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Efficient catalyst-free tricomponent synthesis of new spiro[cyclohexane-1,4′-pyrazolo[3,4-*e*][1, 4]thiazepin]-7′(6′*H*)-ones

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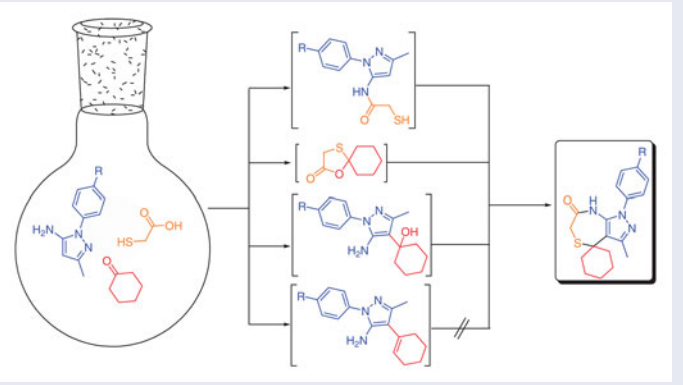
ABSTRACT

A series of spirocyclohexane-1,4′-pyrazolothiazepinones were synthesized by one-pot multicomponent cyclocondensation reactions between 5-amino-1-arylpyrazoles, cyclohexanone and mercaptoacetic acid with good yields and easy purification protocols. Some control experiments involving isolation of reaction intermediates were performed leading to the proposal of three alternative mechanistic pathways conducting to the named spiroheterocycles. All target molecules were fully characterized by IR, NMR, melting point and HRMS.

GRAPHICAL ABSTRACT



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Spiroheterocycles; 1,4-thiazepin-3-ones; aminopyrazoles; tricomponent reaction; catalyst-free

Introduction

It is well known that seven-membered heterocycles are valuable scaffolds in search for new drug-like molecules; examples of this are the azepines, oxazepines, and benzodiazepines as modulators of central nervous system (CNS) diseases like psychosis, depression and epilepsy.[1] In addition to CNS activities,[2–8] some sulfur and nitrogen derivatives have diverse biological desirable effects as antidiabetes;[9,10] antiproliferatives[11,12] and

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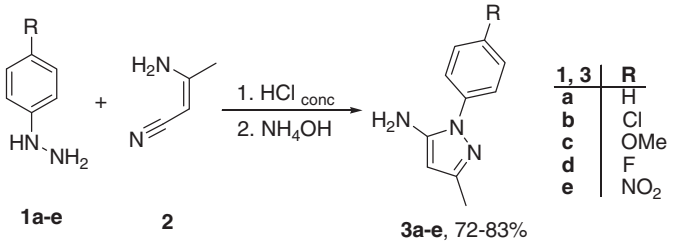
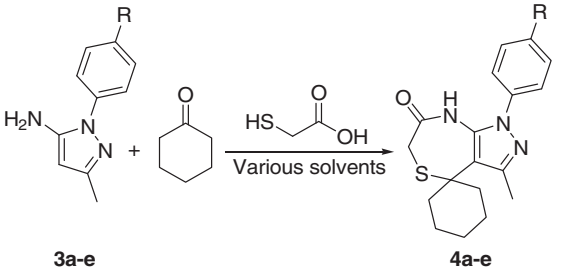


Scheme 1. Synthesis of aminopyrazole precursors.



Scheme 2. Synthesis of spirocyclohexane-1,4′-pyrazolothiazepinones **4a–e**.

antimicrobials.[13] Besides, pyrazole-fused thiazepines have been tested recently with promising results as cytotoxic[14] and antiparasitic agents.[15]

Multicomponent reactions (MCRs) are efficient and versatile tools to obtain diverse bioactive compounds in few steps and purifications in comparison to multistep strategies.[16] This approach makes possible to build relatively easy and quick, libraries of complex organic compounds,[17] although with the difficulty of establishing mechanistic pathways leading to the target molecule.

Considering that construction of seven-member rings is not the most favored route by Baldwin's rules,[18] it is a true synthetic challenge to obtain this type of heterocycles in relatively simple conditions and without the addition of catalysts. In this work, we present an easy, accessible and simple-purification protocol to synthesize some novel spirofused cyclohexane-1,4′-pyrazolothiazepinones. Additionally, three possible mechanisms were studied through control experiments involving the isolation of key reaction intermediates conducting to above-mentioned spirothiazaheterocycles.

