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The *CSIC*[†] [*C*arbanion Mediated *S*ulfonate (*S*ulfonamido) *I*ntramolecular *C*yclization] Reaction: Scope and Limitations

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Abstract: The CSIC (Carbanion-mediated Sulfonate -Sulfonamide- Intramolecular Cyclization) reaction has been extended to new carbonyl containing substrates, showing the scope and limitations of this process. Suitable derivatives of ketones (e.g acetophenone (**1**)), β-keto esters (e.g ethyl acetoacetate (**4**)), γ-keto esters (e.g ethyl 2-oxocyclohexaneacetate (**5**) and ethyl levulinate (**6**)) proved reluctant to undergo this protocol. Cyclopropyl methyl ketone (**2**) gave the heterocycle (**3**), only in the "sulfonamide" synthetic sequence of the CSIC reaction. Cyclic azaketones (e.g tropinone (**7**)) failed also, but 4-piperidones (**9**, **10**) afforded the novel 3,8-disubstituted 4-amino-8-aza-1-oxa-2-thiaspiro[4.5]dec-3-ene 2,2-dioxide (**12**, **15a-c**) and 8-substituted 4-amino-1,8-diaza-2-thiaspiro[4.5]dec-3-ene 2,2-dioxide (**18a**, **18b**, **21a**, **21b**) ring systems; the former compounds are the first examples of such ring systems substituted at the 3-position, whereas the latter represent the first ever representatives of spiro fused systems containing the 4-amino-2,3-dihydroisothiazole 1,1-dioxide moiety. Base promoted (NaH or DBU) cyclization of precursors **11b**, **14a-c**, **17b**, **17c** and **20** give the final adducts in good overall yield. Finally, we were unsuccessful with some conveniently functionalized anthranilonitrile derivatives (**8a-d**), in an attempt to extend the CSIC reaction to β-aminonitriles. As a result of these studies the substrate dependent reactivity in the CSIC reaction has been analyzed in depth and some restrictions and limitations have been observed and discussed.

INTRODUCTION

The CSIC [Carbanion mediated Sulfonate (Sulfonamido) Intramolecular Cyclization] reaction is an aldol type cyclization that takes place when alkanesulfonates of cyanohydrins or sulfonamides of aminonitriles are treated with non-nucleophilic bases such as DBU or sodium hydride to produce the 4-amino-5*H*-1,2-oxathiole 2,2-dioxide and 4-amino-2,3-dihydroisothiazole 1,1-dioxide ring systems, respectively (Scheme 1). The mechanism is straightforward and involves the removal of a proton from the methylene neighbouring the SO_2 group, the carbanion that is generated attacks the cyano group to give eventually the cyclic enamine system.[1] This reaction is both rapid and clean, being complete within times ranging from minutes to a few hours at ambient temperature, aqueous work-up on some occasions being all that is necessary for the isolation of pure compounds.

We[2] and others[3] have recently shown that, not only complex, chiral polyoxygenated derivatives from sugars or nucleosides,[1] but also simple ketones (acetone, benzyl methyl ketone and acetol derivatives)[2a,b,3] and a-

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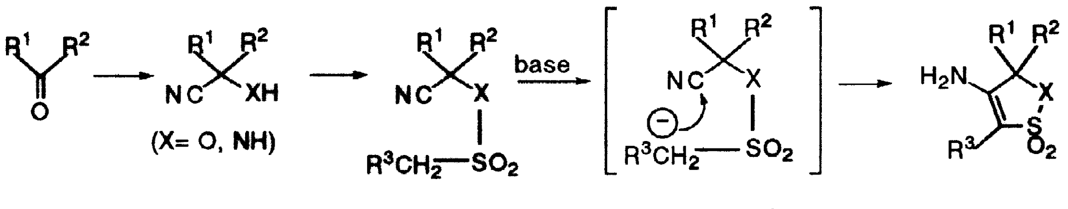
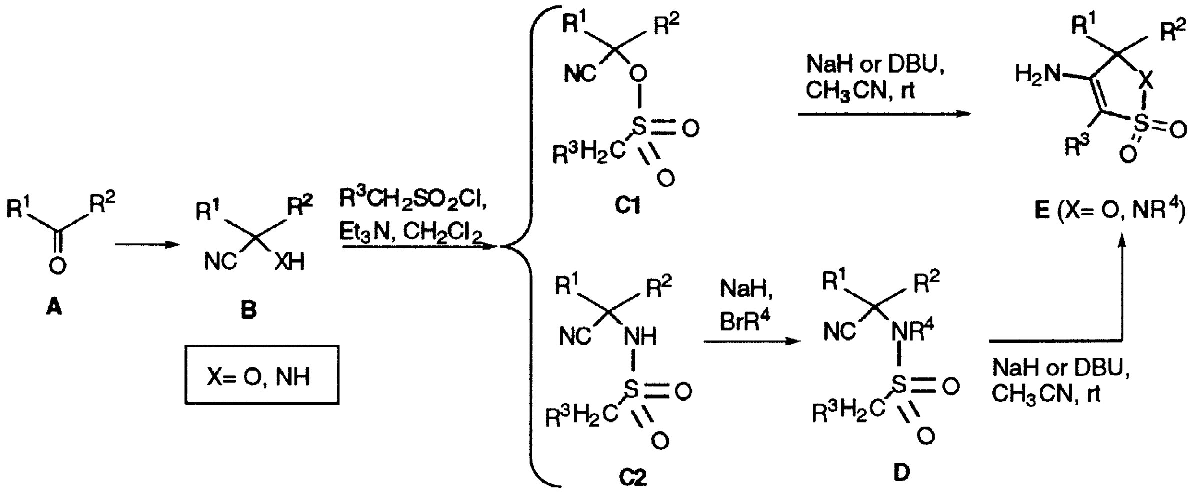


Scheme 1

liphatic aldehydes[2c] may be successfully used as the starting materials in the CSIC reaction. This finding has been an important discovery in the CSIC reaction, that has opened this protocol to new structural and functional possibilities, highlighting the rich potential chemistry embodied in such simple heterocycles.

In Scheme 2 we show the three or four steps of the standard protocol to accomplish the CSIC process. The sequence: cyanohydrin formation, sulfonation and base treatment gives intermediates **B** (X= O), (**C1**) and the final adduct **E** (X= O). The sequence: aminonitrile formation + sulfonation + *N*-benzylation + and base treatment gives intermediates **B** (X= NH), **C2**, **D** and the final adduct **E** (X= NR^4).



Scheme 2

At this stage of our studies on the CSIC reaction we were particularly concerned with the scope of this simple process. In fact, little was known about the substrate and functional group limitations in the CSIC reaction. Even more, we would like to gain more insight in this reaction in order to predict successful synthetic schemes and obtain more useful manipulations. In this context, in this report we extend our initial observations[2] to new type of carbonyl [*unsaturated ketones*: acetophenone (**1**), cyclopropyl methyl ketone (**2**); *keto esters*: ethyl acetoacetate (**4**), ethyl 2-oxocyclohexaneacetate (**5**), ethyl levulinate (**6**); *cyclic azaketones*: tropinone (**7**), *N*-

substituted 4-piperidones (**9**, **10**)] and anthranilonitrile derivatives (**8a-d**) as starting materials, showing the scope and limitations of the CSIC reaction.

RESULTS AND DISCUSSION

A) Unsaturated ketones

Initial studies with unsaturated ketones such as acetophenone (**1**) were disappointing. We were unable to obtain the desired sulfonate or sulfonamide intermediates to run the CSIC reaction. This negative result prevented us from testing similar aryl or vinyl related substrates. However, and in contrast, a typical "vinyl-like" compound, such as the imine of cyclopropyl methyl ketone (**2**), following the sulfonamide protocol shown in Scheme 2, *via* intermediates **2a-c**, gave compound (**3**) in 26% overall yield from ketone **2** (91% yield in the CSIC reaction) (Table 1; entry b). In the ^{1}H NMR spectrum we could detect and analyze indicative signals for H5 and NH_2, corroborated with the signals for C3, C4 and C5 in the ^{13}C NMR spectrum (Figure 1). These values are in good agreement with the usual data, previously found, for these heterocycles.[2a,b] Unfortunately, and starting again with cyclopropyl methyl ketone (**2**), we were unable to run similar CSIC protocol with sulfonate intermediates.

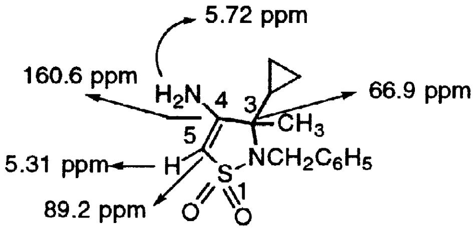


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Figure 1

B) Keto esters

Of great interest for our current studies on the structure-reactivity relationships for the synthesis of these 1,2-oxathiole and 2,3-dihydroisothiazole heterocyclic systems[2] was the analysis of the CSIC reaction with keto esters. Unfortunately, our expectations were not fulfilled and no heterocyclic products could be isolated. For β-keto esters, the sulfonate sequence of the CSIC protocol (Scheme 2) with ethyl acetoacetate (**4**), allowed us to prepare the cyanohydrin (**4a**) and the corresponding mesylate (**4b**) (Table 1; entry c), but this intermediate, after basic treatment, gave no CSIC reaction. The sulfonamide protocol was similarly unsuccessful: intermediate **4c**, after reaction with sodium hydride, led to the β-enamino ester (**4d**) (Table 1 ; entry c) as the only detected and

