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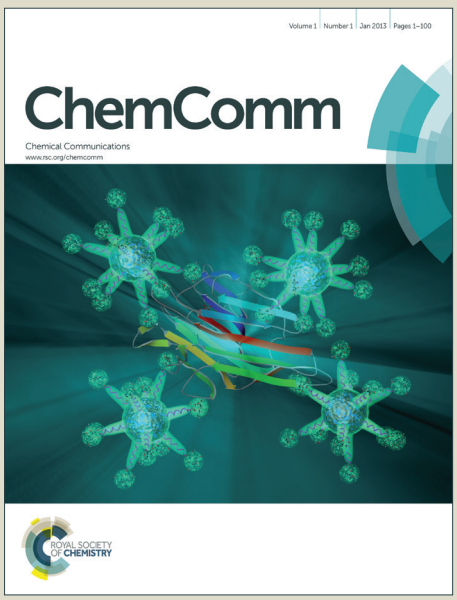

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Diversity-Oriented Heterocyclic Synthesis using Divergent Reactivity of *N*-Substituted Iso(thio)cyanates

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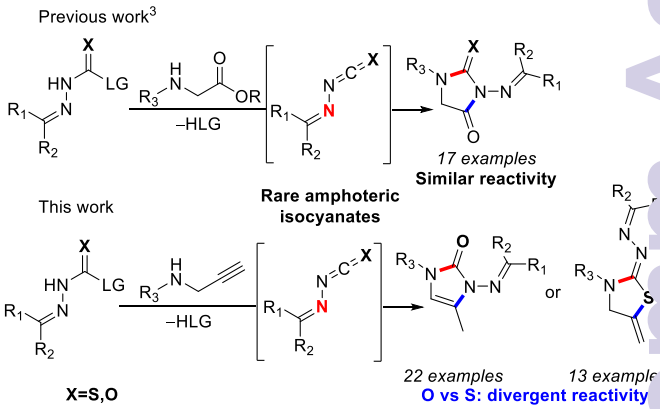
Carbon-substituted isocyanates and isothiocyanates are common building blocks in organic synthesis. In contrast, synthetic uses of *N*-substituted isocyanates and isothiocyanates are severely underdeveloped: few have been reported and their reactivity had not been compared. Herein, we compare the reactivity of blocked (masked) *N*-isocyanate and *N*-isothiocyanate precursors in cascade reactions. Divergent reactivity is observed with secondary propargylic and allylic systems, leading to new syntheses of imidazolones, thiazolidines, and a tool to form complex azomethine imines.

Carbon-substituted isocyanates are very important reagents in chemical manufacturing, and are used as building blocks to assemble agrochemicals, pharmaceuticals, polyurethanes, etc.[1] Over 100,000 publications and patents describe uses of *C*-isocyanates, and >10 million tons are used annually in polyurethane production alone. In stark contrast, *N*-substituted isocyanates have only been a scientific curiosity (<60 publications!)[3c] and their synthetic potential remains severely underdeveloped. Their amphoteric / ambident nature, which results in a tendency to dimerize, can likely explain this scarcity. However, we have recently shown that controlled reactivity is possible using blocked *N*-isocyanate precursors, which form the desired *N*-isocyanates *in situ* upon heating or using base catalysis. Using this approach allowed the development of alkene cycloaddition reactions,[2] and of several cascade reactions forming nitrogen heterocycles possessing the NNCO motif.[3] These latter provided syntheses of saturated nitrogen heterocycles,[3a] amino-hydantoins,[3b] acyl-phtalazinones,[3c] acyl-pyrazoles[3c] and azauracils.[3c] Importantly, this work also allowed a comparison of the reactivity of different *N*-substituted isocyanates (amino-, imino- and amido- *N*-isocyanates). Naturally, we became interested in using their sulfur analogues, *N*-iso**thio**cyanates,[4] in heterocyclic synthesis.[5] In a recent study, we have reported a single example of a cascade reaction involving an α-amino ester and a blocked *N*-isothioisocyanate reagent to form a thiohydantoin (Scheme 1, top).[3b] This work highlighted the need for a thorough study of *N*-iso**thio**cyanate reactivity and for a comparison with *N*-isocyanates (which to the best of our knowledge has not been reported in the literature). Herein, we report such a study highlighting the divergent reactivity observed in cascade reactions of *N*-isocyanates and *N*-isothiocyanates, forming imidazolones and thiazolidines products under similar conditions with propargylic amines (Scheme 1, bottom). In addition, we show that only *N*-isothiocyanate precursors are effective to form complex azomethine imines upon heating with allylic amines.