Discussion

The synthesis of spirothiazepinones started by the preparation of 1-aryl-3-methyl-5-aminopyrazole derivatives **3a–e** with different substitution pattern in 4-position of aryl moiety, by classic cyclocondensation reaction of arylhydrazines **1a–e** with 3-aminocrotononitrile **2** in acid media (Scheme 1).[19–21]

Compound **3a** was used as scoping substrate in reaction with cyclohexanone and mercaptoacetic acid (MAA) in equimolar quantities in various solvents to obtain spirocyclohexane-1,4′-pyrazolothiazepinones (Scheme 2), where benzene gave rise to the best results thus allowing to optimize the reaction (Table 1).

Table 1. Scoping conditions for synthesis of compound **4a**.

Entry	Solvent	Temperature (°C)	Time (h).	Yield of **4a** (%)[b]
1	MeCN	Reflux	48	NR[c]
2	MeCN /4.0 A MS	Reflux	20	5
3	THF	Reflux	>90	NR[c]
4	Toluene	Reflux[a]	72	6
5	Toluene	70[a]	72	NR[c]
6	DMF	100	2	Deg[d]
7	DMF	70	10	NR[c]
8	Benzene	Reflux[a]	72	15
9	Solvent-free	Fussion	0.033	Deg[d]

[a]Dean-Stark apparatus was used.
[b]Reaction conditions: 0.5 mmol of **3a**, equimolar quantities of cyclohexanone and MAA, 5 mL of each solvent.
[c]No reaction observed.
[d]Compound **3a** was degraded.

Table 2. Stoichiometric scoping of reaction.

Entry	Molar relation cyclohexanone*	Molar relation MAA*	Time (h).	Yield of **4a** (%)[a]
1	1	1	72	15
2	1	2	60	18
3	2	2	60	24
4	**2**	**3**	**24**	**74**
5	2	4	60	50
6	3	3	36	25

*Related to **3a**.
[a]Reaction conditions: 0.5 mmol of **3a,** 5 mL of benzene, water removed by using Dean-Stark apparatus.

In solvent scoping, polar solvents such as DMF and MeCN, did not yield target molecule or exhibited lower yields in comparison to benzene or toluene with Dean-Stark apparatus to azeotropically remove water formed during the reaction; and it is also important to note that the product was not soluble in benzene, which is why turned out as the best option in terms of isolation and purification of **4a**.

The low yield obtained with these above-mentioned attempts of reaction, suggested us a dependence of product formation with respect to the amount of MAA, making us consider if such reagent was also acting as an internal catalyst. According to this, an optimization of stoichiometric relation of cyclohexanone and MAA was necessary to improve yield of **4a** (Table 2).

In the stoichiometric study is clear that reaction proceeds optimally with two equivalents of cyclohexanone and three of MAA, reducing time and getting remarkable improvement in the yield of product **4a**, thus confirming that this reactant exerts action as an internal catalyst in the reaction. In addition, a higher amount of this reagent interfered with nucleophilicity of aminopyrazole, decreasing this way the overall yield of final product.

With this optimal conditions, compounds **3b–d** were then converted successfully to products **4b–d** with good yields (Table 3); however, **3e** did not afford expected product, giving rise to cyclohexenylpyrazole derivative **5e** instead (Scheme 3).

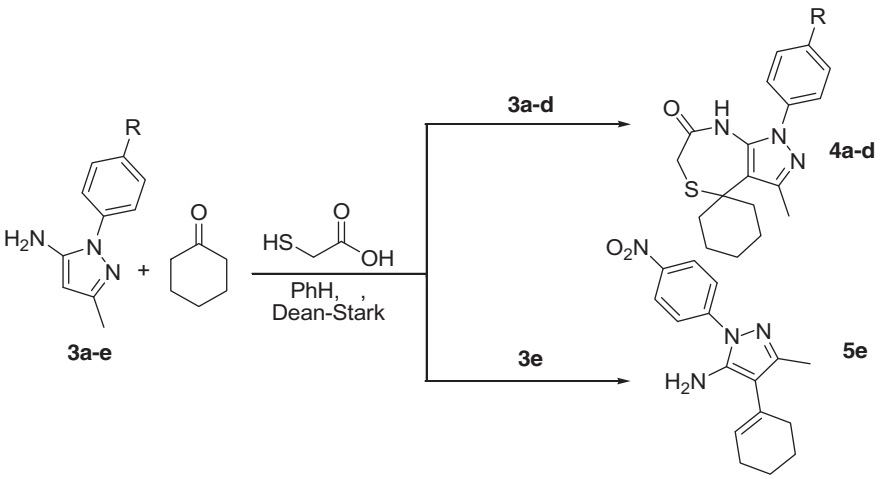
Complementary reaction studies and mechanistic proposals

Obtaining compound **5e** instead of expected spirothiazepinone gave us an idea of the reaction mechanism followed by substrates during transformation into final products

Table 3. Yields of compounds **4a–d** and **5e**.

