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Synthesis of 3*H*-1,2,4-Triazol-3-ones via $NiCl_2$-Promoted Cascade Annulation of Hydrazonoyl Chlorides and Sodium Cyanate

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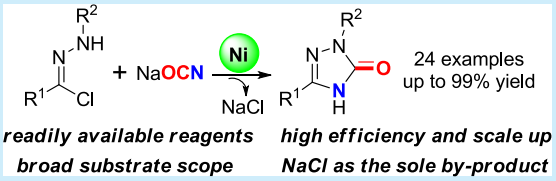
ABSTRACT: A nickel-promoted cascade annulation reaction for the facile synthesis of 3*H*-1,2,4-triazol-3-ones from readily available hydrazonoyl chlorides and sodium cyanate has been developed. The transformation occurs through a cascade nickel-promoted intermolecular nucleophilic addition−elimination process, intramolecular nucleophilic addition, and a hydrogen-transfer sequence. The method has been successfully applied for the construction of the core skeleton of the angiotensin II antagonist.



1,2,4-Triazol-3-ones are identified as a kind of important five-membered heterocyclic molecules, which display various potent biological activities.[1] The privileged *N*-heterocycles have been successfully applied in various fields with prominent potency (Figure 1). For instance, 2,4,5-trisubstituted-3*H*-1,2,4-triazol-3-ones with an acidic biphenylsulfonamide moiety are utilized as dual AT_1/AT_2 receptor antagonists with enhanced affinity.[2] A series of 2,4-dihydro-3*H*-1,2,4-triazol-3-ones have been identified as PPARα agonists for clinical studies.[3] Therefore, tremendous attention has been directed toward the synthetic routes to 1,2,4-triazol-3-ones over the past few decades.

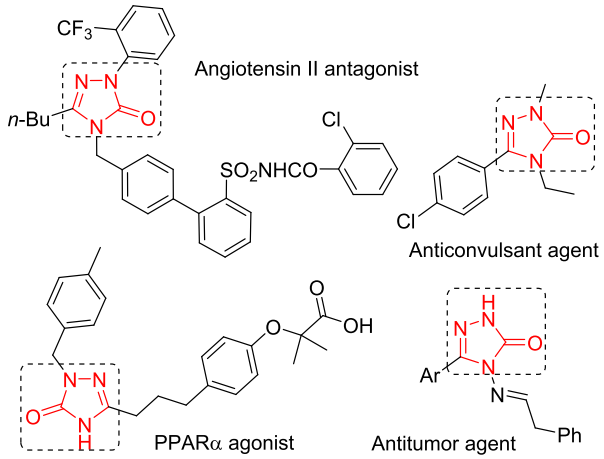


Figure 1. Selected examples of bioactive 1,2,4-triazol-3-one molecules.

Although numerous synthetic methods for producing 1,2,4-triazol-3-ones have been reported,[4] most of the traditionally developed strategies have suffered from several drawbacks, such as preactivation of substrates, multistep procedures, harsh reaction conditions, low efficiency, or generation of undesirable byproducts. Considering the urgent demand for environmental friendliness and sustainability, green synthesis has emerged as a mainstream alternative to conventional synthetic pathways. An elegant example was presented by Cheng and coworkers, which realized the facile synthesis of 1,2,4-triazol-3-ones through the metal-free mediated annulation of 2-hydrazinylpyridine or benzamidrazone and atmospheric pressure of CO_2.[5] In 2021, we disclosed an efficient approach for the construction of 1,2,4-triazol-3-ones via a palladium-catalyzed cascade carbonylative reaction of hydrazonoyl chlorides and NaN_3 with TFBen (benzene-1,3,5-triyltriformate) as a convenient CO surrogate.[6] In this transformation, the toxic and flammable CO gas was avoidable, but the employment of hazardous NaN_3 slightly weakened the significance and application of the protocol. Consequently, we wish to seek another greener and more economic route to assemble structurally diverse 1,2,4-triazol-3-ones.