Scheme 1. Divergent Reactivity of *N*-isothiocyanates



We were drawn to the use of secondary propargylic amines in cascade reactions as we felt that the intermediate formed by addition on the *N*-isocyanate or *N*-isothiocyanate could undergo a 5-exo-dig cyclization (Scheme 1, bottom). Either nitrogen or oxygen (sulfur) (**X** = O, S) could attack the alkyne and double bond isomerization also offered the possibility of forming an aromatic heterocycle. Such cascade reactivity would also allow the formation of biologically active compounds[6] more readily than the typical cyclizations approaches used for the synthesis of imidazolones[7] and thiazolidines.[8] Thus we decided to first optimize the reaction

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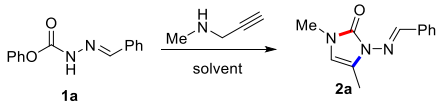
conditions using a hydrazone-based *N*-isocyanate precursor **1a** and *N*-methylpropargylamine under thermal conditions (**Table 1**). In parallel, *N*-isothiocyanate was subjected precursor **1q** similar reaction condtions (Eq 1).

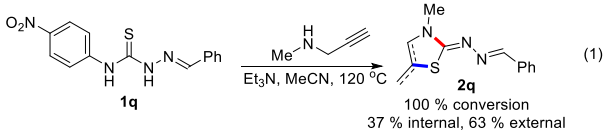
Table 1 : Optimization of *N*-isocyanate cascade involving *N*-methylpropargylamine[a]



1a **2a**

Entry	Source	Temp. (°C)	Base	Time (h)	Solvent	Yieldb (%)
1	µW	100	none	3	MeCN	5
2	µW	100	Et_3N	1	MeCN	79
3	µW	100	Et_3N	2	MeCN	87 (86)
4	µW	100	Et_3N	3	MeCN	90
5	µW	150	Et_3N	2	MeCN	86
6	Oil bath	100	Et_3N	14	$PhCF_3$	68

a) Conditions: Hydrazone (1.0 equiv), *N*-methylpropargylamine (1.1 equiv.), base (20 mol%) and MeCN (0.3 M) were added to an oven-dried microwave vial heated in oil bath or microwave (µW) reactor. b) NMR yield base on 1,3,5-trimethoxybenzene internal standard, isolated yield in parentheses.



1q **2q**

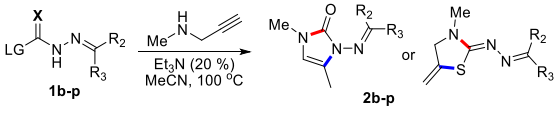
100 % conversion
37 % internal, 63 % external

(1)