Table 1. CSIC Reaction of different carbonyl and anthranilonitrile derivatives

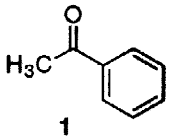
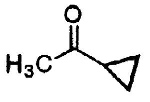
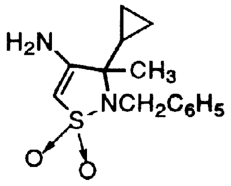
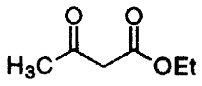
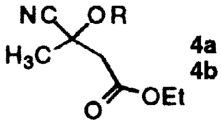
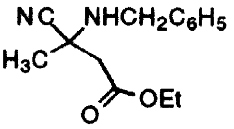
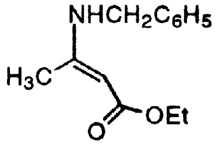
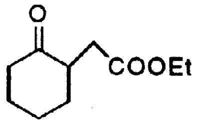
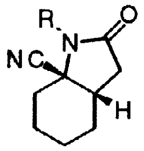
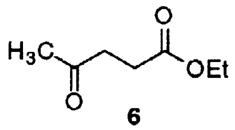
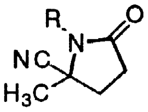
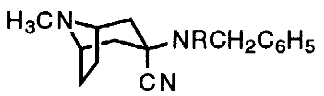
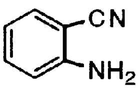
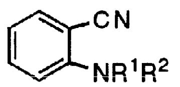
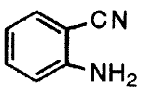
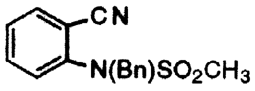
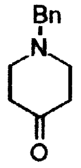
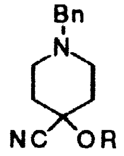
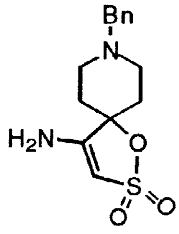
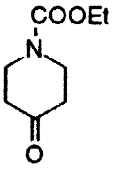
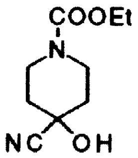
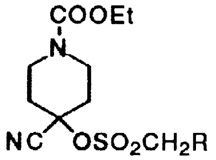
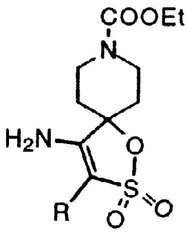
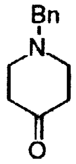
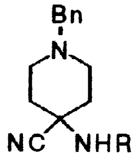
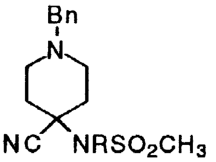
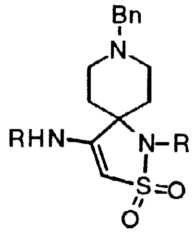
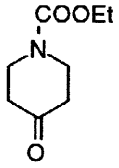
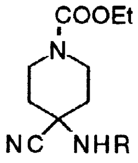
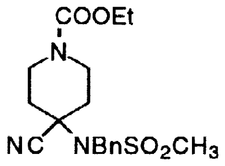
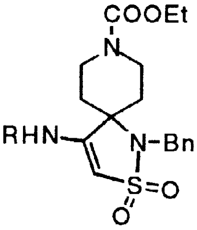
Entry	**Starting materials**	**Intermediates** (yield)	**Heterocycles** (yield)
a	 **1**	—	—
b	 **2**	 **2a** R^1, R^2= H (81%) **2b** R^1= SO_2CH_3, R^2= H (83%) **2c** R^1= SO_2CH_3, R^2= Bn (42%)	 **3** (91%)[a]
c	 **4**	 **4a** R= H (91%) **4b** R= SO_2CH_3 (47%)  **4c** (46%)  **4d** (52%)	— —
d	 **5**	 **5a** R= H (67%)[ref. 4] **5b** R= SO_2CH_3 (63%)	—
e	 **6**	 **6a** R= H (75%) **6b** R= SO_2CH_3 (76%)	—
f	 **7**	 **7a** R= H (75%) **7b** R= SO_2CH_3 (21%)	—
g	 **8**	 **8a** R^1= H, R^2 = SO_2CH_3 (70%) **8b** R^1, R^2 = SO_2CH_3 (80%) **8c** R^1= H, R^2 = $SO_2CH_2C_6H_5$ (92%)	— — —

Table 1 (cont.). CSIC Reaction of different carbonyl and anthranilonitrile derivatives

Entry	Starting materials	**Intermediates** (yield)	**Heterocycles** (yield)
g	 **8**	 **8d** (73%)[b]	—
h	 **9**	 **11a** R= H[c] **11b** R= SO_2CH_3 (65%)[d]	 **12** (69%)[a]
i	 **10**	 **13** (76%)  **14a** R = H (88%) **14b** R = CH_3 (97%) **14c** R = Ph (95%)	 **15a** R = H (84%)[e] **15b** R = CH_3 (81%)[a] **15c** R = Ph (91%)[a]
j	 **9**	 **16a** R= H (54%) **16b** R= Me (68%) **16c** R= Ph (75%) **16d** R= Bn (91%)  **17a** R = H (96%) **17b** R = Me (40%) **17c** R = Bn (43%)	 **18a** R= H, R^1= Bn (90%)[a] **18b** R= CH_3SO_2, R^1 = CH_3 (48%)[a]
k	 **10**	 **19a** R= H (98%) **19b** R= SO_2CH_3 (85%)  **20** (54%)	 **21a** R= H (57%)[a] **21b** R= CH_3SO_2 (4%)[f]

(a) With NaH; (b) From compound **8a**; (c) The crude product was used in the next step without further purification; (d) From compound **9**; (e) With DBU; (f) From intermediate **19b**.

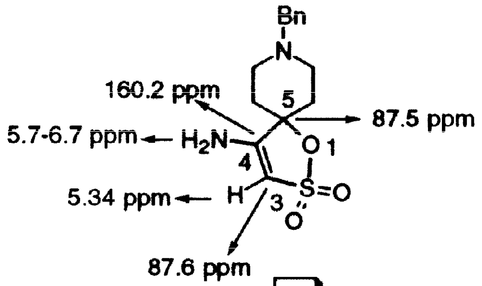
isolated compound. The reaction with γ-keto esters such as ethyl 2-oxocyclohexaneacetate (**5**) were also unsatisfactory. This compound, as recently described,[4] gave the aminonitrile **5a**, that after sulfonation, afforded **5b** (Table 1; entry d), which was totally reluctant to undergo the CSIC reaction, probably due to steric constraints. To test this hypothesis an acyclic analogous γ-keto ester as ethyl levulinate (**6**) was submitted to similar, standard protocols. We could isolate and characterize some precursors (**6a**, **6b**) (Table 1; entry e), but no CSIC reaction could be performed with the products under our conditions.

C) Cyclic Azaketones: *N*-Substituted 4-piperidones/ Tropinone.

There exists in the literature some references describing the synthesis of spiro fused compounds containing the 4-amino-5*H*-1,2-oxathiole 2,2-dioxide moiety as one component. The simplest of these is fused to a cyclohexane ring,[3] more complex derivatives have been synthesized from quinuclidine[1c] and adamantane,[1b] sugars and nucleosides.[1a] All of these spiro fused bicyclics have been synthesized from methanesulfonates of their respective cyanohydrins. To date there are no such compounds in which the C3 position has been substituted (*i.e.* the carbon atom lying between the SO_2 group and the amino bearing C4) which is rather surprising since these "spirosultones" would be easily available from alkylsulfonates different from the methanesulfonates. Neither has any successful attempt to make 4-amino-2,3-dihydroiso-thiazole 1,1-dioxide containing spiro bicyclic heterocycles been described. We wished to know if C3 alkylated derivatives could be obtained and we were unsure if the cyclization of aminonitriles would be possible because steric effects in the carbanion intermediate could become a problem in these crowded compounds. Due to their commercial availability and because of the possibility that the final compounds could show interesting biological activities,[5-8] we chose to use the *N*-protected 4-piperidones (**9** and **10**) and tropinone (**7**) (Table 1) as the cyclic azaketone raw materials.

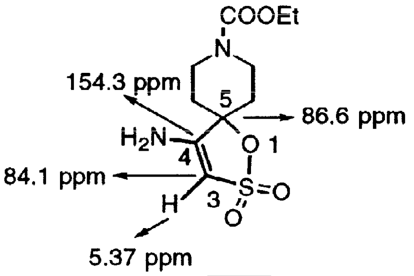
C1) *N*-Substituted 4-piperidones: The sulfonate method for the CSIC reaction. Treatment of these 4-piperidones with sodium cyanide in a biphasic mixture of water and diethyl ether afforded the cyanohydrins **11a** and **13** (Table 1; entries h and i). These could be produced very easily on a gram scale; they were not purified since such compounds are normally unstable. We were able, however, to isolate **13** as a crystalline solid that could be stored below 0 °C with no apparent decomposition.

Treatment of these products with alkylsulfonyl chlorides in the presence of triethylamine gave the intermediates **11b** and **14a-c** in high yields (65-97%), better yields being obtained when compound **13** was used. For the CSIC reaction, we chose NaH as the base since the reaction under these conditions is cleaner than when DBU is used. However, to demonstrate that substechiometric amounts of DBU (catalytic amounts of DBU can be used, but such reactions are rather slow) may be used instead of equimolar amounts of NaH, compound **14a** was cyclized to **15a** (Table 1; entry i) in 84% yield. The reaction in this case took place in 20 h whereas **11b** gave **12** (entry h; Table 1) in 69% yield in only 10 min using NaH. In fact, the cyclization of the other intermediates **14b** and **14c** yielded the required spirobicyles **15b** and **15c** in extremely good yields. Compounds **15b** and **15c** are the first members of compounds of this type that possess a substituent at the C3 position.



12

Figure 2

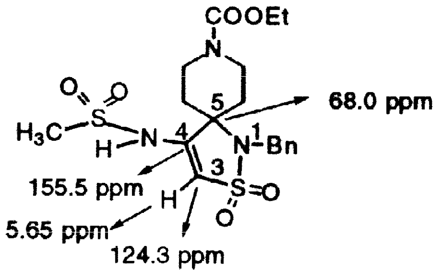


15a

Figure 3

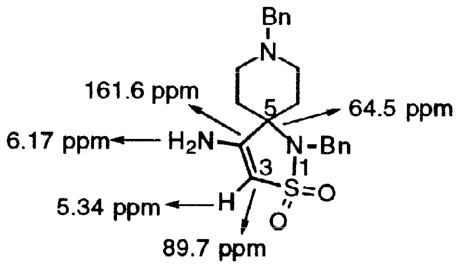
The 1,2-oxathiole portion of these molecules show in their ^{1}H NMR spectra a broad exchangeable doublet at *ca.* 5.7-6.7 ppm due to the NH_2 group and a singlet at 5.34 or 5.37 ppm for H-3, in **12** (Figure 2) and **15a** (Figure 3), respectively. In the ^{13}C NMR spectra the diagnostic signals for the 1,2-oxathiole portion are the following: C3 resonates at 87.6 ppm in compound **12**; at 84.1 ppm in **15a**; C4 appears at 160.2 ppm in **12** and between 152-155 ppm in **15a-c**; C5 appears at 87.5 ppm in compound **12** and at 86.6 ppm in **15a**; very interestingly, the methyl signal at C3 in compound **15b** appears highly shifted at 5.9 ppm.

