EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201601524

Link to VoR: http://dx.doi.org/10.1002/ejoc.201601524

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Schreiner's Thiourea Promoted [2+2] Cycloaddition of Captodative Azetidinones and Nitroolefins

Zoltán Dobi, Tamás Holczbauer and Tibor Soós*

Abstract: *Strained, captodative benzylidene-azetidinones are demonstrated to function as potent reaction partners in thermal [2+2] cycloaddition with nitro alkenes. The relief of strain during the cycloaddition could be leveraged to secure the kinetic and thermodynamic stability for the amino-nitro-cyclobutane ring. Accordingly, this mild and robust procedure can be used to simplify the synthesis of aza-spiro[3.3]heptanes, a motif that serves as a rigid piperidine bioisostere.*

In recent years, development of nonclassical bioisosters with strained ring systems have been evolved as a prominent tactical approach in drug discovery and development.[1] By inserting these structural motifs in drug candidates, several pharmacological properties have been beneficially altered and the challenge of narrowing intellectual property space has also been eased.[2]

As saturated heterocycles, such as piperidines, morpholines and piperazines are often encountered in drugs, significant research efforts have been pursued to create their structurally rigid surrogates.[3] These activities have implied a range of synthetic advances, including the invention of novel methodologies and strategies to incorporate these scaffolds into elaborated molecules. A particular class of substructure, that is of interest to medicinal chemists, is the aza-spiro[3.3]heptanes which can serve as a piperidine analog. The synthetic strategies for construction of these spirocyclic counterparts are scarce and exclusively rely upon the formation of the azetidine ring from cyclobutane derivatives (Figure 1. routes a,b).[4] Surprisingly, there has been no report about the obvious alternative approach that would proceed via cyclobutane ring formation of an azetidine derivative. Herein, we report the realization of this alternative ring formation that was based on the unique reactivity of a captodative benzylidine azetidinone. A complementary motivation underlying this synthetic study was to investigate the effect of strain on chemical reactivity of four membered heterocyles.

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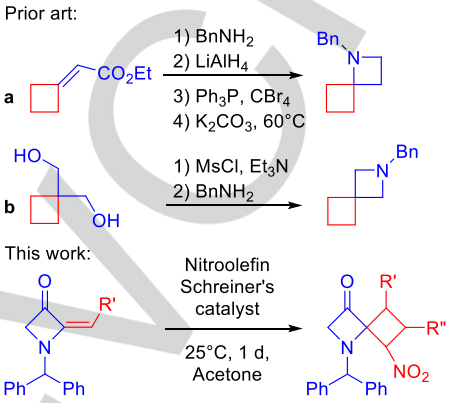


Figure 1. Methods for the preparation of aza-spiro[3.3]heptanes.

Recently, we have reported that the angle strain of four-membered heterocyclic ketones could be exploited in the development of direct cross-ketol and aldol reactions, providing new class of constrained building blocks.[5] As exemplified, the commercially available azetidinone **1** (Figure 2), as an inherently bifunctional synthetic module, could function as a linchpin element in an iterative double-aldol sequence without the need of preformed enols.

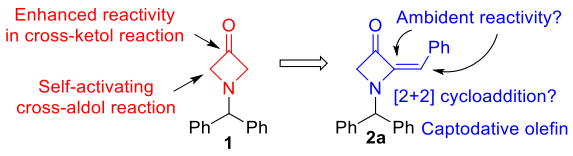


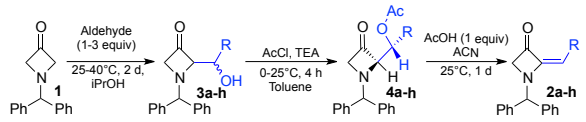
Figure 2. The Effect of Strain Release on Chemical Reactivity of Azetidinone **1**.