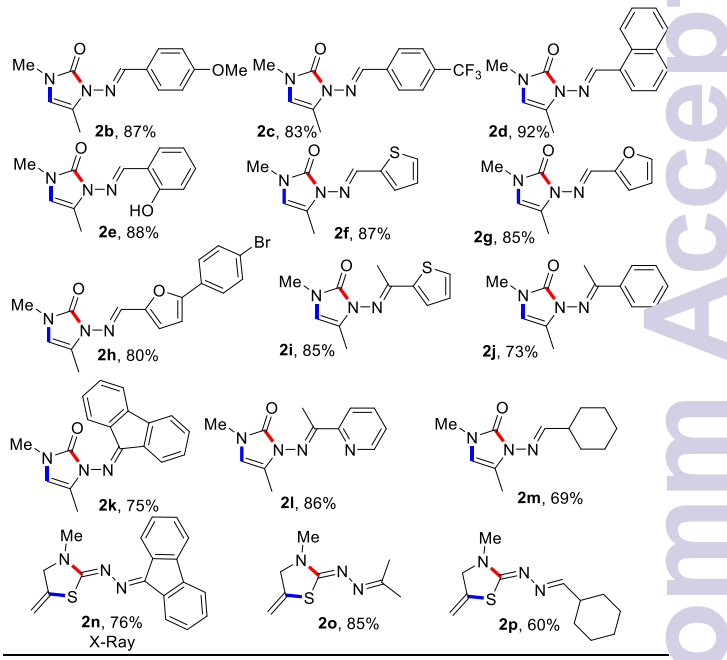
Our first cyclization attempt under microwave (µW) irradiation at 100 °C yielded only 5% of the heterocycle, with mostly the uncyclized semi-carbazone[9] adduct being formed (75%). It was hypothesized that base could help the cyclization as reported by Lubell using NaH.[7k] However, it was also expected that in the presence of a mild conjugate acid double bond isomerization could occur. Gratifyingly, using 20 mol % of Et_3N led to a 79% yield of the aromatic imidazolone **2a** (Table 1, entry 2). Remarkably, this cascade reaction involves: 1) Isocyanate formation; 2) Addition of the amine; 3) Cyclization; and 4) Isomerization to form the desired aromatic imidazolone. The optimal conditions were found to be 2 hours at 100 °C (entry 3-5). It was also observed that the reaction proceeds with conventional heating, but required longer reaction times when $PhCF_3$ was used as solvent (entry 6). In parallel, the related reaction of *N*-isot**hio**cyanate precursor **1q** was attempted (Eq 1). In contrast to the *N*-isocyanate cascade, the sulphur atom cyclized on the alkyne to provide the 5-membered thiazolidine ring, with some product isomerizing after cyclization. Unfortunately, the 1.7:1 exo:endo ratio did not change significantly in the other conditions tested for this cascade reaction (see supplementary information). Despite this, we had optimized conditions in hand, and then looked at the impact of the *N*-iso(thio)cyanate structure on these cascade reactions (**Table 2**).

Gratifyingly, a variety of *N*-isocyanate precursors react efficiently with *N*-methylpropargylamine to form the amino-imidazolones (Table 2). First, the reactivity of several aromatic aldhydrazones was explored (**2b-2h**). Electron-rich and electron-poor aromatic and heteroaromatic *N*-isocyanate precursors were well tolerated, and yielded the desired imidazolones in 80-92% yield. Substrate **2e**, possessing an ortho-phenol moiety, also cyclized efficiently. More complex hydrazones can also be used, such as a *N*-isocyanate precursor possessing the azumolene[10] bicyclic core which rapidly formed the drug analog **2h**. The reactivity of ketohydrazones was then surveyed, and showed that imidazolones can again be formed in high yield (73-86%, **2i**-**2n**). A bulky hydrazone precursor proved a competent reagent (**2k**), and both electron-rich (**2i**) and electron-poor (**2l**) substrates cyclized with similar efficiency. Finally, an aliphatic hydrazone also generated the desired heterocycle (**2m**), albeit in a slightly lower yield. In contrast, the structure *N*-isothiocyanate precursor had an impact on product distribution. Indeed, using a fluorenone derived *N*-iso**thio**isocyanate precursor also led through cyclization via addition of the sulfur atom, but no isomerization occurred resulting in the selective formation of product **2n** possessing an exocyclic alkene, and for which an X-ray structure was obtained.[‡] Similar reactivity was also observed other thiosemicarbaones (**2n, 2o**).

Table 2. Hydrazone scope for the cascade reactions, using *N*-methyl propargylamine[a]