Sodium or potassium cyanate (NaOCN or KOCN) is a kind of cheap and less toxic salt that has usually been applied to transition-metal-catalyzed cross-coupling reactions with aryl halides or arylboronic acids for the construction of a range of carbamates or ureas. In 2011, Kianmehr and coworkers developed a copper-catalyzed coupling of aromatic boronic acids with potassium cyanate and alcohol for the preparation of arylcarbamates under mild conditions (Scheme 1a).[7] Later, Buchwald and coworkers reported a palladium-catalyzed cross-coupling of aryl chlorides or triflates with sodium cyanate for building unsymmetrical ureas via aryl isocyanates or their phenyl carbamate intermediates (Scheme 1b).[8] The protocol

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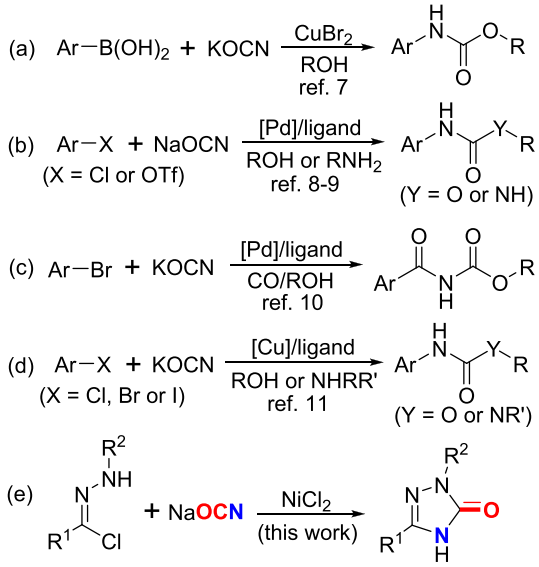
Scheme 1. Coupling Reactions of Sodium/Potassium Cyanate

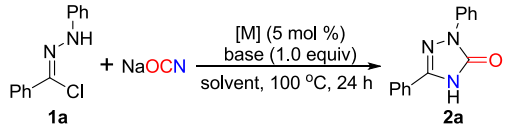


had been adopted to synthesize aryl carbamates by employing diverse alcohols as the nucleophiles.[9] The acyl carbamates could be assembled by the Pd-catalyzed four-component carbonylation of aryl and heteroaryl bromides, potassium cyanate, and alcohols, which was described by Skrydstrup and coworkers (Scheme 1c).[10] Notably, Ma's group achieved a series of similar coupling reactions of aryl halides with potassium cyanate under copper catalysis and a bidentate ligand (Scheme 1d).[11] Sodium/potassium cyanate was also utilized as a reactive partner in the Rh(I)-catalyzed asymmetric ring-opening of oxabicyclic alkenes to construct chiral oxazolidinone scaffolds[12] or a copper-catalyzed coupling reaction through C−H bond functionalization for the formation of acetanilide derivatives.[13] Although various impressive coupling reactions involving cyanate salts have been exploited, the application of salts cyanate to the production of heterocyclic compounds is still limited and highly desirable.

Encouraged by the excellent viability of the cyanate anion in transition-metal-catalyzed cross-coupling reactions and our continuous interest in the efficient synthesis of structurally diverse *N*-heterocycles,[14] we herein report a general and atom-economical approach for the preparation of biologically valuable 1,2,4-triazol-3-ones from the nickel-mediated cascade annulation of hydrazonoyl chlorides and sodium cyanate (Scheme 1e). Hydrazonoyl chlorides have frequently been applied as a versatile building block to build diverse heterocycles.[15] The first nickel-catalyzed coupling reaction with metal cyanates was developed by Tkatchenko in 1986, but the reaction efficiency was generally lower.[16] In our transformation, notable features include the use of an inexpensive earth-abundant nickel promoter, readily available starting materials, a broad substrate scope, high efficiency, and scalability.

First, *N*′-phenylbenzohydrazonoyl chloride **1a** and NaOCN were chosen as model substrates to initiate the investigation. The reaction proceeded smoothly under a $Pd_2(dba)_3$/*t*-BuXPhos catalytic system with NEt_3 as a base in 1,4-dioxane at 100 °C for 24 h. Gratifyingly, the 3*H*-1,2,4-triazol-3-one product **2a** was isolated in 77% yield (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions[a]