Entry	–R	Time (h)	Yield of **4** (%)[b]	Yield of **5** (%)[b]
a	–H	24	74	–
b	–Cl	25	70	–
c	–OMe	20	76	–
d	–F	24	66	–
e	$-NO_2$	36	–[a]	67

[a]Not observed.
[b]Yields of isolated compounds.



Scheme 3. Optimized reaction for synthesis of **4a–d** and **5e**.

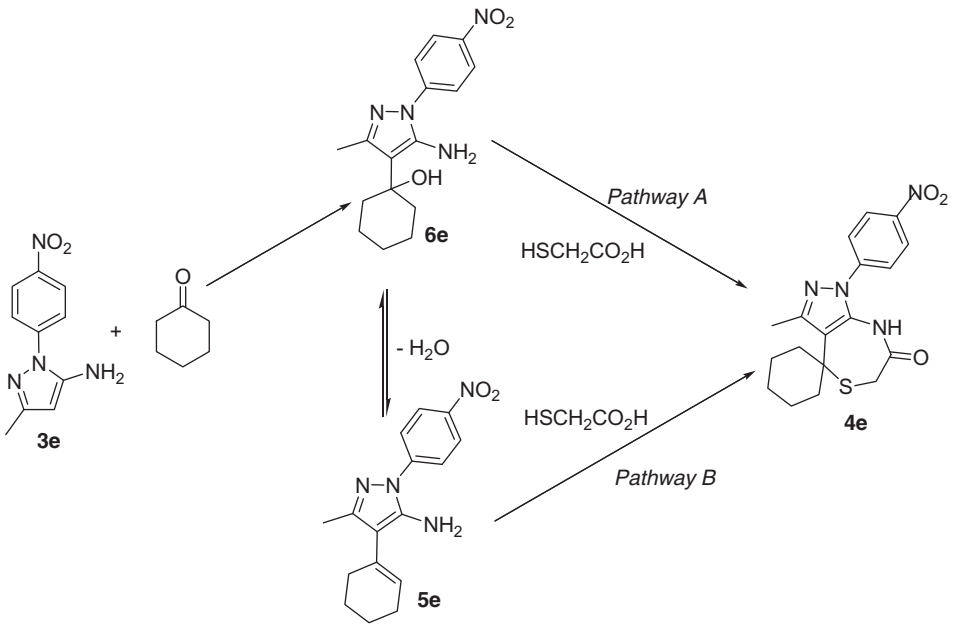
4a–d, assuming that such compound could be considered an intermediate by itself or just a dehydrated by-product of the true intermediate in a key mechanistic pathway (Scheme 4).

Looking to define the route followed during the formation of the final products, the synthesis of intermediates **5a** and **6a** were attempted under the general conditions used in the tricomponent reaction, giving rise only to the compound **5a** (Scheme 5).

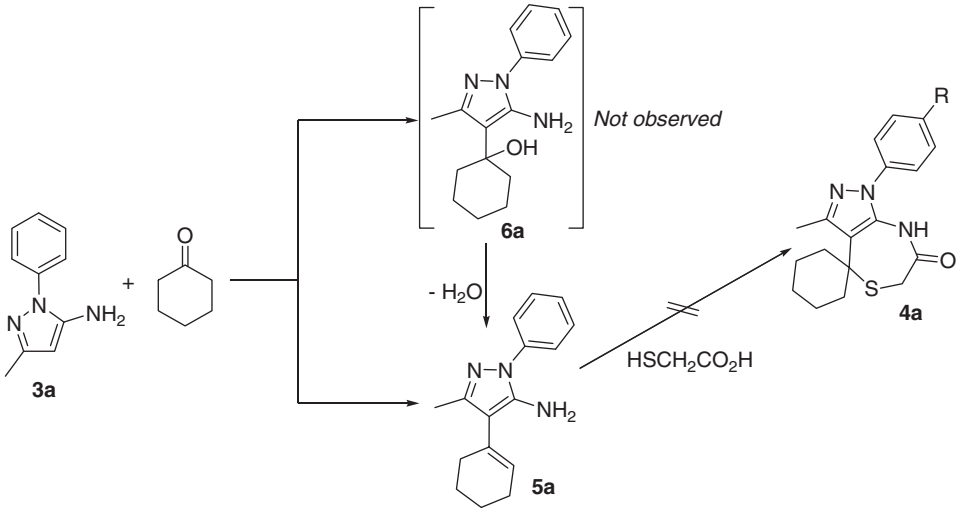
These results gave us an idea of the high tendency of **6a** to undergo dehydration under the studied conditions; besides, compound **5a** was tried to react with MAA without success (Scheme 5), thus implying that this by-product does not take part in the formation of **4a**, discarding *pathway B* described in scheme 4.

