R	α-Bromoacetamide	X		Substitution product	Yield[b] (%)
1	**8**	4,5-$(OCH_3)_2$	**14**	CH_2	**17**		65
2	**8**	4,5-$(OCH_3)_2$	**15**	O	**18**		62
3	**8**	4,5-$(OCH_3)_2$	**16** 		**19**		79
4	**9**	4,5-OCH_2O	**14**	CH_2	**20**		42

Table 4 (*continued*)

Entry[a]	TDAE substrate	R	α-Bromoacetamide	X	Substitution product	Yield[b] (%)
5	**9**	4,5-OCH_2O	**15**	O	**21** 	68
6	**9**	4,5-OCH_2O	**16** 		**22** 	62

[a] Reaction conditions: 3 equiv of α-bromoacetamides **14**–**16**, 1 equiv of **8**–**9** and 1 equiv of TDAE in anhydrous DMF were stirred at −20 °C for 1 h and then warmed up to 70 °C for 2 h.
[b] % All yields refer to the chromatographically isolated pure products and are relative to chloride **8**–**9**.

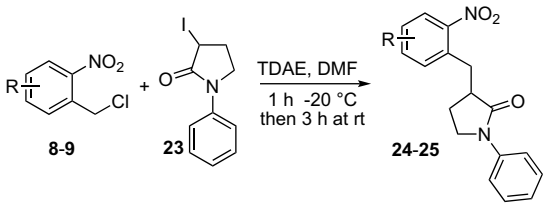
Variations observed are in accordance with optimization results (Table 2): good yields with **2a** and **2c′** (68–85%) and fair yields with **2b** and **2b′** (entries 3 and 4) due to the steric hindrance and electronic effect of the methyl group.

3.3. Extension to α-haloacetamide derivatives in benzodioxole and dimethoxybenzene series

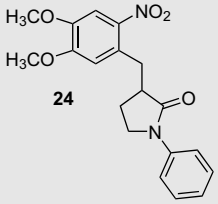
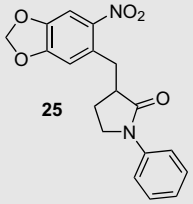
In order to obtain highly functionalized compounds, we extended this reactivity with more complex α-haloacetamide derivatives (Table 4). Due to their stability and their ease availability compared with α-iodoacetamides, three α-bromoacetamides were prepared according to the previous reaction conditions used with **2c** (3 equiv, 70 °C, 3 h). The three α-bromoacetamides **14**–**16** were obtained by a simple methodology[16] using the reaction of 2-bromoacetyl bromide and the corresponding secondary amine solubilized in butan-2-one in the presence of calcium carbonate. The moderate yields obtained (42–79%) are in accordance with previously results observed with *N*,*N*-diethyl-2-bromoacetamide (Table 2).

In addition to this study, we targeted another original α-haloacetamide, 3-iodo-1-phenylpyrrolidinone (**23**) (Table 5). This compound was prepared by the trans-halogenation of the corresponding commercially available bromo derivative. We used the iodo compound because of the negative influence of the steric hindrance previously observed with **2b** and improved with the use of **2b′** (Table 2, entry 4). The reaction of compounds **8** and **9** with **23**, according to **2c′** reaction conditions, led to expected pyrolidinone derivatives **24** and **25** in 44–83% yield.

Table 5
Reaction of 4,5-dimethoxy-2-nitrobenzyl chloride and 6-nitropiperonyl chloride with 3-iodo-1-phenylpyrrolidinone



8-9 **23** **24-25**

Entry[a]	TDAE substrate	R	Substitution product	Yield[b] (%)
1	**8**	4,5-$(OCH_3)_2$	**24** 	83
2	**9**	4,5-OCH_2O	**25** 	44

[a] Reaction conditions: 3 equiv of **23**, 1 equiv of **8**–**9** and 1 equiv of TDAE in anhydrous DMF were stirred at −20 °C for 1 h and then warmed up to rt for 3 h.
[b] % All yields refer to the chromatographically isolated pure products and are relative to chloride **8**–**9**.

4. Conclusion

In conclusion, we have demonstrated that α-haloesters and α-haloamides are able to undergo a nucleophilic substitution with the carbanions obtained from *o*-nitrobenzyl chloride derivatives using TDAE. Compared with the classical method using organometallic compounds or transitional metal catalysts,[17] the TDAE strategy is an easy, original and selective method to create carbon–carbon bonds from the carbon–halide bond of α-haloesters or α-haloamides. The pharmacological evaluation of these new 3-phenylpropanoates and 3-phenylpropanamides is under active investigation.