C2) *N*-Substituted 4-piperidones: The sulfonamide method for the CSIC reaction. The 4-amino-1-aza-2-thiaspiro[5.4]dec-3-ene 2,2-dioxides (**18**, **21**) (Table 1; entries j, k) are completely unknown in the literature. We described recently the synthesis of the related monocyclic 4-amino-2,3-dihydroisothiazole 1,1-dioxides[2a] and thought it opportune to investigate the possibility of making this new ring system. The aminonitriles required for the synthesis of **18** or **21** were prepared readily from compounds **9** and **10** *via* the Strecker reaction.[9] Treatment of these ketones with the appropriate amines, in the presence of an inorganic cyanide, gave the aminonitriles **16a-d** and **19a**. When we attempted to react compounds **16c**[6] and **16d** with methanesulfonyl chloride and triethylamine in dichloromethane, these compounds underwent *retro*-Strecker reactions. The other aminonitriles (**16a**,[10] **16b** and **19a**) gave the expected methanesulfonamides (**17a**, **17b** and **19b**) in good to excellent yields. Derivative **17a** was benzylated under standard conditions (NaH, DMF, benzyl bromide) to give **17c** (Table 1; entry j). Similarly, intermediate **19b** gave under the same conditions the expected product **20** in moderate yield (54%) with minor amounts of the unexpected compound **21b** (4%) (Table 1; entry k). The structure of this methanesulfonyl-transfer spiroheterocycle was established by spectroscopic and elemental analysis. In the ^1H NMR spectrum, in addition to the clear signals for the carbethoxy, benzyl, methanosulfonyl and piperidine protons, a broad singlet was detected at 5.65 ppm for H3 (Figure 4), not affected upon D_2O addition; in the HMQC analysis, this signal showed a cross peak with a carbon (CH acccording to the DEPT experiment) at 124.3 ppm (C3) in the ^{13}C NMR spectrum. These data strongly support the presence of a 2,3-dihydroisothiazole nucleus at the presumed position, with a methanosulfonyl group at the *exo* amino group at C4, as shown in structure **21b**. This was confirmed with the presence of additional quaternary signals for C4 (155.3 ppm) and C5 (68.0 ppm) in the ^{13}C NMR spectrum (Figure 4).



21b

Figure 4



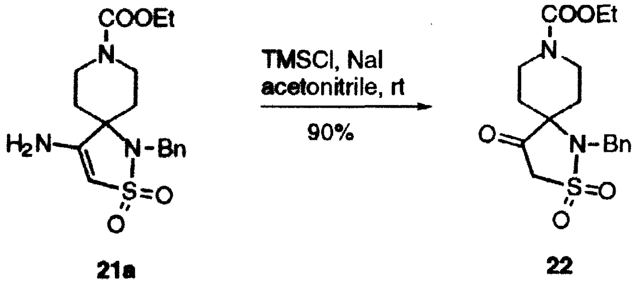
18a

Figure 5

With the desired *N*-benzyl sulfonanides (**17c** and **20**) and the *N*-methyl sulfonanide (**17b**) in hand we attempted the CSIC reaction.

Compounds **17c** and **20** were found to undergo this protocol without any side reactions to obtain the spiroheterocycles **18a** and **21a** in 90% and 57% yields, respectively (Table 1; entries j, k). The H3 and NH_2 signals in the ^1H NMR spectra and the C3, C4 and C5 peaks in the ^{13}C NMR spectra of these compounds were those expected for these molecules and were useful in their structural analysis (see Figure 5 for compound **18a** and **Experimental Section**). Very interestingly, during the formation of compund **21a** from **20** we did not detect the presence of product **21b** (compare with the benzylation of intermediate **19b**, affording a mixture of products **20** and **21b**).

Compound **17b** would not react under standard conditions (NaH, CH_3CN, 25 °C); refluxing the reaction and addition of more NaH (4.5 equiv) resulted finally in the isolation of the 4-methylsulfonamido derivative **18b** as the sole product in low yield (48%) (Table 1; entry k). The spectroscopic data and microanalysis of this compound confirmed the presence of the heterocyclic ring and the CH_3SO_2NH group. In fact, and as found in product **21b**, in the ^1H NMR spectrum we observed, in addition to signals for the *N*-methyl, methanosulfonyl and benzyl groups, a multiplet in the aromatic region integrating for six protons (H3 and C_6H_5); in agreement with this, in the ^{13}C NMR spectrum, signals for C3 (128.9 ppm), C5 (62.1 ppm) and C4 (165.4 ppm) were present.



Scheme 3

Finally, we tried to obtain the free piperidine derivative from hydrolysis of the carbamate function in compound **21a**. In order to do this we sought mild reaction conditions in view of the presumed low stability of the enamine moiety to an acidic medium. Thus, the trimethylsilyl iodide method[11] appeared as the method of choice, and was tested. In these conditions, and contrary to our expectactions, the keto derivative **22** (Scheme 3) was obtained in good yield (90%). This type of heterocycle is known and has been obtained from intramolecular base promoted cylization of sulfonamides derived from α-aminoesters.[12]

C3) Tropinone. The success obtained with piperidone substrates (see above) moved us to explore analogous synthetic sequences dor CSIC reactions with commercially available tropinone (**7**), as starting material. Aminonitrile formation[13] followed by sulfonation gave intermediate (**7b**) (Table 1; entry f), that under basic conditions did not afford the expected cyclization product. Apparently, the extra bridge present in these tropinone derivatives induces some conformational constraints that precludes further CSIC reaction.

D) Anthranilonitrile derivatives

An exciting derivation of the processes described above would constitute the CSIC reaction of conveniently functionalized β-aminonitriles. For this purpose we prepared different sulfonamide derivatives (**8a-d**) (Table 1; entry g) of commercial anthranilonitrile **8**. Unfortunately, in no case, did basic treatment afford the expected heterocycles, and no further studies were addressed in this direction.

In summary, we have extended the CSIC reaction to cyanohydrin and aminonitrile alkylsulfonates and alkylsulfonamides derived from different carbonyl derivatives. Some conclusion can be drawn:

1. Unsaturated ketones are not reliable materials for this protocol. Acetophenone for instance was resistant to the CSIC reaction sequence; probably, this is due to the reversibility of the sequential cyanohydrin (or

aminonitrile) formation, that in this substrate -and in other analogues too- is very shifted to the carbonyl product. However, cyclopropyl methyl ketone gave only the isothiazole heterocycle, but in moderate overall yield.

2. Keto esters: These interesting carbonyl compounds, with an additional carboxylate group, as in other different α- and γ-keto esters (ethyl acetoacetate ethyl 2-oxoccyclohexanecarboxylate and ethyl levulinate) were reluctant to undergo the CSIC reaction. We attribute the failure of the CSIC reaction in these cases to the presence of additional acidic protons -vicinal to the carbalkoxy moiety- in the molecules; as a result, competitive deprotonation arises giving complex reaction mixtures.

3. Cyclic azaketones: Carbonyl derivatives of 4-piperidones afforded 3-substituted 4-amino-1-oxa-2-thiaspiro[4.5]dec-3-ene 2,2-dioxide and 4-amino-1-aza-2-thiaspiro[4.5]dec-3-ene 2,2-dioxide ring systems. The reactions proceeded smoothly as expected and the resulting heterocycles have been obtained in moderate to good yield. In these protocols methanesulfonyl transfer is low yielding and could be made from the products anyway. It is just a derivatisation. By contrast, a related molecule, as tropinone failed. This shows how a constraining system affects CSIC reaction.

4. Anthranilonitriles: Conveniently functionalized β-aminonitrile intermediates derived fom anthranilonitrile, under the usual standard basic heterocyclization conditions, did not afford the expected ring closure. As yet the CSIC reaction is limited to α-aminonitrile intermediates.

EXPERIMENTAL SECTION

General Methods. Reactions were monitored by TLC using precoated silica gel aluminium plates containing a fluorescent indicator (Merck, 5539). Detection was performed by UV (254 nm) followed by charring with sulfuric-acetic acid spray, 1% aqueous potassium permanganate solution or 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous Na_2SO_4 was used to dry organic solutions during workups and the removal of solvents was carried out under vacuum with a rotary evaporator. Flash column chromatography was performed using Kieselgel 60 (230-400 mesh, Merck) and hexane-ethyl acetate mixtures as eluent unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded with a Varian Gemini or Varian VXR-300S spectrometer, using tetramethylsilane as internal standard.

General method for the CSIC reaction.

A) Sodium hydride as base. To a solution of the sulfonate or sulfonamide in acetonitrile (0.056M) sodium hydride (60% dispersion in oil, 1.5 equiv) was added. The mixture was stirred at rt for the required time for completion of the reaction (tlc analysis; usually 1 to 3 h). Water was added and the mixture was extracted with ethyl acetate (three times); the combined organic layers was washed with brine, dried with sodium sulfate, filtered and evaporated. The crude was submitted to flash chromatography eluting with hexane/ethyl acetate mixtures to give the product.

B) DBU as base. To a solution of of the sulfonate or sulfonamide in acetonitrile (0.37M) DBU (0.6 equiv) was added and the mixture stired at rt for 20 h. After evaporation the crude product was submitted to chromatography as above.