The *pathway A* then seems to involve intermediate **6a** which successfully provides the electrophilic center for the nucleophilic attack of the MAA, to end up with the expected cyclocondensation to the spirothiazepinone ring **4a** (Scheme 6).

The instability of **6a** (tendency to dehydrate) and the fact that **5a** did not react with MAA, questioned both pathways (A y B) in the general reaction mechanism, although previous reports described the participation of such type of intermediates in cyclocondensation reactions.[22] For this reason, other possible intermediates were proposed considering the tricomponent approach used in the main reaction (Scheme 7); which makes possible that cyclohexanone and MAA could react first, giving rise to a spirooxathiolanone derivative **7**, which should be reactively enough to interact with aminopyrazole to produce the expected spiroheterocycle **4a** (*Pathway C*, Scheme 7).



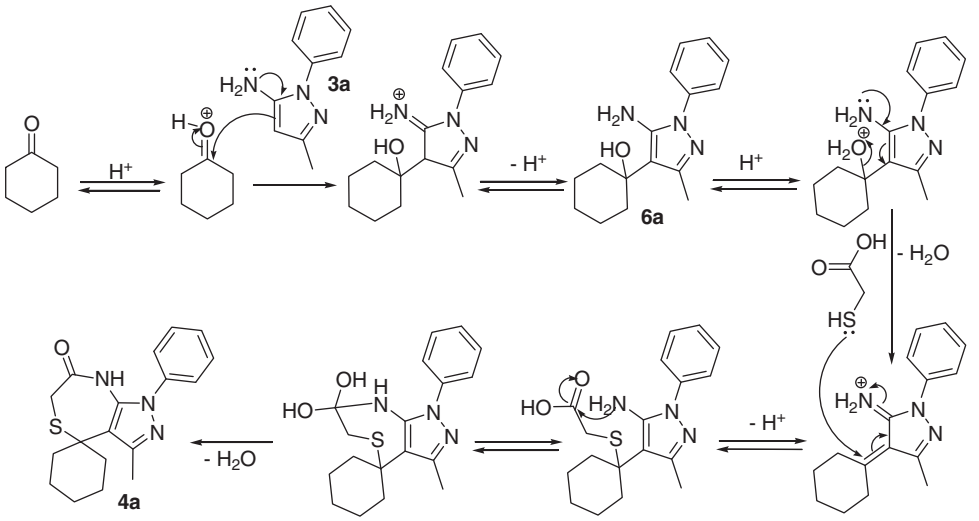
Scheme 4. Possible routes to the final product involving the generation of compound **5e**.



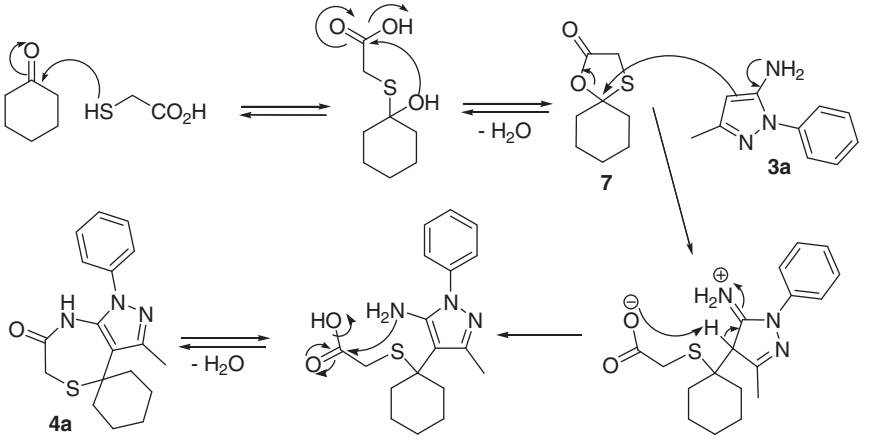
Scheme 5. Control experiment performed to study the potential participation of **5a** and **6a** in the general reaction.