5. Experimental section

5.1. General

Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. Element analyses were performed by the centre de Microanalyse of the University of Aix-Marseille 3. Both ^1H and ^{13}C NMR spectra were determined on a Bruker AC 200 spectrometer. The ^1H the ^{13}C chemical shifts are reported from $CDCl_3$ peaks: ^1H (7.26 ppm) and ^{13}C (76.9 ppm). Absorptions are reported with the following notations: s, singulet; d, doublet; t, triplet; q, quartet; m, a more complex multiplet or overlapping multiplets. The following adsorbents were used for column chromatography: silica gel 60 (Merck, particule size 0.063–0.200 mm, 70–230 mesh ASTM). TLC was performed on 5 cm×10 cm aluminium plates coated with silice gel 60 F_{254} (Merck) in an appropriate solvent.

The *N*,*N*-diethyl-2-iodoacetamide (**2c′**) and the ethyl 2-iodopropionate (**2b′**) were prepared in quantitative yields by a simple trans-halogenation of *N*,*N*-diethyl-2-chloroacetamide and ethyl 2-bromopropionate with NaI (3 equiv, 48 h in acetone) followed by a silica gel chromatography using petroleum ether/ethyl acetate as eluent.

The secondary α-bromoacetamides, 2-bromo-1-(piperidin-1-yl)ethanone **14**, 2-bromo-1-morpholino ethanone **15**, 2-bromo-1-4-(3,4-dichloropiperzin-1-yl)ethanone **16** were prepared according to previously described method.[11]

5.2. Procedure for TDAE reaction

General procedure for the reaction of *o*- and *p*-nitrobenzyl derivatives **1**, **4**, **6**–**9** and α-halocarbonyl derivatives **2a**–**c′**, **14**–**16**, **23** using TDAE. Into a two-necked flask equipped with a nitrogen inlet was added, under nitrogen at −20 °C, 6 mL of anhydrous DMF solution of *o*- and *p*-nitrobenzyl derivative (2 mmol, 1 equiv) and corresponding α-halocarbonyl derivatives (**2a**: 2 equiv; **2b**: 5 equiv; **2b′**, **2c**, **2c′**, **14**–**16**, **23**: 3 equiv). The solution was stirred and maintained at this temperature for 15 min and then was added dropwise via a syringe the TDAE (1 equiv). A red to green colour immediately developed with the formation of a white fine precipitate. The solution was vigorously stirred for 1 h and warmed up (**2a**, **2c**, **14**–**16**: 70 °C for 2 h; **2b**: rt for 48 h; **2b′**, **2c′**, **23**: rt for 3 h). After this time, the crude was extracted by dichloromethane (50 mL), washed with water (3×100 mL) and dried by Na_2SO_4. Evaporation of the solvent left an orange to brown viscous liquid as crude product. Purification by silica gel chromatography (CH_2Cl_2/petroleum ether (5:5) with **2a**, **2b**, and **2b′**, petroleum ether/ethyl acetate (5:5) with **2c**, **2c′**, **14**–**16**, CH_2Cl_2 with **23**) gave the corresponding product of substitution.

The analytical data of the previously synthesized products **3a**, **3b**, **5a**, **5c**, **12a** are in accordance to the references.[18]

5.2.1. Ethyl 2-methyl-3-(2-nitrophenyl)propanoate (*5b*)

Yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.12 (t, *J*=7.1 Hz, 3H, CH_3), 1.21 (d, *J*=7.0 Hz, 3H, CH_3), 2.78–2.89 (m, 1H, CH), 3.00–3.26 (m, 2H, CH_2), 4.03 (q, *J*=7.1 Hz, 2H, CH_2), 7.32–7.37 (m, 2H, ArH), 7.46–7.54 (m, 1H, CH), 7.92 (d, *J*=8.3 Hz, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 14.0, 17.6, 36.6, 40.4, 60.4, 124.8, 127.6, 132.7, 132.8, 134.6, 149.3, 175.5. Anal. Calcd for $C_{12}H_{15}NO_4$ (237.25): C, 60.75; H, 6.37; N, 5.90. Found: C, 61.12; H, 6.52; N, 6.02.