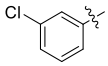
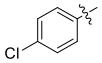
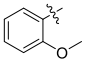
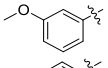
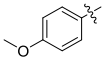
Following these findings, we became intrigued whether the strain-driven reactivity[6] of four-membered heterocyclic ketones could have been extended by incorporating an exo-olefin functionality. More specifically, we aimed to investigate the 2-benzylidene derivatives of azetidinone **1** that might function as a reactive captodative olefin.[7] This initiative obviously posed the following questions. First of all, can such captodative compounds be readily synthetized? What will be the consequence of ring strain on the reactivity? Finally, can these derivatives be exploited in building potentially useful structures to expand the reach of interesting structural patterns?

To deal with the first question, the synthesis of the captodative olefin **2a** was attempted following a straightforward three-step aldol condensation protocol developed by Masuda.[8] The synthesis began with the direct cross-aldol reaction of

azetidinone **1** and benzaldehyde without added catalyst. As we have reported earlier, one could only isolate the *anti*-aldol adduct because the isolation of the *syn* product was hampered by its tendency to undergo rapid *syn-anti* isomerization.[5] While at first glance, one might have thought that aldol adduct **3a** could have been directly converted to the condensation product **2a**, no formation of the captodative olefin was observed because the retro-aldol reaction outperformed the water elimination reaction under the requisite forcing reaction conditions. Thus, the *anti*-aldol adduct **3a** was acetylated to facilitate the subsequent elimination procedure. The thermal elimination of **4a** was then carried out in neat upon rapid thermal treatment (185°C, 2 min).

Table 1. Synthesis of captodative olefins **2a–h**.



R	aldol product	acetate	captodative olefin
	**3a** (62%) (dr = 4:1)	**4a** (72%)	**2a** (89%)
	**3b** (78%) (dr = 4:1)	**4b** (30%)	**2b** (87%)
	**3c** (63%) (dr = 1.2:1)	**4c** (58%)	**2c** (89%)
	**3d** (80%) (dr = 1.1:1)	**4d** (69%)	**2d** (92%)
	**3e** (81%) (dr = 2:1)	**4e** (56%)	**2e** (96%)
	**3f** (87%) (dr = 2:1)	**4f** (27%)	**2f** (83%)
	**3g** (65%) (dr = 1.5:1)	**4g** (71%)	**2g** (93%)
	**3h** (49%) (dr = 6:1)	**4h** (30%)	**2h** (91%)

This procedure, developed by Matsuda, did afford the desired captodative olefin **2a**, however, it proved to be less robust and reproducible in our hand despite repeated attempts. The poor and non-reproducible yields were presumed to be due to the decomposition of the vulnerable captodative olefin **2a** under the harsh condition, therefore, an alternative, mild procedure had to be developed. After a few elimination attempts at ambient temperature, it became evident that the elimination process could only be promoted by acids, but not by bases. Several observations are of note: When a small amount of acetic acid was added to the starting material, an autocatalytic elimination occurred that could be completely inhibited by triethylamine. Another interesting feature is the solvent dependence of reaction rate and outcome. The reaction rate is largely decelerated in apolar solvents such as hexanes, toluene, ethyl acetate. In acetic acid, however, decomposition of the captodative olefin **2a** to a ring opened derivative **5** was observed (Figure 3). This interesting diketo compound **5** could decompose even further to glycine derivative **6** in the EtOH/AcOH mixture. After multiple iterations of reaction conditions, we found that one equivalent of AcOH in acetonitrile efficiently promoted the elimination as a single olefinic product **2a** yielded without side product formations. From the structure of captodative olefin **2a** determined by X-ray crystallography,[9] it was concluded that the elimination proceeded in a stereoselective *trans* manner. Experiments that probe the scope of aromatic aldehydes in captodative olefin formation reaction are also summarized in Table 1. As hoped, an array of electron-rich and electron-poor aldehydes can effectively serve as starting materials in this procedure. Most importantly, all elimination reaction steps were stereoselective, robust and scalable. Finally, it is noteworthy that utilization of aliphatic aldehydes as starting materials are not tolerated in this procedure, as the resulting captodative derivative proved to be unstable.