Aiming to prove the reactivity and participation of intermediate **7** in the aforementioned mechanistic route of the main tricomponent reaction; such intermediate was synthesized by a methodology previously reported,[23] isolated and then allowed to react under the main reaction conditions with aminopyrazole **3a**, yielding the expected seven-member spiroheterocycle **4a**, as single product (Scheme 8).

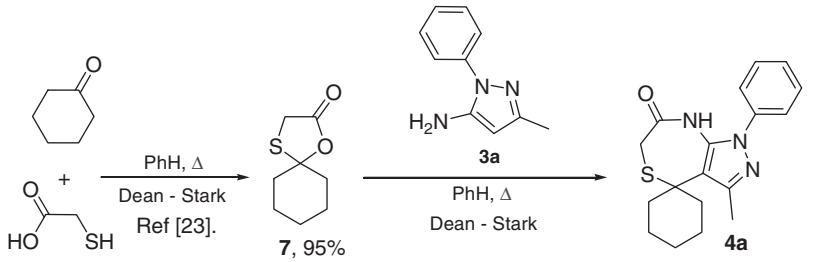
Given that **7** conducted successfully to product **4a**, it is reasonable to establish a reaction mechanism that involves this intermediate as shown in Scheme 7, but during our study of the tricomponent reaction we realized that there is another alternative route



Scheme 6. Plausible mechanism of formation of **4a** via intermediate **6a**.

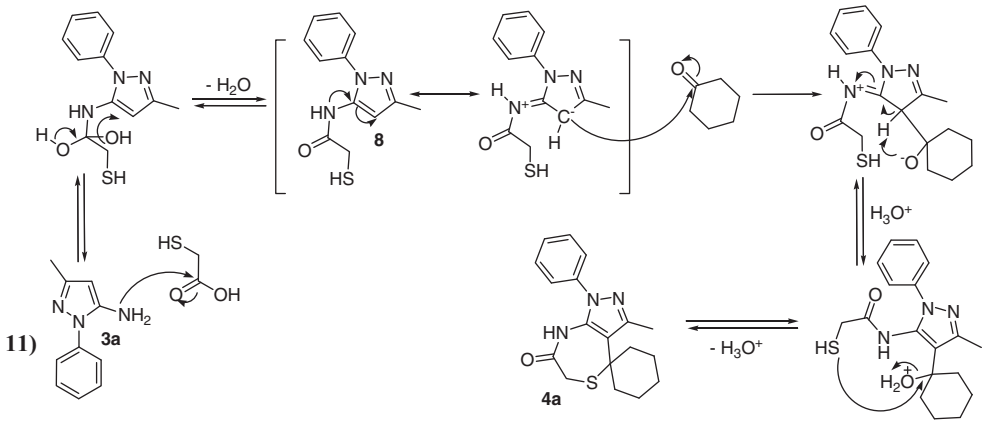


Scheme 7. Alternative *pathway C* proposed to explain the formation **4a**.

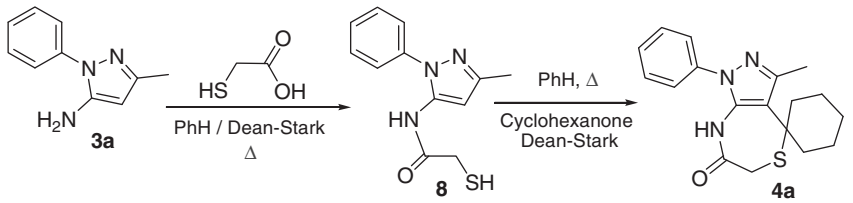


Scheme 8. Control experiment to determine the plausibility of proposed *pathway C*.

consisting in the reaction of aminopyrazole with MAA by an acyl nucleophilic substitution, to produce a 2-sulfanyl acetamide intermediate **8**, which also seems to participate in the main reaction in the presence of cyclohexanone to yield also **4a** (*Pathway D*, Scheme 9).



Scheme 9. Alternative *pathway D* proposed to get **4a** in tricomponent reaction.



Scheme 10. Control experiment to determine the plausibility of proposed *pathway D*.