2-Amino-2-cyclopropyl propionitrile (2a). To a solution of ammonium chloride (567 mg, 10.6 mmol) in water (5 mL), 30% ammonium hydroxide (1.4 mL, 10.6 mmol) and cyclopropyl methyl ketone (849 mg, 10 mmol) were added. The mixture was cooled in an ice-bath and under stirring potassium cyanide (690 mg, 10.6 mmol) was slowly added. Then, the mixture was warmed at rt for 5 h. The organic mass was extracted with methylene chloride (3 x 5 mL), washed with brine, dried (Na_2SO_4), filtered and evaporated to give a crude product (902 mg, ≈ 81%), pure enough to be used in the next step [^{1}H NMR (200 MHz, $CDCl_3$) δ 1.82 (br s, 2 H), 1.47 (s, 3 H), 1.11-0.82 (m, 2 H), 0.60-0.43 (m, 3 H)].

2-Cyclopropyl-2-methanesulfonamidopropionitrile (2b). To a cold (0 °C) solution of crude **2a** (769 mg, 6.99 mmol) and triethylamine (2.92 mL, 20.98 mmol, 3 equiv) in methylene chloride (20 mL), methanesulfonyl chloride (0.83 mL, 10.49 mmol, 1.5 equiv) was slowly added with stirring, under argon. After 15 h at rt, the mixture was diluted with ethyl acetate and the suspension was filtered over Celite-545. The solution was evaporated and the crude product submitted to flash chromatography eluting with gradient mixtures of hexane/ethyl acetate (20% to 100%) to give **2b** (1.0 g, 83%) as a colourless oil: IR (film) υ 3300, 3000, 2950, 1740, 1440, 1330, 1250, 1150, 1050, 980, 840, 760 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.70 (br s, 1 H,), 3.14 (s, 3 H), 2.02 (s, 3 H), 1.19-1.30 (m, 1 H), 0.79-0.60 (m, 4 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 117.8, 56.2, 42.7, 26.4, 20.1, 3.5, 2.3. Anal. Calcd for $C_7H_{12}N_2O_2S$: C, 44.66; H, 6.43; N, 14.88; S, 17.03. Found: C, 44.37; H, 6.53; N, 14.68; S, 16.95.

2-Cyclopropyl-2-(N-benzyl)methanesulfonamidopropionitrile (2c). A suspension of compound **2b** (400 mg, 2.13 mmol, 1 equiv) and potassium carbonate (588 mg, 4.26 mmol, 2 equiv) in acetonitrile (15 mL) was stirred for 10 min at rt; then, neat benzyl bromide (5.07 µL, 4.26 mmol, 2 equiv) was added. This mixture was refluxed for 2 h. After cooling, this mass was filtered over Celite-545, and the filtrate was evaporated. The resulting crude was submitted to flash chromatography eluting with gradient mixtures of hexane/ethyl acetate (5% to 100%) to give **2c** (248 mg, 42%) as a white solid: mp 68-70 °C; IR (film) υ 3450, 3020, 1460, 1340, 1325, 1210, 1150, 1100, 1060, 950, 800, 750 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44-7.25 (m, 5 H), 4.74 (d, *J*= 16.8 Hz, 1 H), 4.64 (d, *J*= 16.8 Hz, 1 H), 3.04 (s, 3 H), 1.82 (s, 3 H), 1.35-1.24 (m, 1 H), 0.86-0.61 (m, 4 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.8, 128.6, 127.6, 127.2, 117.3, 62.8, 50.7, 41.1, 28.1, 19.4, 5.6, 4.0. Anal. Calcd for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06; S, 11.52. Found: C, 60.37; H, 6.53; N, 10.38; S, 11.35.

4-Amino-3-cyclopropyl-3-methyl-2-phenylmethyl-2,3-dihydroisothiazole 1,1-dioxide (3). Following the **General method (A)**, compound **2c** (47 mg, 0.17 mmol) gave heterocycle **3** (43 mg, 91%) as a white solid: mp 145-147 °C; IR (KBr) υ 3440, 3360, 1650 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50 (m, 2 H), 7.33-7.20 (m, 3 H), 5.72 (br s, 2 H), 5.31 (s, 1 H), 4.38 (s, 2 H), 1.04 (s, 3 H), 0.55-0.45 (m, 5 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160,6, 140.1, 128.9, 128.8, 127.6, 89.2, 66.9, 43.1, 18.5 (x2), 1.7, 1.4; MS (70 eV) m/z 279 (M^++1, 1), 278 (M^+, 1), 263 (4), 237 (13), 213 (6), 174 (6), 158 (4), 109 (4), 91 (100), 65 (10). Anal. Calcd for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06; S, 11.52. Found: C, 60.51; H, 6.61; N, 10.25; S, 11.24.

1-Benzyl-4-cyano-4-hydroxypiperidine (11a). A solution of 1-benzyl-4-piperidone (**9**) (2.0 mL, 10.79 mmol) in diethyl ether (30 mL) was stirred rapidly with a solution of NaCN (0.58 g, 11.9 mmol) and

$NaHCO_3$ (1.82 g, 21.6 mmol) in water at rt for 5 h. The ether was removed and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined ethereal extracts were dried (Na_2SO_4) and were evaporated to yield crude **11a** as a colourless syrup that solidified on standing. This product that contained unreacted starting material was used directly for the next step.

1-Benzyl-4-cyano-4-methanesulfonyloxypiperidine (11b). Crude **11a** (10.79 mmol theor.) in CH_2Cl_2 (35 mL) containing triethylamine (4.5 mL, 32.4 mmol) was cooled to 0 °C. Methanesulfonyl chloride (1.65 mL, 21.6 mmol) was added dropwise and the mixture was stirred at 0 °C for 30 min. The mixture was filtered over Celite and was evaporated, the crude product was purified by flash chromatography (2:1, hexane: ethyl acetate) giving **11b** as a pale yellow syrup (2.07 g, 65% from *N*-benzyl-4-piperidone): IR (KBr) υ 2230, 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.40-7.10 (m, 5 H), 3.52 (s, 2 H), 3.31 (s, 3 H), 2.67 (m, 2 H), 2.20 (m, 4 H), 1.75 (m, 2 H). Anal. Calcd for $C_{14}H_{18}N_2O_3S$: C, 57.12; H, 6.16; N, 9.52; S, 10.89. Found: C, 57.25; H, 6.14; N, 9.85; S, 10.77.

4-Amino-8-benzyl-8-aza-1-oxa-2-thiaspiro[4.5]dec-3-ene 2,2-dioxide (12). Following the **General method (A) 11b** (2.07 g, mmol) after flash chromatography (1:1 hexane: ethyl acetate) gave **12** (1.44 g, 70%) as a pale yellow solid: mp 228-229 °C (from ethyl acetate); IR (KBr) υ 3480, 1650, 1080 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.40-7.20 (m, 5 H), 6.77 (br s, 2 H), 5.34 (s, 1 H), 3.52 (s, 2 H), 2.79 (br m, 2 H), 2.20 (br m, 4 H), 1.66 (br m, 2 H); ^{13}C (acetone-d_6, 50 MHz) δ 160.2, 134.4, 129.7, 128.9, 127.7, 87.6, 87.5, 63.1, 49.5, 34.6. Anal. Calcd for $C_{14}H_{18}N_2O_3S$: C, 57.12; H, 6.16; N, 9.52; S, 10.89. Found: C, 57.37; H, 6.26; N, 9.44; S, 10.84.

1-Carbethoxy-4-cyano-4-hydroxy-piperidine (13). 1-Carbethoxy-4-piperidone (**10**) (82.0 mL, 13.25 mmol) in diethyl ether (40 mL) was stirred rapidly with a solution of NaCN (0.95 g, 14.58 mmol) and $NaHCO_3$ (2.23 g, 26.5 mmol) in H_2O (25 mL) at rt for 1 h. The aqueous layer was extracted with ether (3 x 20 mL) and the combined extracts were dried (Na_2SO_4) and evaporated to yield a white solid (2.53 g). Recrystallisation of this solid (1.54 g) from hexane: ethyl acetate gave **13** (1.18 g, 76% recovery) as colourless needles: mp. 85-87 °C; IR (KBr) υ 3380, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.13 (m, 2 H), 3.73 (m, 3 H), 3.52 (m, 2 H), 2.05 (m, 2 H), 1.24 (m, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.4, 121.0, 67.0, 61.8, 39.8, 36.7, 14.3. Anal. Calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.25; H, 7.14; N, 13.95.

1-Carbethoxy-4-cyano-4-methanesulfonyloxypiperidine (14a). To a solution of **13** (0.99 g, 4.99 mmol) and triethylamine (2.10 mL, 15.0 mmol) in dichloromethane (15 mL) was cooled to 0 °C and methanesulfonyl chloride (0.76 mL, 10.0 mmol) was added dropwise. The reaction was stirred at 0 °C for 30 min and then at rt for 1.5 h. The mixture was filtered over Celite and was evaporated, the residue was purified by flash chromatography (2:1-1:1 hexane: ethyl acetate) to give **14a** as a waxy solid (1.21 g, 88%): mp. 56-58 °C (from 2:1 hexane: ethyl acetate); IR (KBr) υ 1700, 1350, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.14 (q, *J*= 7.1 Hz, 2 H), 3.72 (m, 2 H), 3.19 (s, 2 H), 3.50 (m, 2 H), 2.25 (br m, 4 H), 1.24 (t, *J*= 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.9, 116.6, 61.9, 40.3, 39.5, 35.9, 14.6. Anal. Calcd for $C_{10}H_{16}N_2O_5S$: C, 43.47; H, 5.84; N, 10.14; S, 11.60. Found: C, 43.36; H 5.64; N, 10.22; S 11.31.

1-Carbethoxy-4-cyano-4-ethanesulfonyloxypiperidine (14b). To a solution of **13** (119 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added triethylamine (418 µL, 3.0 mmol), the solution was cooled to 0 °C. After 10 min ethanesulfonyl chloride (142 µL, 1.50 mmol) was added slowly, the temperature was allowed to reach rt over 1 h. Water (3 mL) was added and the mixture was extracted with ethyl acetate (3 x 5 mL). The organic phase was dried (Na_2SO_4) and evaporated to give a crude product that was purified by column chromatography (3-10% ethyl acetate in hexane) to yield **14b** (270 mg, 97%) as a colourless oil: IR (film) υ 1710, 1440, 1360, 1180 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.12 (q, *J*= 7.4 Hz, 2 H), 3.89-3.76 (m, 2 H), 3.54-3.41 (m, 2 H), 3.29 (q, *J*= 7.1 Hz, 2 H, $\mathrm{COOC}H_2\mathrm{CH}_3$), 2.34-2.13 (m, 4 H), 1.50 (t, *J*= 7.4 Hz, 3 H), 1.24 (t, *J*= 7.1 Hz, 3 H, $\mathrm{COOCH_2C}H_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.0, 116.8, 76.6, 61.9, 47.7, 39.5, 35.9, 14.6, 8.1. Anal. Calcd for $C_{11}H_{18}N_2O_5S$: C, 45.51; H, 6.25; N, 9.65; S, 11.04. Found: C, 45.72; H, 6.33; N, 9.47; S, 11.13.