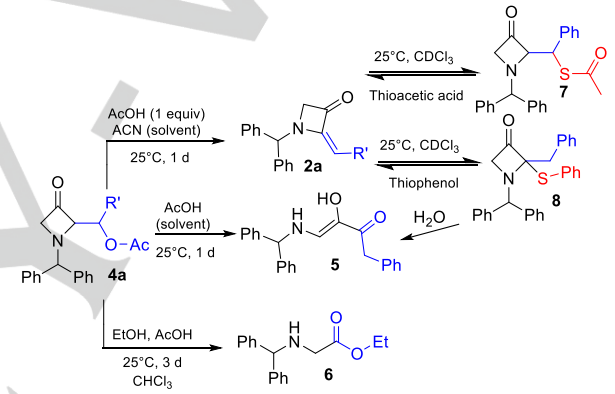


Figure 3. Exploring the reactivity of captodative olefin **2a**.

Next, we have conducted some preliminary experiments to ascertain the ambident nature of the captodative olefin **2a**. In an initial trial, the reaction of captodative olefin with thiophenol was probed. Gratifyingly, highly selective reaction occurred and the sense of regioselectivity reflected the dominant directivity of the amino functionality. It is worth mentioning that the degradation of captodative olefin during its preparation, as highlighted in Figure 3, seems to follow this type of reactivity. We next examined a reaction with a more acidic sulphur compound, the thioacetic acid with **2a**. Interestingly, this nucleophile also underwent a selective addition reaction, however, the reaction occurred with different regioselectivity. In the presence of stronger acid, the amino group seems to be protonated and the captodative olefin functioned not as an enamine, but as a Michael acceptor.

Having established the acid modulated ambident reactivity of the captodative system, we also sought to utilize azetidinone alkene derivatives **2a–h** for gaining access to spirocyclic structures. Given their dominant enamine character, we envisioned installing nitro alkenes to captodative olefins **2a–h** in a [2+2] reaction to form cyclobutane[10] derivatives. While common enamines could form amino-nitro cyclobutanes, those compounds are notoriously unstable.[11] They are either in thermal equilibrium with the corresponding enamine and nitro alkene or undergo ring opening in the presence of water (Figure 4).[11e] Nevertheless, we hypothesized that the inherent angle-

strain of azetidinones could be leveraged to secure kinetic and thermodynamic stability for the amino-nitro-cyclobutane ring.

The envisioned [2+2] reaction was first examined using the representative captodative olefin **2a** and nitroalkene **9a** as coupling partners, along with *p*-nitrophenol as hydrogen donor catalyst.[12] Gratifyingly, the desired spirocyclic product **10aa** was observed as a sole product with all-*trans* cyclobutane ring at room temperature with good conversion. To our delight, the cyclobutane ring of **10aa** proved to be stable; no decomposition was observed during its isolation indicating that the strain relief upon cycloaddition drives the thermodymanics of the reaction. As the strained captodative olefin is a vulnerable entity, these reactions had to be performed at ambient temperature with the rigorous exclusion of O or S nucleophiles, such as alcohols, aromatic an aliphatic thiols. Even the stabilizer of the chloroform, the ethanol, had to be removed for successful reaction. An attempt to extend the heterocyclic part of the strained captodative alkenes was also probed, however, the thia analog **2i** failed to react with nitroolefin **9a**.

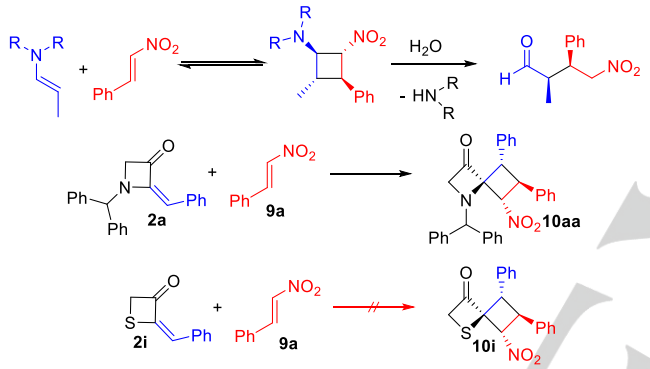
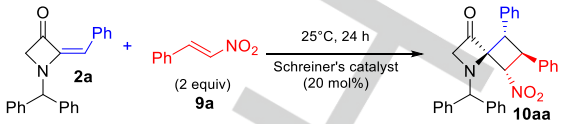


Figure 4. Formation and decomposition of cyclobutanes generated in a [2+2] cycloaddition reaction.