5.2.2. Ethyl 3-(4-chloro-2-nitrophenyl)propanoate (*10a*)

Yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.22 (t, *J*=7.1 Hz, 3H, CH_3), 2.69 (t, *J*=7.0 Hz, 2H, CH_2), 3.19 (t, 2H, CH_2), 4.11 (q, *J*=7.1 Hz, 2H, CH_2), 7.37 (d, *J*=8.3 Hz, 1H, CH), 7.51 (dd, *J*=8.3, 2.0 Hz, 1H, CH), 7.93 (d, *J*=2.0 Hz, 1H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 14.1, 27.8, 34.5, 60.6, 124.9, 133.1, 133.2, 133.4, 134.1, 149.5, 172.0. Anal. Calcd for $C_{11}H_{12}ClNO_4$ (257.67): C, 51.27; H, 4.69; N, 5.44. Found: C, 51.32; H, 4.71; N, 5.69.

5.2.3. 3-(4-Chloro-2-nitrophenyl)-N,N-diethylpropanamide (*10c*)

Yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.08 (t, *J*=7.0 Hz, 3H, CH_3), 1.10 (t, *J*=7.0 Hz, 3H, CH_3), 2.66 (t, *J*=7.3 Hz, 2H, CH_2), 3.14–3.40 (m, 6H, 3×CH_2), 7.42–7.51 (m, 2H, CH), 7.86–8.00 (m, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 13.0, 14.2, 28.5, 33.6, 40.3, 41.9, 124.6, 132.9, 133.1, 134.1, 135.1, 149.5, 170.3. Anal. Calcd for $C_{13}H_{17}ClN_2O_3$ (284.74): C, 54.84; H, 6.02; N, 9.84. Found: C, 54.76; H, 6.20; N, 9.44.

5.2.4. Ethyl 3-(5-methyl-2-nitrophenyl)propanoate (*11a*)

Yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.15 (t, *J*=7.1 Hz, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.61 (t, *J*=7.6 Hz, 2H, CH_2), 3.12 (t, *J*=7.6 Hz, 2H, CH_2), 4.04 (q, *J*=7.1 Hz, 2H, CH_2), 7.06–7.12 (m, 2H, 2×CH), 7.78 (d, *J*=8.2 Hz, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 13.9, 21.0, 28.3, 34.6, 60.2, 124.8, 127.9, 132.5, 135.6, 144.2, 146.6, 172.1. Anal. Calcd for $C_{12}H_{15}NO_4$ (237.25): C, 60.75; H, 6.37; N, 5.90. Found: C, 60.33; H, 6.45; N, 5.82.

5.2.5. Ethyl 2-methyl-3-(5-methyl-2-nitrophenyl)propanoate (*11b*)

Yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.08 (t, *J*=7.1 Hz, 3H, CH_3), 1.16 (d, *J*=7.0 Hz, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.72–2.83 (m, 1H, CH), 2.95–3.18 (m, 2H, CH_2), 3.99 (q, *J*=7.1 Hz, 2H, CH_2), 7.07–7.11 (m, 2H, 2×CH), 7.81 (d, *J*=8.1 Hz, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 13.9, 17.4, 21.1, 36.7, 40.3, 60.1, 125.0, 128.0, 133.1, 134.6, 143.9, 146.7, 175.4. Anal. Calcd for $C_{13}H_{17}NO_4$ (251.28): C, 62.14; H, 6.82; N, 5.57. Found: C, 62.20; H, 6.92; N, 5.73.

5.2.6. N,N-Diethyl-3-(5-methyl-2-nitrophenyl)propanamide (*11c*)

Yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 0.92 (t, *J*=7.0 Hz, 3H, CH_3), 0.94 (t, *J*=7.1 Hz, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.51 (t, *J*=7.0 Hz, 2H, CH_2), 2.98–3.25 (m, 6H, 3×CH_2), 6.98 (d, *J*=8.3 Hz, 1H, CH), 7.07 (s, 1H, CH), 7.66 (d, *J*=8.3 Hz, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 12.6, 13.8, 20.8, 28.9, 33.4, 39.8, 41.4, 124.4, 127.5, 132.6, 136.2, 143.9, 146.4, 170.2. Anal. Calcd for $C_{14}H_{20}N_2O_3$ (264.32): C, 63.62; H, 7.63; N, 10.60. Found: C, 63.42; H, 7.77; N, 10.41.