1b-p **2b-p**

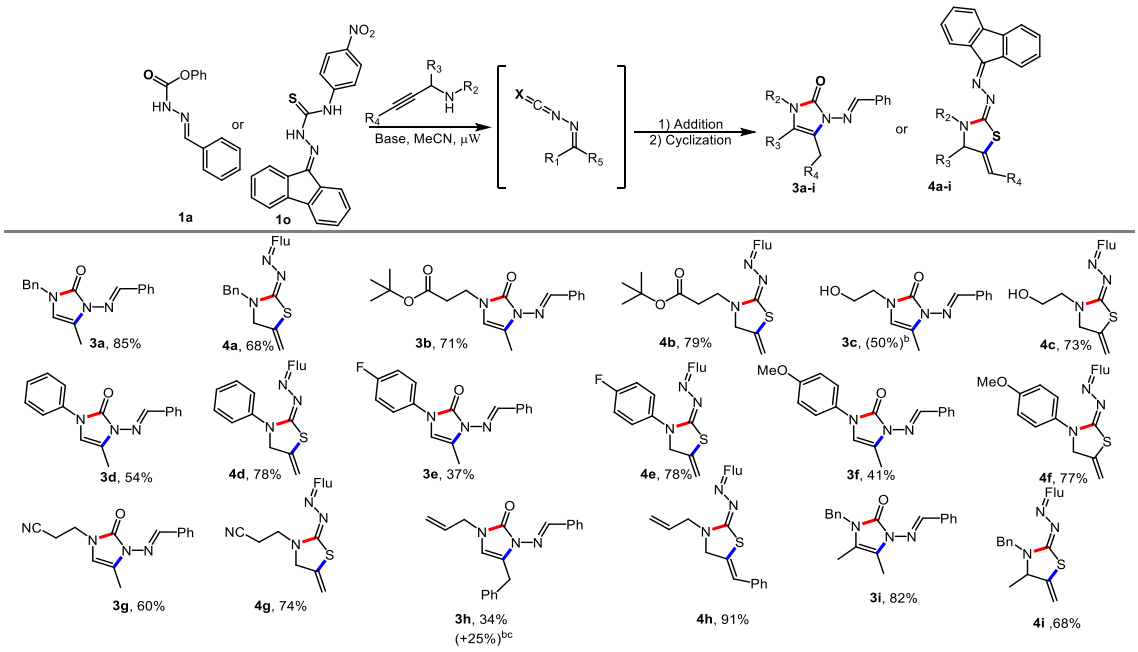


a) Conditions: Hydrazones (1.0 equiv), *N*-methylpropargylamine (1.1 equiv.), Et_3N (20 mol%) and MeCN (0.3 M) were added to an oven-dried microwave vial and heated at 100 °C for 2-6 hours.

The scope of propargylic amines was then performed using *N*-isocyanate and *N*-isothiocyanate precursors (**Table 3**). This study was performed using benzaldehyde-derived *N*-isocyanate precursor **1a** and fluorenone-derived *N*-isothioisocyanate **1n**. Both precursors could be obtained in multigram quantities without the need for purification by column chromatography. Interestingly, the cascade reactions

with *N*-isothiocyanate precursor **1n** are more efficient (68-91%), and significantly less sensitive to variations in the structure of the propargylic amine than the *N*-isocyanate reactions (37-85%). Nevertheless, reactions with propargylic amines possessing *N*-benzyl group, *N*-alkyl chains with an ester, a nitrile or a free hydroxyl group, *N*-aryl groups, and also an internal phenyl-substituted alkyne all delivered the desired thiazolidines or imidazolones. Interestingly, the use of the internal alkyne to form thiazolidine **4h** appeared to be beneficial to the cascade reaction (91%). In contrast the *N*-isocyanate cascade using the internal alkyne led to a moderate 34% yield of the desired imidazolone **3h**, as substitution partially prevented the isomerization (25% of the exocyclic imidazolinone **3i** was also formed). Overall, a comparison of the reactivity shows that cascade reactions of *N*-isothiocyanates are more robust likely due to a more facile cyclization.

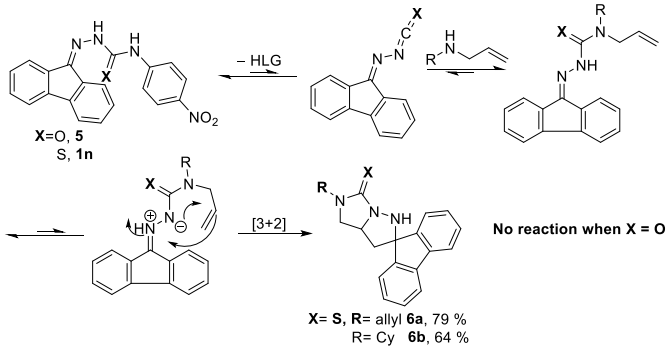
Table 3. Divergent heterocyclic synthesis using *N*-isocyanates and *N*-isothiocyanates: Scope using several propargylic amines[a]



a) Condition: Hydrazones (1.0 equiv), propargylamines (1.1 equiv.), Et_3N (20 mol%) and MeCN (0.3 M) were added to an oven-dried microwave vial and heated at 100-150 °C for 2-6 hours, b) Based on NMR yield C) Yield for product with an exocyclic alkene. Flu= fluorenyl

We then became interested in the possibility that a reaction could also occur with allylic amines, and probed this using diallylamine. The results are shown in **Scheme 2**.