Despite *p*-nitrophenol being an efficient catalyst, further screens for an improved catalyst were pursued.[9] This search eventually identified Schreiner's thiourea[13] as the most efficient promoter. In cases of phenolic catalyst or acetic acid, the isolated yields were significantly lower, because the captodative olefin **2a** suffered decomposition in their presence. Chiral hydrogen donating catalysts were also probed, however, no chiral induction was observed.[9] As revealed in a subsequent solvent screening (Table 2), this unique [2+2] addition can be easily accomplished in a wide range of aprotic solvents. The best yield was achieved in chloroform, but the diastereoselectivity was modest. A reaction conducted in toluene gave a lower yield; however, the product precipitated out from that solvent which can be a tradeoff for practicality. The optimal solvent was the acetone, because the reaction proceeded in this solvent with high yield and diastereoselectivity.

Table 2. Solvent screening for [2+2] cycloaddition of benzylidene-azetidinone and nitrostyrene

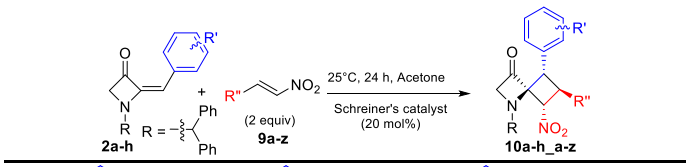


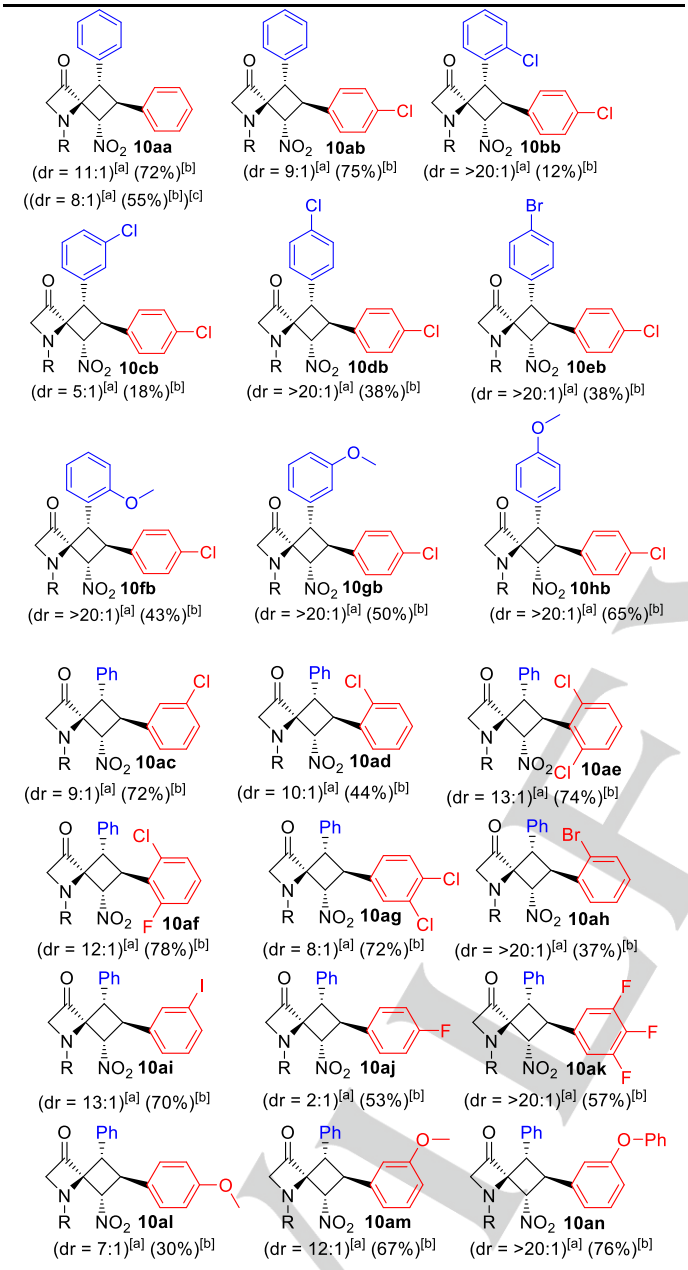
Entry	Solvent	dr[a]	Yield[b]
1	DMSO	12:1	70
2	Toluene	3.5:1	65
3	Chloroform	2.3:1	74
4	THF	>20:1	32
5	Ethyl acetate	2.25:1	68
6	Acetonitrile	>20:1	48
7	**Acetone**	**11:1**	**72**
8	DMF	>20:1	28