5.2.7. Ethyl 3-(4,5-dimethoxy-2-nitrophenyl)-2-methyl propanoate (*12b*)

Yellow solid, mp 55 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.10 (t, *J*=7.1 Hz, 3H, CH_3), 1.20 (d, *J*=6.8 Hz, 3H, CH_3), 2.78–2.85 (m, 1H, CH), 3.10 (d, *J*=7.2 Hz, 2H, CH_2), 3.88 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 3.99 (q, *J*=7.1 Hz, 2H, CH_2), 6.70 (s, 1H, CH), 7.57 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 14.0, 17.7, 37.3, 40.4, 56.1, 56.2, 60.2, 108.1, 114.0, 129.9, 141.0, 147.3, 152.6, 175.8. Anal. Calcd for $C_{14}H_{19}NO_6$ (297.30): C, 56.56; H, 6.44; N, 4.71. Found: C, 56.82; H, 6.61; N, 4.59.

5.2.8. 3-(4,5-Dimethoxy-2-nitrophenyl)-N,N-diethyl propanamide (*12c*)

Yellow solid, mp 105 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.03 (t, *J*=6.4 Hz, 6H, 2×CH_3), 2.63 (t, *J*=7.1 Hz, 2H, CH_2), 3.14–3.35 (m, 6H, 3×CH_2), 3.85 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 6.83 (s, 1H, CH), 7.51 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 12.9, 14.1, 29.7, 33.7, 40.2, 41.8, 56.1, 56.3, 107.9, 114.0, 131.9, 140.9, 147.2, 153.0, 170.7. Anal. Calcd for $C_{15}H_{22}N_2O_5$ (310.35): C, 58.05; H, 7.15; N, 9.03. Found: C, 58.22; H, 7.36; N, 9.03.

5.2.9. Ethyl 3-(6-nitrobenzo[d][1,3]dioxol-5-yl)propanoate (*13a*)

Yellow solid, mp 78 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.22 (t, *J*=7.1 Hz, 3H, CH_3), 2.66 (t, *J*=7.4 Hz, 2H, CH_2), 3.15 (t, *J*=7.4 Hz, 2H, CH_2), 4.18 (q, *J*=7.1 Hz, 2H, CH_2), 6.07 (s, 2H, CH_2), 6.78 (s, 1H, CH), 7.47 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 14.1, 29.1, 34.7, 60.5, 102.9, 105.7, 110.8, 132.9, 142.7, 146.6, 151.7, 172.3. Anal. Calcd for $C_{12}H_{13}NO_6$ (267.23): C, 53.93; H, 4.90; N, 5.24. Found: C, 53.80; H, 4.98; N, 5.18.

5.2.10. Ethyl 2-methyl-3-(6-nitrobenzo[d][1,3]dioxol-5-yl)-propanoate (*13b*)

Yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.17 (t, *J*=7.2 Hz, 3H, CH_3), 1.21 (d, *J*=6.7 Hz, 3H, CH_3), 2.76–2.87 (m, 1H, CH), 2.99–3.20 (m, 2H, CH_2), 4.07 (q, *J*=7.2 Hz, 2H, CH_2), 6.07 (s, 2H, CH_2), 6.73 (s, 1H, CH), 7.50 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 14.1, 17.7, 37.4, 40.6, 60.4, 102.8, 105.8, 111.4, 132.1, 142.9, 146.7, 151.5, 175.7. Anal. Calcd for $C_{13}H_{15}NO_6$ (281.26): C, 55.51; H, 5.38; N, 4.98. Found: C, 55.71; H, 5.66; N, 4.87.

5.2.11. N,N-Diethyl-3-(6-nitrobenzo[d][1,3]dioxol-5-yl)-propanamide (*13c*)

Yellow solid, mp 90 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.06 (t, *J*=7.1 Hz, 3H, CH_3), 1.08 (t, *J*=7.1 Hz, 3H, CH_3), 2.63 (t, *J*=7.8 Hz, 2H, CH_2), 3.14 (t, *J*=7.8 Hz, 2H, CH_2), 3.23 (q, *J*=7.1 Hz, 2H, CH_2), 3.33 (q,

J=7.1 Hz, 2H, CH_2), 6.04 (s, 2H, CH_2), 6.83 (s, 1H, CH), 7.43 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 13.0, 14.1, 29.8, 33.7, 40.1, 41.8, 102.7, 105.4, 111.2, 134.0, 142.6, 146.4, 151.6, 170.5. Anal. Calcd for $C_{14}H_{18}N_2O_5$ (294.30): C, 57.13; H, 6.16; N, 9.52. Found: C, 57.09; H, 6.30; N, 9.50.