entry	[M]	base	solvent	yield (%)[b]
1	$Pd_2(dba)_3$	NEt_3	1,4-dioxane	77[c]
2	$Cu(OTf)_2$	NEt_3	1,4-dioxane	71
3	$FeCl_3$	NEt_3	1,4-dioxane	84
4	$NiCl_2$	NEt_3	1,4-dioxane	95
5	$ZnCl_2$	NEt_3	1,4-dioxane	90
6	$Sc(OTf)_3$	NEt_3	1,4-dioxane	67
7	BF_3OEt_2	NEt_3	1,4-dioxane	34
8	$NiCl_2$ $6H_2O$	NEt_3	1,4-dioxane	84
9		NEt_3	1,4-dioxane	31
10	$NiCl_2$	NEt_3	toluene	82
11	$NiCl_2$	NEt_3	THF	72
12	$NiCl_2$	NEt_3	CH_3CN	43
13	$NiCl_2$	NEt_3	DMF	61
14	$NiCl_2$	DIPEA	1,4-dioxane	58
15	$NiCl_2$	DBU	1,4-dioxane	21
16	$NiCl_2$	$NaHCO_3$	1,4-dioxane	56
17	$NiCl_2$		1,4-dioxane	37
18	$NiCl_2$	NEt_3	1,4-dioxane	74−86[d]
19	$NiCl_2$	NEt_3	1,4-dioxane	86[e]
20	**$NiCl_2$**	**NEt_3**	**1,4-dioxane**	**94**[f]
21	$NiCl_2$	NEt_3	1,4-dioxane	80[g]
22	$NiCl_2$	NEt_3	1,4-dioxane	48[f,h]

[a]Reaction conditions: **1a** (0.3 mmol), NaOCN (2.0 equiv), [M] (5 mol %), and NEt_3 (1.0 equiv) in solvent (2.0 mL) at 100 °C under a N_2 atmosphere for 24 h. [b]Isolated yield. [c]*t*-BuXPhos (5 mol %) as a ligand. [d]Reaction was conducted at 80 (74%) or 120 °C (86%). [e]Under air. [f]$NiCl_2$ (2.5 mol %). [g]$NiCl_2$ (0.5 mol %). [h]KOCN instead of NaOCN.

Considering palladium as a precious metal catalyst, several low-cost metal salts were examined, including $Cu(OTf)_2$, $FeCl_3$, and $NiCl_2$, and the highest 95% yield was observed with regard to $NiCl_2$ (Table 1, entries 2−4). Then, other nickel catalysts were surveyed but inferior results were obtained. (See the details in the Supporting Information.) Owing to the availability of $Cu(OTf)_2$ and $FeCl_3$, we envisaged that the reaction was driven by a Lewis acid and did not undergo a catalytic process, as verified by the validity of $ZnCl_2$ and $Sc(OTf)_3$ (Table 1, entries 5 and 6). Another frequently used Lewis acid, BF_3OEt_2, showed inferior reactivity, and only a 37% yield was observed (Table 1, entry 7). $NiCl_2{\cdot}6H_2O$ also promoted the transformation with high efficiency (Table 1, entry 8). The transformation could occur in the absence of any metal to afford the product **2a** in 31% yield, further confirming the above hypothesis (Table 1, entry 9). The solvent effect was tested by using diverse organic solvents, and 1,4-dioxane was the optimal choice (Table 1, entries 10−13). Other organic or inorganic bases were screened in the reaction, whereas a lower efficiency was observed than that of NEt_3 (Table 1, entries 14−16). The reaction proceeded in the absence of a base to give the product **2a** in 37% yield, revealing the key role of the base (Table 1, entry 17). Lowering or elevating the reaction temperature resulted in a decrease in the reaction yields (Table 1, entry 18). When the reaction was performed under an air atmosphere, product **2a** could be obtained in 86% yield (Table 1, entry 19). Notably, reducing the loading amount of $NiCl_2$ to