Once again, a control experiment was performed to determine the plausibility of proposed mechanism; this time, a third component approximation was used. Putting in reaction two of the three reactants until complete transformation, and then adding the missing one. In this case, **3a** and MAA were reacted until consumption of aminopyrazole, and then cyclohexanone was added dropwise to the mixture and the reaction was continued until this last component was completely consumed. This experiment yielded spirothiazepinone **4a** as expected (Scheme 10).

These control experiments lead us to propose three different mechanistic pathways (A, C and D) conducting to **4a** under the general conditions used in the tricomponent approach.

Spectroscopic discussion of synthesized spirocyclohexanepyrazolo[1,4]thiazepin-7-ones (4a–d)

Compounds **4a–d** exhibited diagnostic signals in ^{1}H-NMR spectra, such as a singlet corresponding to α-carbonyl CH_2 in δ = 3.18–3.23 ppm and aliphatic signals (four multiplets) assigned to CH_2 of cyclohexane in 1.24–2.21 ppm. Additionally, pyrazolic CH_3 protons appeared as a singlet at 2.47–2.51 ppm while in the low field region of spectra around 7.24 ppm a broad singlet was assigned as the lactam N–H proton (also confirmed through chemical exchange experiments with D_2O). Regarding ^{13}C-NMR and DEPT-135 spectra, signal count corresponded to the number of carbon atoms expected for title compounds. CH_3 appeared as one signal in the range δ = 16.80–16.95 ppm

while CH_2 in cyclohexane fragment were observed as three negative phase signals in DEPT-135 spectra around 22.07, 25.38, and 30.94 ppm. Spiranic quaternary carbon atom appeared at δ = 49.43–49.56 ppm, and α-carbonyl CH_2 was observed around 36.9 ppm. Aromatic region of spectra displayed signals according to the substitution patterns of aromatic rings in each molecule.

Finally, the purity of all the obtained compounds was confirmed by means of HRMS-ESI (except in the case of intermediates **5a** and **5e** which were confirmed by CHNS elemental analysis), where the corresponding $[M + 1]^+$ peak was observed and compared to the calculated value in all cases.

Conclusion

In summary, an easy purification protocol without external catalyst was developed for the synthesis of spirofused cyclohexane-1,4′-pyrazolothiazepinones with good yields. Mechanism of this tricomponent reaction was studied by control experiments leading to three possible routes, two of which involve non-obvious intermediates such as spirooxathiolanone and sulfanyl acetamide. This observation allowed us to open the discussion to unexpected borders on the mechanism of a seemingly simple reaction.

Is important to state that due to the presence of interesting pharmacophoric cores in all the spiroheterocycles obtained, they could be considered as promising molecular hybrids in terms of potential bioactivity, and all of them will be evaluated against different targets as part of further studies.

Experimental

Typical procedure for the synthesis of spiro[cyclohexane-1,4′-pyrazolo [3,4-e][1,4]thiazepin]-7(6′H)-ones (4a–d)

3.0 mmol of the corresponding aminopyrazoles (**3a–d**) were mixed with 6.0 mmol of cyclohexanone and 9.0 mmol of mercaptoacetic acid in 20 mL of dry benzene. The resulting mixture was heated to reflux with Dean–Stark trap for 12 h until reaction was completed. The crude was cooled to room temperature and then was left at 4 °C overnight. The resulting solid was filtered and washed with cold benzene and water yielding the spirothiazepin-7-ones **4a–d**.

3′-Methyl-1′-phenyl-1′,8′-dihydrospiro[cyclohexane-1,4′-pyrazolo [3,4-e][1,4]thiazepin]-7′(6′H)-one (4a)

White solid (74%, 726 mg); mp: 257-258 °C; IR (ν_{max} cm^{-1}): 3075, 2927, 2854, 1679, 767. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.29 (qt, J = 12.8, 3.7 Hz, 1H), 1.65 (dd, J = 13.7, 3.2 Hz, 2H), 1.81 (m, 3H), 2.15 (m, 4H), 2.51 (s, 3H), 3.23 (s, 2H), 7.25 (s, 1H), 7.41 (m, 3H), 7.50 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 16.9, 22.1, 25.4, 31.0, 37.1, 49.5, 115.4, 125.4, 128.7, 129.8, 133.4, 137.2, 146.3, 171.3. HRMS (ESI) *m/z:* $[M + H]^+$ Calc. for $C_{18}H_{21}N_3OS$: 328.1478; found: 328.1515.

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