1-Carbethoxy-4-cyano-4-phenylmethylsulfonyloxypiperidine (14c). To a solution of **13** (198 mg, 1.0 mmol) and triethylamine (418 mL, 3.0 mmol) in dichloromethane (5 mL) at 0 °C was added α-toluenesulfonyl chloride (229 mg, 1.2 mmol). The reaction was stirred at rt for 28 h, water (3 mL) was added and the mixture was extracted with ethyl acetate (3 x 5 mL). The dried (Na_2SO_4) extracts were evaporated and the crude product was purified by flash chromatography (0 to 20% ethyl acetate in CH_2Cl_2) and gave **14c** (288 mg, 95%) as a white solid: mp 92-93 °C; IR (KBr) υ 1700, 1365, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.39 (br s, 5 H), 4.49 (s, 2 H), 4.10 (q, *J*= 7.2 Hz, 2 H), 3.76-3.66 (m, 2 H), 3.48-3.35 (m, 2 H), 2.20-2.01 (m, 4 H), 1.22 (t, *J*= 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.9, 130.8, 129.5, 129.0, 126.9, 116.5, 78.7, 61.9, 58.8, 39.5, 35.7, 14.6. Anal. Calcd for $C_{16}H_{20}N_2O_5S$: C, 54.53; H, 5.72; N, 7.95; S, 9.10. Found: C, 54.27; H, 5.66; N, 7.83; S, 9.02.

4-Amino-8-aza-8-carbethoxy-1-oxa-2-thiaspiro[4.5]dec-3-ene 2,2-dioxide (15a). Following the **General method (B) 14a** (1.03 g, 3.74 mmol) after chromatography (20:1-10:1, CH_2Cl_2: MeOH) gave **15a** (0.871 g, 84%) as a colourless solid: mp 227-228 °C (from 1:1 acetonitrile: toluene); IR (KBr) υ 3440, 3360, 1680, 1290, 1160 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 6.77 (br s, 2 H), 5.37 (s, 1 H), 4.07 (m, 4 H), 2.96 (m, 2 H), 2.03 (m, 2 H), 1.63 (m, 2 H), 1.18 (t, *J*= 7.1 Hz, 3 H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 159.2, 154.3, 86.6, 84.1, 60.8, 39.4, 32.7, 14.5. Anal. Calcd for $C_{10}H_{16}N_2O_5S$: C, 43.47; H, 5.84; N, 10.14; S, 11.60. Found: C, 43.33; H, 5.68; N, 10.04; S, 11.37.

4-Amino-8-aza-8-carbethoxy-3-methyl-1-oxa-2-thiaspiro[4.5]dec-3-ene 2,2-dioxide (15b). Following the **General method (A)** compound **14b** (200 mg, 0.69 mmol, 1.0 equiv) after chromatography (1:1 hexane: ethyl acetate - 100% ethyl acetate) afforded **15b** (162 mg, 81%) as a white solid: mp 272-273 °C (from CH_2Cl_2); IR (KBr) υ 3420, 3240, 1680, 1250 cm^{-1}; ^{1}H NMR (acetone-d_6, 200 MHz) δ 5.78 (br s, 2 H), 4.15 (m, 2H), 4.07 (q, *J*= 7.2 Hz, 2 H), 3.07 (m, 2 H), 2.15 (dt, *J*= 13.0 Hz, *J*= 5.0 Hz, 2 H), 1.83 (s, 3 H), 1.73 (m, 2 H), 1.21 (t, *J*= 7.2 Hz, 3 H); ^{13}C NMR (acetone-d_6, 50 MHz) δ 156.0, 152.5, 94.8, 86.4, 61.7, 40.5, 34.0, 14.9, 5.9. Anal. Calcd for $C_{11}H_{18}N_2O_5S$: C, 45.51; H, 6.25; N, 9.65; S, 11.04. Found: C, 45.49; H, 6.12; N, 9.45; S, 10.95.

4-Amino-8-aza-8-carbethoxy-3-phenyl-1-oxa-2-thiaspiro[4.5]dec-3-ene 2,2-dioxide (15c). Following the **General method (A)** compound **14c** (270 mg, 0.76 mmol, 1.0 equiv), after recrystallization of the crude from CH_2Cl_2: hexane, gave **15c** (246 mg, 91%) as a white solid: mp 206-207 °C; IR (KBr) υ 3460, 3320, 3230, 1670, 1630, 1250 cm^{-1}; ^{1}H NMR (acetone-d_6, 200 MHz) δ 7.59-7.32 (m, 5 H), 6.24 (br s, 2 H), 4.19 (m, 2 H), 4.09 (q, *J*= 7.2 Hz, 2 H), 3.15 (m, 2 H), 2.29 (dt, *J*= 13.5 Hz, *J*= 7.2 Hz, 2 H), 1.91 (m, 2 H), 1.22 (t, *J*= 7.2 Hz, 3 H); ^{13}C NMR (acetone-d_6, 50 MHz) δ 155.6, 153.2, 129.9, 128.9, 128.6, 128.5, 85.9, 61.8, 40.5, 34.1, 15.0. Anal. Calcd for $C_{16}H_{20}N_2O_5S$: C, 54.53; H; 5.72; N, 7.95; S, 9.10. Found: C, 54.56; H; 5.54; N, 7.79; S, 9.07.

4-Amino-1-benzyl-4-cyanopiperidine (16a). 1-Benzyl-4-piperidone (**9**) (5.0 mL, 27 mmol) was stirred rapidly with a solution of NH_4Cl (1.73 g, 32.4 mmol) and 30% NH_4OH (2.0 mL, 15 mmol) in water (20 mL) for 20 min. Solid NaCN (1.47 g, 30 mmol) was added slowly, at this point the piperidone derivative was seen to begin to dissolve. Five minutes after the addition of all of the NaCN, a thick white precipitate began to separate, the reaction was stirred for a further 30 min. Water (20 mL) was added and the mixture was extracted with dichloromethane (3 x 30 mL), the solvent was dried (Na_2SO_4) and evaporated to yield a solid that was recrystallised from hexane: ethyl acetate and gave **16a** as white needles (3.15 g, 54%): mp 79-80 °C; IR (KBr) υ 3360, 1630, 1450, 1130 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.40-7.25 (m, 5 H), 3.55 (s, 2 H), 2.80-2.70 (br s, 4 H), 2.50-2.40 (br m, 2 H), 2.20-2.10 (br m, 2 H), 1.98-1.90 (br m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 138.0, 129.7, 129.0, 126.8, 124.2, 116.1, 61.7, 49.0, 36.6. Anal. Calcd for $C_{13}H_{17}N_3$: C, 72.52; H, 7.96; N, 19.52. Found: C, 72.33; H, 7.85; N, 19.34.

1-Benzyl-4-cyano-4-methylaminopiperidine (16b). 1-Benzyl-4-piperidone (**9**) (5.0 mL, 27 mmol) was stirred rapidly with a solution of methylamine hydrochloride (2.02 g, 30 mmol) and 40% $MeNH_2$ (3.0 mL) in water (30 mL). Solid NaCN (1.47 g, 30 mmol) was added slowly and the reaction was stirred at high speed for 24 h. The mixture was extracted with CH_2Cl_2 (3 x 30 mL) and the extract was dried (Na_2SO_4) and evaporated to give a thick yellow oil that solidified on freezing. This crude product was recrystallised from 4:1 hexane: ethyl acetate to give **16b** (4.21 g, 68%) as white needles: mp 52-53 °C; IR (KBr) υ 3372, 1628, 1445, 1135 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.30 (s, 5 H), 3.50 (s, 2 H), 2.72 (m, 3 H), 2.28 (s, 3 H), 2.18 (m, 2 H), 1.93 (m, 2 H), 1.53 (m, 2 H). Anal. Calcd for $C_{14}H_{19}N_3$: C, 73.33; H, 8.35; N, 18.32. Found: C, 73.54; H, 8.22; N, 18.03.

1-Benzyl-4-cyano-4-phenylaminopiperidine (16c)[6]. 1-Benzyl-4-piperidone (**9**) (0.5 mL, 2.7 mmol) was stirred rapidly with a solution of aniline (246 µl, 2.7 mmol), water (0.6 mL) and acetic acid (1.8 mL). Solid KCN (281 mg, 1.6 mmol) was added slowly and the reaction was stirred at high speed for 28 h. The mixture was poured in a mixture of 30% NH_4OH (13 mL, 0.1 mol) and ice (2.5 g). The solid was isolated and washed with cold toluene to give the known compound[6] **16c** as a white solid (590 mg, 75%): mp 132-133 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.30-7.20 (m, 8 H), 6.89 (m, 2 H), 3.64 (s, 1 H), 3.55 (s, 2 H), 2.80 (m, 2 H), 2.51-2.29 (m, 4 H), 1.91 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 143.3, 138.0, 129.2, 128.9, 128.3, 127.2, 120.8, 120.7, 117.8, 62.5, 53.0, 49.2, 36.1. Anal. Calcd for $C_{19}H_{21}N_3$: C, 78.32; H, 7.26; N, 14.42. Found: C, 78.54; H, 7.22; N, 14.23.