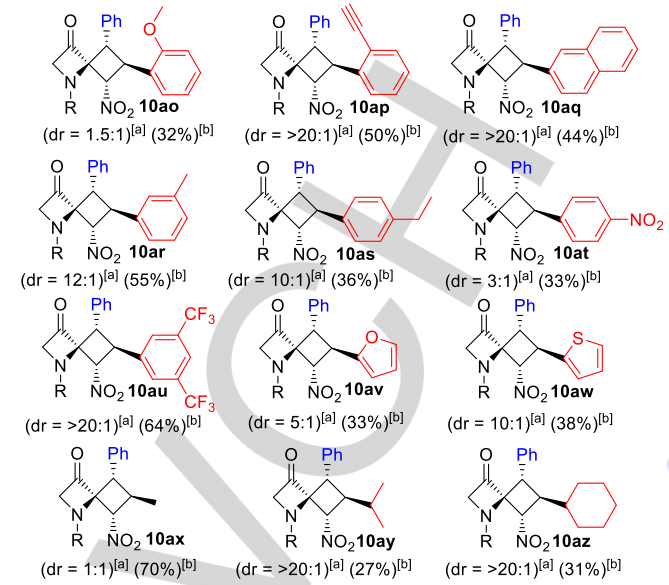
[a] The diastereomeric ratio in the crude reaction product was determined by ^{1}H NMR. [b] Isolated yields of diastereomers.

Using the optimized catalytic conditions, the scope of the cycloaddition was investigated. The scope of the captodative olefins that can be reacted in [2+2] addition is illustrated in Table 3 (**10aa–10hb**). Monosubstituted phenyl derivatives bearing electron-donating groups worked smoothly, however, electron withdrawing group substituted derivatives, as expected, tend to give lower yields. Experiments that probe the scope of the nitroalkene component is summarized in Table 3 (**10ac–10az**). These studies revealed that [2+2] cycloaddition reaction with the representative olefin **2a** works with aromatic or aliphatic nitroalkenes and their structural and electronic modification had an anticipated effect on reactions' efficiency. Enhancement of the steric demand of the nitroalkene deleteriously affected the yields, as exemplified in the formation of **(10ao, 10ad)**. The presence of the electron withdrawing groups on the aromatic rings of β-nitrostyrenes exerted auspicious influence on the reactions' efficiency, especially when they were in ortho or para positions **(10ab, 10db, 10hb, 10ai)**. However, the para-nitro substituted β-nitrostyrene reacted distinctly; two unidentified side products were also formed, that lowered the yield. The β-nitrostyrenes with electron rich aromatic rings have a tempered electrophilic reactivity that resulted in lower yields in the cycloadditions (**10al**, **10as**). As a proof for versatility and generality of this methodology, we have found that aliphatic nitroalkenes are suitable substrates **(10ax, 10ay, 10az)**. It is worth noting that the cycloaddition reaction tolerated various high-value functionalities such as acetylene, bromo and iodo substitutents that provide additional opportunities for further diversification.

Table 3. Scope of [2+2] cycloadditions between captodative olefins **2a–h** and nitroalkenes **9a–z**.







[a] The diastereomeric ratio in the crude reaction product was determined by ^{1} NMR. [b] Isolated yields of diastereomers. [c] The catalyst was changed to nitro-phenol.