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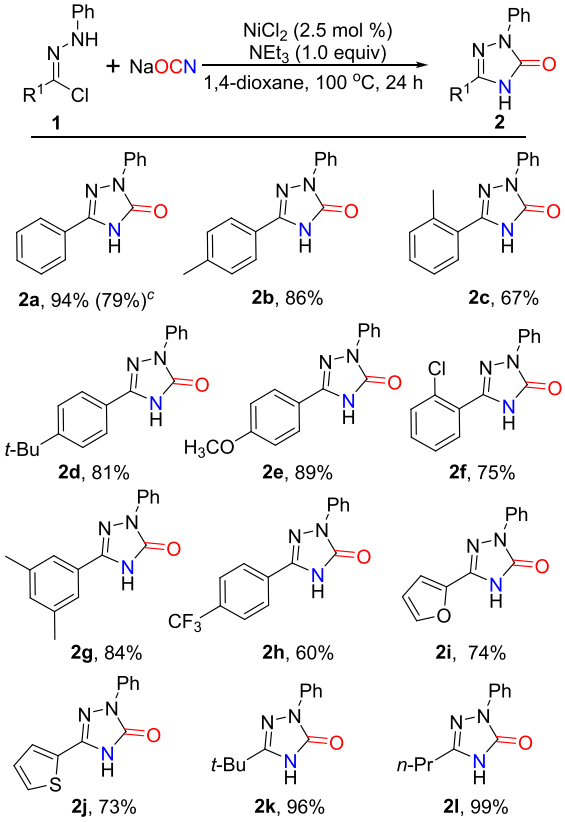
2.5 mol % gave a comparable yield, and 0.5 mol % $NiCl_2$ could enable the formation of **2a** in 80% yield (Table 1, entries 20 and 21). The observation data indicated the high economy and efficiency of this transformation. Switching NaOCN to KOCN led to a sharp decline of the reaction yield (Table 1, entry 22).

With the establishment of the optimized reaction conditions, the scope and limitation of the reaction were examined by the use of various hydrazonyl chlorides derived from different acyl chlorides (Scheme 2). Good compatibility of the protocol was

Scheme 2. Scope of the Hydrazonyl Chlorides from Diverse Acyl Chlorides[a,b]

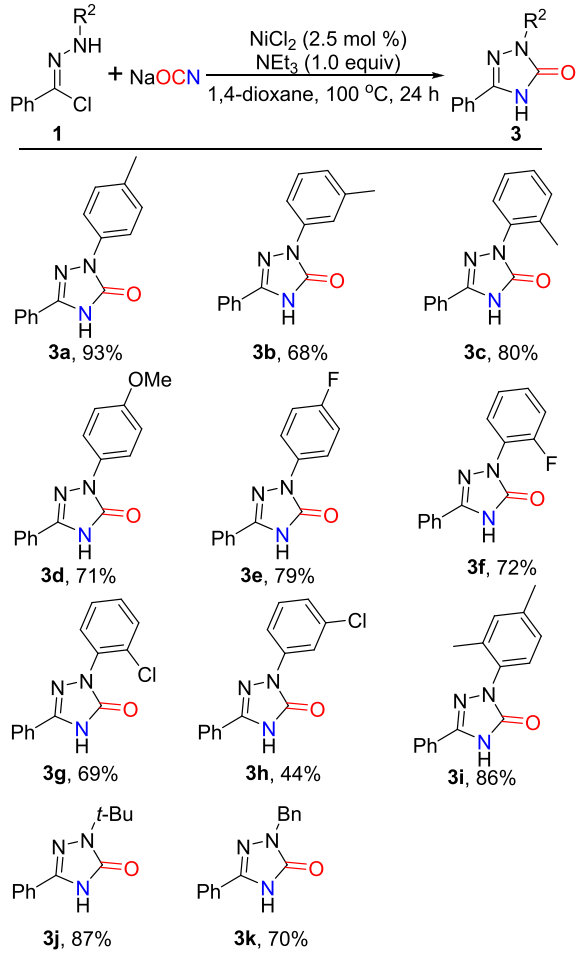


[a]Reaction conditions: **1** (0.3 mmol), NaOCN (2.0 equiv), $NiCl_2$ (2.5 mol %), and NEt_3 (1.0 equiv) in 1,4-dioxane (2.0 mL) at 100 °C under a N_2 atmosphere for 24 h. [b]Isolated yields. [c]1 mmol scale.