1-Benzyl-4-cyano-4-benzylaminopiperidine (16d). 1-Benzyl-4-piperidone (**9**) (100 mg, 0.53 mmol) was stirred rapidly with a solution of benzylamine hydrochloride (83 mg, 0.58 mmol) in water (2 mL). Solid KCN (38 mg, 0.58 mmol) was added slowly and the reaction was stirred at high speed for 30 min. The mixture was poured in a mixture of 30% NH_4OH (13 mL, 0.1 mol) and ice (2.5 g). The solid was isolated and dried to give **16d** (141 mg, 91%): mp 49-50 °C; IR (KBr) υ 3400, 1470, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.32 (m, 10 H), 3.91 (s, 2 H), 3.56 (s, 2 H), 2.86 (m, 2 H), 2.39 (m, 2 H), 2.16 (m, 2 H), 1.85 (m, 2 H), 1.54 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.1, 138.1, 128.9, 128.5, 128.3, 128.2, 127.4, 127.1, 121.6, 62.6, 56.0, 49.4, 48.5, 35.5. Anal. Calcd for $C_{20}H_{23}N_3$: C, 78.65; H, 7.59; N, 13.76. Found: C, 78.74; H, 7.52; N, 13.88.

1-Benzyl-4-cyano-4(methyl)methanesulfonamidopiperidine (17b). To a solution of **16b** (2.30 g, 10.0 mmol) and Et_3N (2.80 g, 20 mmol) in CH_2Cl_2 (35 mL) was added dropwise methanesulfonyl chloride (0.93 mL, 12.0 mmol) at 0 °C. The mixture was stirred for 2 h, was filtered over Celite and evaporated. The residue was purified by flash chromatography (1:1 hexane: ethyl acetate) yielding **17b** as a white solid (1.25 g, 40%): mp 205-206 °C (from 3:1, toluene: acetonitrile); R (film) υ 2990, 1660, 1450, 1090 cm^{-1}; ^{1}H NMR

($CDCl_3$, 200 MHz) δ 7.29 (s, 5 H), 5.55 (br s, 1 H), 3.52 (s, 2 H), 3.17 (s, 3 H), 2.83 (m, 2 H), 2.39 (m, 4 H), 2.01 (m, 2 H). Anal. Calcd for $C_{15}H_{21}N_3O_2S$: C, 58.61; H, 6.89; N, 13.67; S, 10.43. Found: C, 58.55; H, 6.73; N, 13.48; S, 10.12.

1-Benzyl-4-cyano-4-methanesulfonamidopiperidine (17a). To a solution of **16a** (761 mg, 3.53 mmol) and Et_3N (1.50 mL, 10.6 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added methanesulfonyl chloride (0.41 mL, 5.29 mmol). The reaction was stirred at rt for 4.5 h., was filtered over Celite and was evaporated. Column chromatography (3:1-1:1, hexane: ethyl acetate) yielded **17a** (1.00 g, 96%) as a syrup: IR (film) υ 3250, 2985, 1660, 1450, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.29 (s, 5 H), 5.55 (br s, 1 H), 3.52 (s, 2 H), 3.17 (s, 3 H), 2.83 (m, 2 H), 2.39 (m, 4 H), 2.01 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 137.6, 128.7, 128.1, 127.1, 119.3, 62.1, 52.8, 48.8, 42.6, 35.9. Anal. Calcd for $C_{14}H_{19}N_3O_2S$: C, 57.32; H, 6.53; N, 14.32; S,10.93. Found: C, 57.43; H, 6.65; N, 14.21; S, 10.86.

1-Benzyl-4-cyano-4-(benzyl)methanesulfonamidopiperidine (17c). To a solution of **17a** (0.90 g, 3.07 mmol) in DMF (5 mL) under an argon atmosphere was added sodium hydride (159 mg, 3.97 mmol, 1.5 equiv, 60 % dispersion in oil), the mixture was stirred at rt for 5 min and then benzyl bromide (474 μL, 3.99 mmol, 1.5 equiv) was added slowly. The reaction was stirred for 4.5 h, ice-water (5 mL) was added, the solution was extracted with ethyl acetate (3 x 5 mL). The combined organic layer was washed with water (5 mL) and was dried over Na_2SO_4. The solvent was evaporated and the remaining material was purified by flash chromatography (20%-50% ethyl acetate in hexane) to give **17c** (507 mg, 43%) as a yellow solid: mp 40-41 °C (from); IR (KBr) υ 3440, 1350, 1150, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.41-7.22 (m, 10 H), 4.63 (s, 2 H), 3.47 (s, 2 H), 3.11 (s, 3 H), 2.87 (m, 2 H), 2.31 (m, 4 H), 2.08 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 137.6, 128.9, 128.7, 128.3, 127.2, 126.7, 118.9, 62.2, 60.4, 50.6, 50.0, 40.6, 36.2. Anal. Calcd for $C_{21}H_{25}N_3O_2S$: C, 65.77; H, 6.57; N, 10.96; S, 8.36. Found: C, 65.68; H, 6.44; N, 10.87; S, 8.24.

4-Amino-1,8-diaza-1,8-dibenzyl-2-thiaspiro[4.5]dec-3-ene 2,2-dioxide (18a). Following the **General method (A)** compound **17c** (49 mg, 0.13 mmol) after chromatography (50-100%, ethyl acetate in hexane) gave **18a** (44 mg, 90%) as a yellow solid: mp 158-159 °C (from ethyl acetate:hexane); IR (KBr) υ 3370, 3090, 1640, 1240 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 7.52 (m, 2 H), 7.33-7.21 (m, 8 H), 6.17 (br s, 2 H), 5.34 (s, 1 H), 4.45 (s, 2 H), 3.46 (s, 2 H), 2.65 (m, 2 H), 2.45 (m, 2 H), 2.07-2.02 (m, 4 H); ^{13}C NMR (acetone d_6, 75 MHz) δ 161.6, 140.1, 32.9, 138.7, 129.5, 128.6, 128.5, 128.1, 127.8, 127.4, 89.7, 64.5, 62.5, 49.6, 43.3. Anal. Calcd for $C_{21}H_{25}N_3O_2S$: C, 65.77; H, 6.57; N, 10.96; S, 8.36. Found: C, 65.66; H, 6.49; N, 10.85; S, 8.22.

8-Benzyl-4-methanesulphonamido-1-methyl-1,8-diaza-2-thiaspiro[4.5] dec-3-ene 1,1-dioxide (18b). Following the **General method (A)** compound **17b** (0.396 g, 1.29 mmol) after the work-up gave **18b** as a syrup (0. 241 g, 49%): IR (KBr) υ 3440, 1640, 1310, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.62 (br s, 1 H), 7.38-7.18 (m, 6 H), 3.59 (s, 2 H), 3.20 (s, 2 H), 2.83 (m, 2 H), 2.69 (s, 3 H), 2.57 (m, 2 H), 2.04 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.4, 136.3, 128.9, 128.8, 127.9, 63.0, 62.0, 46.8, 45.0, 28.6, 23.9. Anal. Calcd for $C_{16}H_{23}N_3S_2O_4$: C, 49.85; H, 6.01; N, 10.90; S, 16.63. Found: C, 49.62; H, 6.04; N, 10.94; S, 16.46.

4-Amino-1-benzyl-8-carbethoxy-1,8-diaza-2-thiaspiro[4.5]dec-3-ene 2,2-dioxide (21a). Following the **General method (A)** compound **20** (300 mg, 0.82 mmol) after chromatography (50%-100% ethyl acetate in hexane) gave **21a** (170 mg, 57%) as a white solid: mp 79-80 °C (from hexane/ ethyl acetate); IR (KBr) υ 3440, 1690, 1650, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.44-7.24 (m, 5 H), 5.42 (s, 1 H), 4.78

(br s, 2 H), 4.42 (s, 2 H), 4.06 (q, J= 7.1 Hz, 2 H), 3.47 (m, 4 H), 2.05 (m, 4 H), 1.21 (t, J= 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.4, 155.3, 137.7, 128.6, 127.5, 90.3, 63.2, 61.6, 43.0, 40.0, 31.8, 14.5. Anal. Calcd for $C_{17}H_{23}N_3O_4S$: C, 55.87; H, 6.34; N, 11.50; S, 8.77. Found: C, 55.64; H, 6.45; N, 11.63; S, 8.58.

4-Amino-1-carbethoxy-4-cyanopiperidine (19a). 1-Carbethoxy-4-piperidone (**10**) (1.0 g, 5.84 mmol) was stirred rapidly with a solution of NH_4Cl (406 mg, 7.59 mmol) and 30% NH_4OH (1.0 mL) in water (5 mL) for 1 h. Solid KCN (494 mg, 7.59 mmol) was added slowly and the reaction was stirred for a further 21 h. Water (10 mL) was added and the mixture was extracted with dichloromethane (3 x 10 mL), the solvent was dried (Na_2SO_4) and evaporated to yield a solid that was recrystallised from hexane: ethyl acetate gave **19a** as white needles (1.1 g, 98%): mp 47-48 °C; IR (KBr) υ 3380, 1690, 1450, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.96 (q, J= 7.2 Hz, 2 H), 3.80 (m, 2 H), 3.07 (m, 2 H), 1.84 (br s, 2 H), 1.79 (m, 2 H), 1.47 (m, 2 H), 1.09 (t, J= 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 138.0, 129.7, 129.0, 126.8, 124.2, 116.1, 61.7, 49.0, 36.6. Anal. Calcd for $C_9H_{15}N_3O_2$: C, 54.81; H, 7.67; N, 21.30. Found: C, 54.76; H, 7.85; N, 21.44.

1-Carbethoxy-4-cyano-4-methysulfonamidopiperidine (19b). To a solution of 4-amino-4-cyano-1-carbethoxypiperidine (**19a**) (0.78 g, 3.95 mmol) in dry CH_2Cl_2 (10 mL) was added triethylamine (1.65 mL, 11.86 mmol, 3.0 equiv), the solution was cooled to 0 °C and methanesulfonyl chloride (0.46 mL, 5.92 mmol, 1.5 equiv) was added dropwise. The reaction was stirred for 3.5 h., water (5 mL) was added and the mixture was extracted with ethyl acetate (3 x 5 mL). The organic phase was dried (Na_2SO_4) and evaporated to give a crude material that was purified by column chromatography (10-40% ethyl acetate in dichloromethane) yielding **19b** (0.93 g, 85%) as a colourless oil: IR (film) υ 3250, 1675, 1440, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.06 (br s, 1 H), 4.06 (q, J= 7.1 Hz, 2 H), 3.97 (m, 2 H), 3.22 (m, 2 H), 3.13 (s, 3 H), 2.27 (m, 2 H), 1.85 (ddd, J= 14.1 Hz, J= 10.0 Hz, J= 4.0 Hz, 2 H), 1.21 (t, J= 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.0, 118.7, 61.8, 52.7, 42.6, 39.6, 35.5, 14.4. Anal. Calcd for $C_{10}H_{17}N_3O_4S$: C, 43.63; H, 6.22; N, 15.26; S, 11.64. Found: C, 43.67; H, 6.16; N, 15.33; S, 11.43.