Scheme 2. *N*-isothiocyanate precursor allowed a [3+2] cycloaddition of *in-situ* generated azomethine imines



A reaction cascade was observed for *N*-isothiocyanate precursor **1n**, and in contrast only amine addition was observed using either *N*-isocyanate precursor **1k** (HLG = PhOH) or the parent urea **5** (HLG = $ArNH_2$). Using **1n** a new cascade reaction occurred to form **6a**. Similar reactivity was also observed with *N*-cyclohexyl allylamine, but the reaction required 4 hours at 150 °C likely due to conformational issues. This reactivity provides a new tool for the generation of complex azomethine imines from simple precursors, that is unprecedented in the broad literature on azomethine imines.[1] In contrast to the pioneering work of Overman[12] who formed related dipoles via acid-catalyzed proton-transfer on simple thiosemicarbazones, azomethine imine formation occurs under mildly basic conditions.

In summary, we compared the ability of rare *N*-isocyanate and *N*-isothiocyanate amphoteric intermediates to engage in cascade reactions with propargylic and allylic amines. The reactions of *N*-isocyanates with propargylic amines allowed the direct synthesis of imidazolones. In contrast, with *N*-isothiocyanates cyclization occurred via attack of the sulphur atom, and with little to no subsequent isomerization, to yield alkene-substituted thiazolidines. Both reactions proceeded with various *N*-iso(thio)cyanates and propagylic amines, and showed that the cascade involving *N*-isothiocyanates was in general more tolerant of structural variations. Synthetically, this work provides a modular

synthesis of amino-imidazolones and thiazolidines possessing a rare substitution pattern. Finally, exploratory work with allylic amines and *N*-isothiocyanates also provided a new approach to form complex azomethine imines in situ. Overall, this study highlights key differences in reactivity between *N*-isocyanate and *N*-isothiocyanate precursors, which can help to develop new synthetic uses of these rare isocyanates. Efforts along these lines are ongoing and will be reported in due course.

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Notes and references

‡ CCDC 1420524 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

1. For review on isocyanates and their use in industry see: (a) C. Six, F. Richter, *Ullmann's Encyclopedia of Industrial Chemistry* Wiley-VCH, 2012, 63-82. (b) *Isocyanates*, *Organic. Kirk-Othmer Encyclopedia of Chemical Technology*, Wiley, New York, 3rd edn., 1982, 28-62. (c) Z. Wang, *Comprehensive Organic Name Reactions and Reagents*, Wiley, New York, 2009, 1772-1774. For polyurethane application see: (d) H.-W. Engels, H.-G. Pirkl, R. Albers, R. W. Albach, J. Krause, A. Hoffman, H. Casselmann and J. Dormish, *Angew. Chem. Int. Ed.*, 2013, **52**. 9422

2. (a) J.-G. Roveda, C. Clavette, A. D. Hunt, C. J. Whipp, S. I. Gorelsky and A. M. Beauchemin, *J. Am. Chem. Soc*,. 2009, **131**, 8740. (b) C. Clavette, W. Gan, A. Bongers, T. Markiewicz, A. B. Toderian, S. I. Gorelsky and A. M. Beauchemin, *J. Am. Soc.*, 2012, **134**, 16111. (c) W. Gan, P. J. Moon, C. Clavette, N. Das Neves, T. Markiewicz, A. B. Toderian and A. M. Beauchemin, *Org. Lett.*, 2013, **15**, 1890. (d) K. Lavergne, A. Bongers, L. Betit and A. M. Beauchemin, *Org. Lett.*, 2015, **17**, 3612.

3. (a) C. Clavette, J.-F. Vincent-Rocan and A. M. Beauchemin, *Angew. Chem. Int. Ed.*, 2013, **52**, 12705. (b) J.-F. Vincent-Rocan, C. Clavette, K. Leckett and A. M. Beauchemin, *Chem. Eur. J.*, 2015, **21**, 3886. (c) J.-F. Vincent-Rocan, R. A. Ivanovich, C. Clavette, K. Leckett, J. Bejjani and A. M. Beauchemin. *Chem. Sci.*, 2015, **DOI**: 10.1039/c4sc03197? (d) R. A. Ivanovich, Vincent-Rocan, J.-F.; E. B. Elkaeed and A. M. Beauchemin *Org. Lett.*, *2015*, ***DOI****: 10.1021/acs.orglett.5b024642?*. (e) J. Shao, X. Liu, K. Shu, P. Tang, J. Luo, W. Chen and Y. Yu *Org. Lett.*, 2015, **DOI**: 10.1021/acs.orglett.5b02180. For reviews on aminoisocyanates see: (f) W. Reichen *Chem. Rev.*, 1978, **78**, 569. (g) C. Wentrup, J. J. Finnerty and R. Koch, *Curr. Org. Chem.*, 2011, **15**, 1745.