Conclusions

In summary, the research above demonstrates the synthetic utility of strained, azetidinone-based captodative olefins for accessing aza-spirocyclic compounds. The captodative building blocks are reached through a three-step, robust and scalable procedure. We have demonstrated that the strained captodative olefin has acid modulated ambident reactivity. Taking advantage of strain-driven enhanced reactivity and the dominant enamine character of **2a**, we have accomplished the highly diastereoselective [2+2] cycloaddition of cyclobutane ring. Given the importance of the aza-spirocyclic motifs as rigid piperidine bioisostere in medicinal chemistry, the lower yet serviceable yields observed will likely be a welcome advance to chart highly coveted region of chemical space in a concise manner. Further explorations of the strain-driven reactivity of four-membered heterocycles are underway in our laboratory.

Experimental Section

General procedure for the direct aldol reactions between 1-Diphenylmethylazetidin-3-one (1) and benzaldehyde derivatives: **1** (2.0 mmol) was dissolved in 4 mL of isopropanol and a benzaldehyde derivative (1-3 equiv.) was added. The mixture was stirred at 25-40 °C for 2 days then the solvent was evaporated. The residue was purified by column chromatography (SiO_2; hexane / ethyl acetate) to give aldol products **(3a–h).**

General procedure for the acetylation of aldol adduct 3a–h: A solution of **3a–h** (2.0 mmol), triethylamine (4.0 equiv.) and abs. toluene (9 mL) were cooled to 0 °C and acetyl chloride (3.5 equiv.) was added dropwise. After 10 minutes the mixture was allowed to warm to room temperature, stirred for another 4 hours then washed with 3 ml water, 3 ml saturated $NaHCO_3$ solution and 3 ml brine. The organic phase was

dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2; hexanes / ethyl acetate) to give **4a-h.**

General procedure for the elimination reactions: 4a–h (1.0 mmol) was dissolved in 9 mL of acetonitrile and acetic acid (1.0 equiv) was added. The mixture was stirred at room temperature for 24 hours then diluted with 45 ml diethyl ether, washed with 2x12 mL of saturated $NaHCO_3$ solution and with 12 mL of brine. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2; hexanes / ethyl acetate) to give **2a–h.**

General procedure for the [2+2] cycloadditions: 2a–h (0.8 mmol), **9a-z** (2.0 equiv.) and Schreiner's catalyst (0.2 equiv.) were dissolved in 1.6 mL of acetone. The mixture was stirred at room temperature for 24 hours then the solvent was evaporated at reduced pressure. The residue was purified by column chromatography (SiO_2; hexanes / ethyl acetate) to give **10a-h_a-z.**

General handling guide for the 1-azaspiro[3.3]heptane derivatives: The products are rather stable solid molecules with high melting point. However, in liquid phase they can decompose slowly, depending on the solvent. Chloroform must be avoided unless for the NMR studies. The best solvents to prevent decomposition are hexane and diethyl ether. The product is sensitive to common (acidic) silica gel and basic alumina. The chromatography needs to be carried out in neutral silica gel. Our choice was the Biotage® SNAP KP-Sil (pH = 7.2), which was found to be perfect solid phase to purify the crude product.

Acknowledgements

Keywords: Organocatalysis • azetidine • cyclobutane • Spirocycle • [2 + 2] cycloaddition

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[12] Without added H-bond donor additives no reaction occurred in analogous organocatalytic processes, ref 11e, 11g

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10.1002/ejoc.201601524

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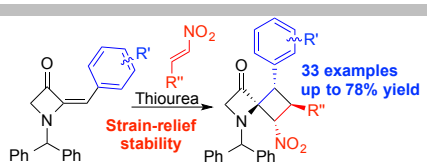
Strained, captodative benzylidene-azetidinones are demonstrated to function as potent reaction partners in thermal [2+2] cycloaddition with nitro alkenes. The relief of strain during the cycloaddition could be leveraged to secure the kinetic and thermodynamic stability for the amino-nitro-cyclobutane ring. Accordingly, this mild and robust procedure can be used to simplify the synthesis of aza-spiro[3.3]-heptane bioisoteres.



*Zoltán Dobi, Tamás Holczbauer, Tibor Soós**

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Schreiner's Thiourea Promoted [2+2] Cycloaddition of Captodative Azetidinones and Nitroolefins

Layout 2:

SHORT COMMUNICATION