1-Carbethoxy-4-cyano-4(benzyl)methanesulfonamidopiperidine (20) and 1-Benzyl-8-carbethoxy-4-methanesulfonamido-1-methyl-1,8-diaza-2-thiaspiro[4.5] dec-3-ene 1,1-dioxide (21b). To a solution of **19b** (0.76 g, 2.75 mmol) in DMF (9 mL) under an argon atmosphere was added NaH (198 mg, 4.95 mmol, 1.8 equiv, 60% dispersion in oil), the solution was stirred at rt for 10 min and benzyl bromide (0.59 mL, 4.95 mmol, 1.8 equiv) was added dropwise. The reaction was stirred at rt for 9 h, ice-water (10 mL) was added and the resulting solution was extracted with ethyl acetate (3 x 5 mL). The organic extract was washed with water (5 mL), was dried (Na_2SO_4) and was evaporated. Purification of the crude residue by flash chromatography (5-100% ethyl acetate in dichloromethane) yielded **20** (0.54 g, 54% as a white solid) and **21b** (60 mg, 4%, colourless oil). **20**: mp 121-122 °C; IR (KBr) υ 3440, 1700, 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz) δ 7.38-7.26 (m, 5 H), 4.60 (s, 2 H), 4.14-4.04 (m, 3 H), 3.10 (s, 3 H), 3.00 (m, 2 H), 2.31 (m, 2 H), 1.90 (dt, J= 12.8 Hz, J= 4.3 Hz, 2 H), 1.19 (t, J= 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.8, 137.2, 128.9, 127.9, 126.9, 118.2, 61.7, 60.3, 50.5, 40.8, 40.6, 35.9, 14.5. *Anal.* Calcd for $C_{17}H_{23}N_3O_4S$: C, 55.87; H, 6.34; N, 11.50; S, 8.77. Found: C, 55.64; H, 6.23; N, 11.39; S, 8.98. **21b**: IR (KBr) υ 3370, 1640, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.29 (m, 5 H), 5.65 (s, 1 H), 4.53 (s, 2 H), 4.08 (q, J= 7.1 Hz, 2 H), 3.93 (m, 2 H), 3.42 (m, 2 H), 2.91 (s, 3 H), 2.91 (s, 3 H), 1.71 (s, 1 H), 1.21 (t, J= 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.3, 135.9, 128.8, 128.5, 127.9, 124.3, 68.0, 61.4, 52.8, 42.7, 40.4, 38.7, 29.7, 28.8, 14.5. Anal. Calcd for $C_{18}H_{25}N_3O_6S_2$: C, 48.74; H, 5.68; N, 9.47; S, 14.46. Found: C, 48.55; H, 5.39; N, 9.28; S, 14.31. .

1-Benzyl-8-carbethoxy-1,8-diaza-4-keto-2-thiaspiro[4.5]dec-3-ene 2,2-dioxide (22). To a solution of Me_3SiCl (22 μl, 0.17 mmol, 1.1 equiv) in acetonitrile (2 mL), sodium iodide (26 mg, 0.17 mmol, 1.1 equiv) was added at rt, under argon. After 30 min a solution of **21a** (57 mmol, 0.16 mmol) in acetonitrile (1 mL) was added. The mixture was stirred 15 min and quenched with a saturated aqueous solution of sodium thiosulfate (0.2 mL), evaporated to dryness. The crude was submitted to flash chromatography (0% to 20% of methanol:methylene chloride mixtures) to give **22** (51.4 mg, 90%) as a white solid: mp 134-135 °C; IR (KBr) υ 3450, 1760, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39-7.29 (m, 5 H), 4.41 (s, 2 H), 4.12 (q, *J*= 7.1 Hz, 2 H), 4.08 (m, 2 H), 3.98 (s, 2 H), 3.22 (m, 2 H), 1.82 (m, 4 H), 1.24 (t, *J*= 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 199.8, 155.3, 136.9, 128.7, 127.9, 127.5, 69.5, 61.6, 54.7, 41.1, 39.9, 30.3, 14.6. Anal. Calcd for $C_{17}H_{22}N_2SO_5$: C, 55.72; H, 6.05; N, 7.64; S, 8.75. Found: C, 55.62; H, 6.04; N, 7.94; S, 8.46.

Attempted CSIC reaction with ethyl acetoacetate (*via* sulfonate). Ethyl acetoacetae (2 g, 15.4 mmol) dissolved in ethyl ether (15 mL) was added to a solution of sodium bicarbonate (2.58 g, 30.7 mmol, 2 equiv) and potassium cyanide (1.3 g, 20.0 mmol, 1.3 equiv) in water (15 mL). The mixture was stirred for 45 min and extracted with ethyl ether. The organic layer was dried, filtered and evapoated. The crude (2.2 g, 91%) was used withoout further purification in the next step.

A solution of the above crude (300 mg, 1.91 mmol) in methylene chloride (5 mL) was treated with methanesulfonyl chloride (222 μL, 2.86 mmol, 1.5 equiv) and triethylamine (798 μL, 5.73 mmol, 3 equiv). After 5 min, ethyl acetate was added and the organic layer was washed with brine, dried, filtered, evaporated, and the crude submitted to flash chromatography (hexane: ethyl acetate, 20%) to give compound **4** (14.5 mg, 5.8%), **4a** (211 mg, 47%) and **4b** (43.3 mg, 11%). **4a**: oil; IR (film) υ 3450, 2990, 1740, 1256, 1030 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.22 (q, *J*= 7.2 Hz, 2 H), 3.26 (s, 3 H), 3.20 (d, *J*= 16.8 Hz, 1 H), 2.98 (d, *J*= 16.8 Hz, 1 H), 2.01 (s, 3 H), 1.29 (t, *J*= 7.2 Hz, 3 H); ^{13} C NMR (50 MHz, $CDCl_3$) δ 166.5, 116.5, 74.2, 61.4, 43.9, 39.8, 26.6, 13.8. Anal. Calcd for $C_8H_{13}NO_5S$: C, 40.84; H, 5.57; N, 5.95; S, 13.63. Found: C, 40.77; H, 5.53; N, 5.98; S, 13.35. **4b**: oil; IR (film) υ 2986, 1735, 1250, 1030 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.92 (d, *J*= 0.9 Hz, 1 H), 4.18 (q, *J*= 7.2 Hz, 2 H), 3.17 (s, 3 H), 2.45 (d, *J*= 0.9 Hz, 3 H), 1.28 (t, *J*= 7.2 Hz, 3 H). Anal. Calcd for $C_7H_{12}O_5S$: C, 40.38; H, 5.81; S, 15.40. Found: C, 40.57; H, 5.63; S, 15.65.

Attempted CSIC reaction with ethyl acetoacetate (*via* sulfonamide). Benzyl amine hydrochloride (364 mg, 2.53 mmol) and potassium cyanide (166 mg, 2.53 mmol, 1.1 equiv) were added to a solution of ethyl acetoacetate (**4**) (300 mg, 2.30 mmol) in water (4.6 mL). After 4 h at rt the mixture was diluted with methylene chloride and extracted several times (3x5 mL), the organic layer was washed with brine, dried, filtered, evaporated. The crude was submitted to flash chromatography (hexane/ethyl acetate, 10%) to give **4c** (260 mg, 46%) and **4d** (261 mg, 52%). **4c**: oil; IR (film) υ 3450, 2980, 1730, 1256, 1030 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39-7.22 (m, 5 H), 4.20 (q, *J*= 7.2 Hz, 2 H), 3.97-3.82 (m, 2 H), 2.82 (d, *J*= 16 Hz, 1 H), 2.74 (d, *J*= 16 Hz, 1 H), 2.53 (br s, 1 H), 1.64 (s, 3 H), 1.28 (t, *J*= 7.2 Hz, 3 H). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.66; H, 6.61; N, 11.23. **4d**: oil; IR (film) υ 3465, 2990, 1730, 1640, 1260, 1030 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.94 (br s , 1H), 7.33-7.25 (m, 5H), 4.52 (s, 1 H), 4.42 (d, *J*= 6.4 Hz, 2 H), 4.09 (q, *J*= 7.2 Hz, 2 H), 1.90 (s, 3 H), 1.25 (t, *J*= 7.2 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.6, 161.8, 138.7, 128.8, 127.3, 126.7, 83.2, 58.3, 46.8, 19.3, 14.6. Anal. Calcd for $C_{13}H_{16}NO_2$: C, 71.53; H, 7.39; N, 6.42. Found: C, 71.42; H, 7.62; N, 6.39.

7a-Cyano-1-methanesulfonyl-octahydro-*cis*-1*H*-indol-2-one (5b). To a solution of compound

5a [4] (597 mg, 3.63 mmol) in acetonitrile (15 mL), under argon, cooled in an ice bath, sodium hydride (363 mg, 9.09 mmol, 2.5 equiv) and methanesulfonyl chloride (0.56 mL, 7.27 mmol, 2 equiv) were added. After stirring for 16 h at rt the mixture was treated with water and extracted with ethyl acetate. The organic layer was washed with brine, dried, filtered and evaporated. The crude was submitted to flash chromatography (hexane/ethyl acetate, 30%) to give compound **5b** (439 mg, 63%) as a white solid: mp 130-132 °C; IR (KBr) υ 2920, 2830, 1740, 1430, 1330, 1215, 1130, 1090, 950, 800, 750 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.37 (s, 3 H), 2.82-2.78 (m, 1 H), 2.66-2.48 (m, 2 H), 2.16-2.07 (m, 1 H), 1.97-1.90 (m, 1 H), 1.79-1.43 (m, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.6, 118.1, 61.0, 42.3, 38.5, 34.5, 33.1, 24.8, 20.6, 19.9. Anal. Calcd for $C_{10}H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.56; S, 13.23. Found: C, 49.36; H, 5.54; N, 11.39; S, 13.51.