*5.2.12. 3-(4,5-Dimethoxy-2-nitrophenyl)-1-(piperidin-1-yl)propan-1-one (**17**)*

Yellow solid, mp 98 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.30–1.60 (m, 6H, 3×CH_2), 2.61 (t, J=7.9 Hz, 2H, CH_2), 3.12 (t, J=7.9 Hz, 2H, CH_2), 3.29 (t, J=5.2 Hz, 2H, CH_2), 3.44 (t, J=5.2 Hz, 2H, CH_2), 3.82 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 6.79 (s, 1H, CH), 7.49 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 24.2, 25.3, 26.2, 29.8, 33.7, 42.5, 46.3, 56.0, 56.2, 107.7, 113.8, 131.8, 140.7, 147.1, 152.9, 169.8. Anal. Calcd for $C_{16}H_{22}N_2O_5$ (322.36): C, 59.61; H, 6.88; N, 8.69. Found: C, 59.41; H, 6.99; N, 8.55.

*5.2.13. 3-(4,5-Dimethoxy-2-nitrophenyl)-1-morpholino propan-1-one (**18**)*

Yellow solid, mp 135 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 2.66 (t, J=7.2 Hz, 2H, CH_2), 3.18 (t, J=7.2 Hz, 2H, CH_2), 3.39–3.57 (m, 8H, 4×CH_2), 3.87 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 6.82 (s, 1H, CH), 7.54 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 29.8, 33.7, 41.9, 45.8, 56.1, 56.3, 66.5, 66.6, 107.9, 113.9, 131.5, 140.8, 147.3, 153.1, 170.4. Anal. Calcd for $C_{15}H_{20}N_2O_6$ (324.33): C, 55.55; H, 6.22; N, 8.64. Found: C, 55.34; H, 6.40; N, 8.36.

*5.2.14. 1-[4-(3,4-Dichlorophenyl)piperazin-1-yl]-3-(4,5-dimethoxy-2-nitrophenyl)propan-1-one (**19**)*

Yellow solid, mp 68 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 2.73 (t, J=8.1 Hz, 2H, CH_2), 3.08 (m, 4H, 2×CH_2), 3.21 (t, J=8.1 Hz, 2H, CH_2), 3.69–3.74 (m, 4H, 2×CH_2), 3.88 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 6.72 (dd, J=2.8, 9.0 Hz, 1H, CH), 6.84 (s, 1H, CH), 6.91 (d, J=2.8 Hz, 1H, CH), 7.21 (d, J=9.0 Hz, 1H, CH), 7.57 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 30.0, 33.9, 41.1, 45.0, 48.8, 49.0, 56.2, 56.4, 108.0, 113.9, 115.7, 117.7, 123.0, 130.4, 131.5, 132.7, 140.8, 147.4, 149.9, 153.2, 170.3. HRMS (EI): calcd for $C_{21}H_{23}Cl_2N_3O_5$ (M^+) 468.1088, found 468.1079.

*5.2.15. 3-(6-Nitrobenzo[d][1,3]dioxol-5-yl)-1-(piperidin-1-yl)-propan-1-one (**20**)*

Yellow solid, mp 113 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.57 (m, 6H, 3×CH_2), 2.69 (t, J=7.9 Hz, 2H, CH_2), 3.18 (t, J=7.9 Hz, 2H, CH_2), 3.41–3.54 (m, 4H, 2×CH_2), 6.08 (s, 2H, CH_2), 6.89 (s, 1H, CH), 7.49 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 24.4, 25.5, 26.3, 29.8, 33.9, 42.8, 46.5, 102.7, 105.4, 111.1, 133.9, 142.6, 146.5, 151.7, 169.8 Anal. Calcd for $C_{15}H_{18}N_2O_5$ (306.31): C, 58.82; H, 5.92; N, 9.15. Found: C, 58.67; H, 6.02; N, 8.90.