4. For pioneering work on *N*-isothiocyanates, see: (a) R. S. McElhinney, *J. Chem. Soc.*, 1966, 950. (b) U. Anthoni, C. Larsen and P. Nielsen, *H. Acta Chem. Scand.*, 1966, **20**, 1714. (c) U. Anthoni, C. Larsen and P. Nielsen, *H. Acta Chem. Scand.*, 1967, **21**, 2571. (d) U. Anthoni, C. Larsen and P. Nielsen, *H. Acta Chem. Scand.*, 1967, **21**, 2580. (e) U. Anthoni, C. Larsen and P. Nielsen, *H. Acta Chem. Scand.*, 1967, **21**, 2061. (f) U. Anthoni, C. Larsen and P. Nielsen, *H. Acta Chem. Scand.*, 1968, **22**, 309. (g) U. Anthoni, C. Larsen and P. Nielsen, *H. Acta Chem. Scand.*, 1968, **22**, 2493. (h) U. Anthoni, C. Larsen and P. Nielsen, *H. Acta Chem. Scand.*, 1967, **21**, 1201. (i) U. Anthoni, C. Larsen and P. Nielsen, *Acta Chem. Scand.*, 1969, **22**, 1898. (j) C. Larsen, U. Anthoni and P. Nielsen, *H. Acta Chem. Scand.*, 1969, **23**, 320. (k) U. Anthoni, C. Larsen and P. Nielsen, *H. Acta Chem. Scand.*, 1969, **23**, 1439. (l) U. Anthoni and C. Berg, *H. Acta Chem. Scand.*, 1969, **23**, 3602.

5. For a review of isothiocyanates in heterocyclic chemistry see: K. Mukerjee and R. Ashare, *Chem. Rev.*, 1991, **91**, 1.

6. For bioactivity see: (a) C. Congiu, M. T. Cocco and V. Onnis, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 989. (b) X. Lu and Y. Hu, *Bioorg. Med. Chem.*, 2008, **16**, 2550. (c) J. J. Bronson, F. DenBleyker, P. J. Falk, R. A. Mate, H.–T. Ho, M. J. Pucci and J. B. Snyder, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 873. (d) R. W. Carling, K. W. Moore, C. R. Moyes, E. A. Jones, K. Bonner, F. Emms, R. Marwood, S. Patel, A. E. Fletcher, M. Beer, B. Sohal, A. Pike and P. D. Leeson, *J. Med. Chem.*, 1999, **42**, 2706. (e) C. S. Burgey, C. A. Stump, D. N. Nguyen, J. Z. Deng, A. G. Quigley, B.R. Norton, I. M. Bell, S. D. Mosser, C. A. Salvatore, R. Z. Rutledge, S. A. Kane, K. S. Koblan, J. P. Vacca, S. L. Graham and T. M. Williams, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5052. (f) A. Shaw, D. V. Paone, D. N. Nguyen, C. A. Stump, C. S. Burgey, S. D. Mosser, C. A. Salvatore, R. Z. Rutledge, S. A. Kane, K. S. Koblan, S. L. Graham, J. P. Vacca and T. M. Williams, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4795.