5-Cyano-5-methyl-2-pyrrolidone (6a). To a solution of ethyl levulinate (1.0 g, 7 mmol) in water (21 mL) ammonium chloride (561.6 mg, 10.5 mmol, 1.5 equiv) and ammonium hydroxide (1.38 mL, 10.5 mmol, 1.5 equiv) were added. After stirring for 30 min, potassium cyanide (683.8 mg, 10.5 mmol, 1.5 equiv) was added. After stirring for 65 h at rt the mixture was extracted with methylene chloride (5 x 20 mL), the combined organic layers was washed with brine, dried with sodium sulfate, filtered and evaporated. The crude was purified by flash chromatography eluting with MeOH:CH_2Cl_2 (3%) to give compound **6a** (650 mg, 74%) as a white solid: mp 133-135 °C; IR (KBr) υ 3200, 2200, 1680, 1630, 1400, 1350 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (br s, 1 H), 2.70-2.58 (m, 2 H), 2.52-2.41 (m, 1 H), 2.19-2.08 (m, 1 H), 1.71 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.2, 120.9, 53.0, 34.7, 29.8, 26.6. Anal. Calcd for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.22; H, 6.64; N, 22.33.

5-Cyano-*N*-methanesulfomamide-5-methyl-2-pyrrolidone (6b). To a solution of compound **6a** (375 mg, 3.02 mmol) in dry tetrahydrofuran (15 mL), under argon, cooled at -78 °C, LiBu (2.27 mL, 3.62 mmol, 1.2 equiv, 1.6M in hexane) was added to the reaction mixture; after 30 min methanesulfonyl chloride (351 μl, 4.53 mmol, 1.5 equiv) was slowly added to the reaction *via* syringe. The mixture was warmed at -50 °C during 1 h 30 min; then, the reaction was quenched by water addition, and the mass was extracted with ethyl acetate (5 x 10 mL). The organic phase was dried, filtered, evaporated and submitted to chromatography (hexane/ethyl acetate, 40%) to give product **6b** (468 mg, 76%) as an oil: IR (KBr) υ 2980, 2900, 1730, 1340, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.34 (s, 3 H), 2.76-2.64 (m, 3 H), 2.37-2.23 (m, 1 H), 1.98 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.8, 118.9, 57.7, 41.7, 33.6, 29.2, 27.0. Anal. Calcd for $C_7H_{10}N_2O_3S$: C, 41.57; H, 4.98; N, 13.85; S, 15.86. Found: C, 41.29; H, 4.85; N, 13.78; S, 15.71.

3β-(Benzylamino)-8-methyl-8-azabicyclo[3.2.1]octane-3α-carbonitrile (7a). Benzylamine hydrochloride (227 mg, 1.58 mmol, 1.1 equiv) and potassium cyanide (103 mg, 1.58 mmol, 1.1 equiv) were added to a solution of *N*-methyltropinone (**7**) (200 mg, 1.44 mmol) in water (5 mL). After 20 h at rt the mixture was cooled at 4 °C, filtered and washed with ammonium hydroxide until pH= 10-11. The solid was dissolved in methylene chloride, dried with sodium sulfate, filtered and evaporated to give pure compound (**7a**) (277 mg, 75%) as a white solid: mp 46-48 °C ; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5 H), 3.81 (d, *J*= 6.8 Hz, 2 H), 3.23 (br s, 1 H), 2.31 (s, 3 H), 2.05-1.98 (m, 8 H), 1.45 (t, *J*= 7.0 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.0, 128.4, 127.3, 124.3, 59.4 (x2), 50.1, 48.1, 40.6 (x2), 39.0, 25.5. Anal. Calcd for $C_{16}H_{21}N_3$: C, 75.26; H, 8.29; N, 16.46. Found: C, 75.36; H, 8.44; N, 16.23.

3β-(*N*-Benzyl)methanesulfonylamido-8-methyl-8-azabicyclo[3.2.1]octane-3α-carbonitrile (7b). Methanesulfonyl chloride (151 μL, 1.96 mmol, 1.5 equiv) was slowly added to a solution of compound (**7a**) (200 mg, 0.78 mmol) and triethylamine (546 μL, 3.92 mmol, 5 equiv) in methylene chloride

(3 mL). After 3 h at rt the reaction was complete, ethyl acetate was added and the mixture filtered over Celite-545. After evaporation, the crude was purified by chromatography (hexane/ethyl acetate, 50%) to give product (**7b**) (53 mg, 21%) as an oil: IR (film) υ 2900, 1600, 1540, 1480, 1400, 1280, 1060, 940, 820 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50-7.25 (m, 5 H), 4.71 (s, 2 H), 3.19 (m, 2 H), 2.61 (d, *J*= 7.2 Hz, 1 H), 2.53 (d, *J*= 7.2 Hz, 1 H), 2.19 (m, 2 H), 1.90 (m, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.0, 128.3, 128.2, 127.2, 113.9, 62.1, 59.1, 45.0, 43.0, 42.1, 41.3, 27.7. Anal. Calcd for $C_{17}H_{23}N_3O_2S$: C, 61.23; H, 6.95; N, 12.60; S, 9.61. Found: C, 61.35; H, 6.64; N, 12.57; S, 9.33.

***o*-Dimethanesulfonylaminobenzonitrile (8b)**. To a solution of anthranilonitrile (**8**) (0.72 g, 6.10 mmol) in CH_2Cl_2 (30 mL) containing Et_3N (4.03 mL, 30.5 mmol) at 0 °C was added dropwise methanesulphonyl chloride (1.74 mL, 21.37 mmol). The solution was stirred at rt. for 45 min, filtered over Celite-545 and evaporated. Purification by column chromatography (3:1-1:1 hexane: ethyl acetate) gave pure **8b** (1.34 g, 80%) as a colourless solid: mp. 172-173 °C (1:1 hexane: ethylacetate); IR (KBr) υ 3040, 2990, 2920, 2200, 1340, 1140 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.49-7.84 (m, 4 H), 3.54 (s, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 134.2, 133.9, 131.7, 131.0, 129.8, 122.6, 43.6. Anal. Calcd for $C_9H_{13}N_2O_4S_2$: C, 38.98; H, 4.72; N, 10.10; S 23.12. Found: C, 38.87; H, 4.65; N, 10.86; S, 23.01.

***o*-Methanesulfonamidobenzonitrile (8a)**. To a solution of **8b** (204 mg, 0.74 mmol) in THF (10 mL) was added NaH (40 mg, 1.0 mmol, 60% dispersion in oil) and water (30 μL), in order to generate NaOH *in situ*. The mixture was stirred at rt. for 30 min, water was added and the solution was extracted with dichloromethane (3 x 20 mL). Evaporation of the dried (Na_2SO_4) extract gave a residue that was purified by flash chromatography (20:1-10:1 CH_2Cl_2: MeOH) to give **8a** (102 mg, 70%) as a colourless solid: mp 97-98 °C, (1:1 CH_2Cl_2:hexane); IR (KBr) υ 3460, 3030, 2990, 2930, 2195, 1340, 1140 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.73 (m, 1 H), 7.64 (m, 2 H), 7.27 (m, 1 H), 7.02 (br s, 1 H), 3.14 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.3, 134.6, 133.1, 125.4, 121.5, 116.0, 104.3, 40.5. Anal. Calcd for $C_8H_8N_2O_2S$: C, 48.97; H, 4.11; N, 14.28; S, 16.34. Found: C, 48.76; H, 4.05; N, 14.11; S, 16.23. Attempts to cyclize **8a** and **8b** failed.

***o*-Benzylosulfonamidobenzonitrile (8c)**. To a solution of anthranilonitrile **8** (258 mg, 2.18 mmol) and Et_3N (1.15 mL, 8.72 mmol) in CH_2Cl_2 (15 mL) was added α-toluenesulphonyl chloride (0.83 g, 4.35 mmol). The reaction was stirred for 15h. at rt., was filtered over Celite-545 and was evaporated. Purification by flash chromatography (4:1-1:1 hexane: ethyl acetate) yielded **8c** (546 mg, 92.3%) as a white solid: mp. 132-134 °C (1:1 CH_2Cl_2:hexane); IR (KBr) υ 3460, 3040, 2995, 2200, 1340, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.80-7.10 (m, 9 H), 6.86 (br s, 1 H), 4.48 (s, 2 H). Anal. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29; S, 11.77. Found: C, 61.54; H, 4.23; N, 10.19; S, 11.56. This product did not cyclize.

***o*-Benzyl(methanesulfonyl)aminobenzonitrile (8d)**. To a solution of **8a** (758 mg, 3.86 mmol) in DMF (2 mL) was added NaH (230 mg, 5.79 mmol), the mixture was stirred for 20 min. at rt. and then benzyl bromide (0.47 mL, 3.97 mmol) was added. The reaction was stirred for 2.5 h., water (10 mL) was added and the precipitate that formed was collected by filtration. Recrystallisation of this material (2:1, hexane:ethyl acetate) gave **8d** (0.81 g, 73%) as colourless plates: mp 126-128 °C; IR (KBr) υ 3040, 2990, 2940, 2200, 1580, 1345, 1150 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70-7.28 (m, 4 H), 7.28 (s, 5 H), 4.93 (s, 2 H), 3.15 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.4, 134.8, 133.7, 133.7, 132.5, 129.0, 128.6, 128.4, 128.3, 113.7, 117.0, 40.8, 55.0. Anal. Calcd for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.74; S, 11.20. Found: C, 62.77; H, 4.87; N, 9.65; S, 11.08. This product did not cyclize.

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REFERENCES AND NOTES

†The *CSIC* name reaction applied to this type of synthetic transformation has the same initials of the first Spanish public research organization (Consejo Superior de Investigaciones Científicas) where the intramolecular version of this reaction was discovered for the first time in 1988 (see ref. 1a), has been further developed (see ref 1b, for instance) and is being analyzed in depth (see ref. 2).

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