*5.2.16. 1-Morpholino-3-(6-nitrobenzo[d][1,3]dioxol-5-yl)-propan-1-one (**21**)*

Yellow solid, mp 156 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 2.70 (t, J=7.2 Hz, 2H, CH_2), 3.19 (t, J=7.2 Hz, 2H, CH_2), 3.40–3.74 (m, 8H, 4×CH_2), 6.09 (s, 2H, CH_2), 6.88 (s, 1H, CH), 7.50 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 29.8, 33.8, 42.0, 45.9, 66.6, 66.8, 102.8, 105.6, 111.3, 133.6, 142.7, 146.7, 151.8, 170.3. Anal. Calcd for $C_{14}H_{16}N_2O_6$ (308.29): C, 54.54; H, 5.23; N, 9.09. Found: C, 54.16; H, 5.15; N, 8.85.

*5.2.17. 1-[4-(3,4-Dichlorophenyl)piperazin-1-yl]-3-(6-nitrobenzo[d][1,3]dioxol-5-yl)propan-1-one (**22**)*

Yellow solid, mp 97 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 2.71 (t, J=7.6 Hz, 2H, CH_2), 3.12 (m, 6H, 3×CH_2), 3.49–3.79 (m, 4H, 2×CH_2), 6.04 (s, 2H, CH_2), 6.70 (dd, J=2.6, 8.9 Hz, 1H, CH), 6.83 (s, 1H, CH), 6.91 (d, J=2.6 Hz, 1H, CH), 7.24 (d, J=8.9 Hz, 1H, CH), 7.44 (s, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 29.8, 33.8, 41.1, 44.9, 48.7, 48.9, 102.8, 105.5, 111.1, 115.6, 117.6, 122.8, 130.4, 132.7, 133.5, 142.5, 146.6, 149.9, 151.7, 170.0. HRMS (EI): calcd for $C_{20}H_{19}Cl_2N_3O_5$ (M^+) 452.0775, found 452.0769.

*5.2.18. 3-(4,5-Dimethoxy-2-nitrobenzyl)-1-phenyl pyrrolidin-2-one (**24**)*

Yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.70–7.95 (m, 1H, CH_2), 2.15–2.36 (m, 1H, CH_2), 2.89–3.10 (m, 1H, CH), 3.21 (dd, J=6.5 Hz, J_{AB}=13.5 Hz, 1H, CH_2), 3.54 (dd, J=6.0 Hz, J_{AB}=13.5 Hz, 1H, CH_2), 3.68 (m, 2H, CH_2), 3.89 (s, 6H, 2×CH_3), 6.93 (s, 1H, CH), 7.06–7.13 (m, 1H, CH), 7.32 (dd, J=7.6, 8.1 Hz, 2H, 2×CH), 7.55 (s, 1H, CH), 7.58 (d, J=7.6 Hz, 2H, 2×CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 24.2, 33.1, 44.5, 46.5, 56.1, 56.3, 107.8, 114.0, 119.5, 124.3, 128.6, 129.6, 139.3, 141.5, 147.3, 152.8, 174.8. HRMS (EI): calcd for $C_{19}H_{20}N_2O_5$ (M^+) 357.1445, found 357.1440.

*5.2.19. 3-[(6-Nitrobenzo[d][1,3]dioxol-5-yl)methyl]-1-phenylpyrrolidin-2-one (**25**)*

Yellow solid, mp 164 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.75–1.94 (m, 1H, CH_2), 2.22–2.34 (m, 1H, CH_2), 2.95–3.03 (m, 1H, CH), 3.14 (dd, J=7.0 Hz, J_{AB}=13.6 Hz, 1H, CH_2), 3.47 (dd, J=6.0 Hz, J_{AB}=13.6 Hz, 1H, CH_2), 3.75 (q, J=4.0 Hz, 2H, CH_2), 6.08 (s, 2H, CH_2), 6.93 (s, 1H, CH), 7.09–7.17 (m, 1H, CH), 7.36 (dd, J=7.3, 8.5 Hz, 2H, 2×CH), 7.49 (s, 1H, CH), 7.61 (d, J=8.5 Hz, 2H, 2×CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 24.7, 33.9, 44.2, 46.5, 102.8, 105.5, 111.3, 119.7, 124.4, 128.7, 131.8, 139.3, 143.2, 146.7, 151.6, 174.6. HRMS (EI): calcd for $C_{18}H_{16}N_2O_5$ (M^+) 341.1132, found 341.1128.

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