7. For recent syntheses of imidazolones see: (a) J. Barluenga, F. Gomez, F. Palacios and V. Gotor, *Synthesis*, 1981, 561. (b) H. Gnichtel and M. Sinell, *Liebigs Ann. Chem.*, 1988, 919. (c) M. Mehrotra, D. D. Sternbach, R. D. Rutkowske and P. L. Feldman, *J. Org. Chem.*, 1995, **60**, 7063. (d) F. Palacios, A. M. Ochoa, R. Retana, J. Oyarzabal and J. M. Expeleta, *Tetrahedron*, 1998, **54**, 2291. (e) R. Lenarsic, M. Kocevar and S. Polanc, *J. Org. Chem.*, 1999**, 64**, 2558. (f) S. Bombek, R. Lenarsic, M. Kocevar and S. Polanc, *Synthesis*, 2001, **8**, 1237. (g) S. I. Zav'yalow, G. Ezhova, N. E. Kravchenko, L. b. Kulikova, O. V. Dorofeeva, E. E. rumyantseva and A. G. Zavozin, *Pharm. Chem. J.*, 2004, **38**, 25. (h) S. Bombek, F. Pozgan, M. Kocevar and S. Polanc, *New. J. Chem.*, 2005, **29**, 948. (i) C. Neochoritis, C. A. Tsoleridis and Stephanidou-Stephanatou, *Tetrahedron*, 2008, 64, 3527. (j) J. Nezensek, U. Groselj, K. Stare, J. Svete and B. Stanovnik, *Tetrahedron*, 2012, *68*, 516. (k) C. Proulx, and W. D. Lubell, *Org. Lett.*, 2012, **14**, 4552. (l) J. Bezensek, U. Groselj, K. Stare, J. Svete and B. Stanovnik, *Arkivoc*, 2014, **2**, 294.

8. For recent syntheses of thiazolidines see: (a) B. S. Thyagarajan and J. A. Simon Nee Glowwienka, *Synth. Commun.*, 1988, **18**, 197. (b)H. Takahashi, S. Yasui, S. Tsunoi and I. Shibata, *Eur. J. Org. Chem.*, 2013, **1**, 40. (c) M. Rashid, A. Husain, M. Shaharyar, R. Mishra, A. Hussain and O. Afzal, *Eur. J. Med. Chem.*, 2014, **83**, 630. (d) H. M.–F. Viart, T. S. Larse, C. Tassone, T. L. Andresen and M. H. Clausen, *Chem. Commun.*, 2014, **50**, 7800. (e) M. Fizer, M. Slivka, E. Rusanov, A. Turov and V. J. Lendel, *Heterocyclic. Chem.*, 2015, **52**, 949. (f) S. M. Gomha, S. M. Riyadh, E. A. Mahmmoud and M. M. Elaasser, *Heterocycles*, 2015, **91**, 1227. (g) M. Mahdavi, M. Bialam, M. Saeedi, F. Jafarpour, A. Foroumadi and A. Shafiee, *Synlett*, 2015, **26**, 17. (h) A. Ranjan, A. Mandal, S. G. Yerande and D. H. Dethe, *Chem. Commun.*, 2015, **51**, 14215.

9. For related reactivity see: K. Garland, W. Gan, C. Depatie-Sicard and A. M. Beauchemin, *Org. Lett.*, 2013, **15**, 4074.

10. For biological activity see: P. L. do Carmo, G. Zapata-Sudo, M. M. Trachez, F. Antunes, S. E. F. Guimarães, R. Debom, M. D. F. Rizzi and R. T. Sudo, *J. Vet. Intern. Med.*, 2010, **24**, 1224 and references therein.

11. For reviews on azomethine imine reactivity see: (a) J. G. Schantl, *Azomethine Imines. Science of Synthesis*, Georg Thieme Verlag, Stuttgart, 2004, 731-824. (b) G. Qiu, Y. Kuang and J. Wu, *Adv. Synth. Catal.*, 2014, **356**, 3483. (c) C. Nájera, J. M. Sansano and M. Yus, *Org. Biomol. Chem.*, 2015, **13**, 8596. (d) S. Tšupova and U. Mäeorg, *Heterocycles*, 2014, **88**, 129.

12. For cycloaddition of related azomethine imines, see: (a) A. Gergely, J. B. Morgan and L. E. Overman, *J. Org. Chem.*, 2006, **71**, 9144, (b) L. E. Overman, B. N. Rogers, J. E. Tellew and W. C. Trenkle, *J. Am. Chem. Soc.*, 1997, **119**, 7159. (c) J. D. Katz and L. E. Overman, *Tetrahedron*, 2004, **60**, 9559. (d) G. Belanger, F. –T. Hong, L. E. Overman, B. N. Rogers, J. E. Tellew and W. C. Trenkle, *J. Org. Chem.*, 2002, **67**, 7880.