observed, as it was demonstrated that moderate to excellent yields of the desired 3*H*-1,2,4-triazol-3-one products **2a**−**2h** were obtained when hydrazonyl chlorides from aromatic acyl chlorides were used as substrates. The steric factor had a moderate impact on the reaction (**2b** and **2c**), and the reactivity of hydrazonyl chlorides with electron-donating groups (**2b**−**2e**, **2g**) is generally higher than that of hydrazonyl chlorides bearing electron-withdrawing groups (**2f** and **2h**). The reaction could be performed on a 1 mmol scale in 79% yield for product **2a**. The heterocyclic frameworks, including furan and thiophene, were smoothly incorporated into the 3*H*-1,2,4-triazol-3-one products in good yields (**2i** and **2j**). It should be noted that hydrazonyl chlorides from aliphatic acyl chlorides also successfully participated in the transformation to afford the corresponding 3*H*-1,2,4-triazol-3-ones **2k** and **2l** with alkyl substituents with excellent efficiency.

The generality of this cascade annulation reaction was further investigated by utilizing hydrazonyl chlorides from diverse hydrazines (Scheme 3). The reaction was amenable to a variety of hydrazonyl chlorides from arylhydrazines for the

Scheme 3. Scope of the Hydrazonyl Chlorides from Diverse Hydrazines[a,b]



[a]Reaction conditions: **1** (0.3 mmol), NaOCN (2.0 equiv), $NiCl_2$ (2.5 mol %), and NEt_3 (1.0 equiv) in 1,4-dioxane (2.0 mL) at 100 °C under a N_2 atmosphere for 24 h. [b]Isolated yields.

production of 3*H*-1,2,4-triazol-3-one products **3a**−**3i** in moderate to good yields. The electronic effect (**3a**−**3h**) and steric hindrance (**3a**−**3c**, **3f**, and **3g**) of the aryl ring both exerted a negligible effect on the reaction. The halogen atoms attached on the aryl ring were well tolerated in the reaction (**3e**−**3h**), albeit with a relatively lower yield of product **3h**, providing a synthetic handle for the further transformation. The hydrazonyl chloride from 2-hydrazineylpyridine could not be prepared by common synthetic methods. With regard to the hydrazonyl chlorides from alkylhydrazines, the reaction also proceeded smoothly for the assembly of *N*-alkyl-substituted 3*H*-1,2,4-triazol-3-ones (**3j** and **3k**) in 70−87% yields. Unfortunately, the dialkyl-substituted hydrazonyl chlorides were unstable under the current reaction conditions.

To gain more insights into the reaction mechanism, several control experiments were performed (Scheme 4). Initially, the radical trapping experiments were carried out by the addition 2.0 equiv of radical scavengers. The results revealed that no sharp decrease in the reaction yield was observed with regard to TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl), BHT (2,4-

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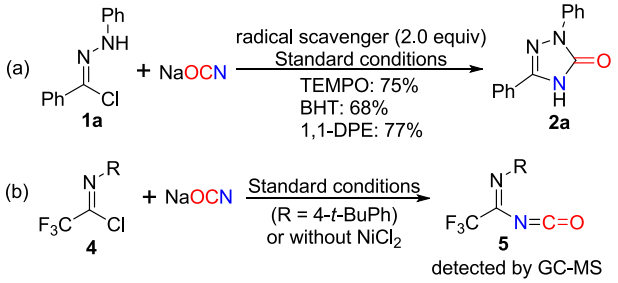
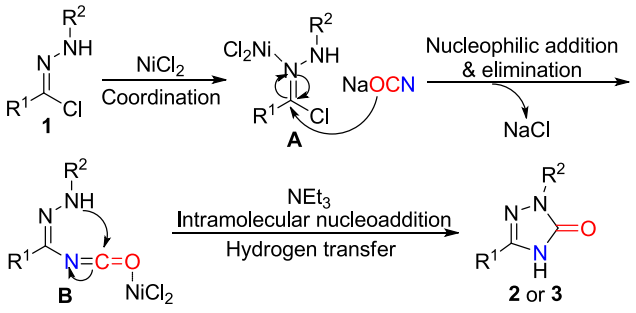
Scheme 4. Mechanistic Investigations



di-*tert*-butyl-4-methylphenol), or 1,1-DPE (1,1-diphenylethylene) (Scheme 4a), indicating that the transformation did not involve a single-electron transfer (SET) process. Considering the difficulty of the isolation of isocyanate species from hydrazonoyl chloride, we synthesized the structurally similar trifluoroacetimidoyl chloride **4** and subjected it to the standard conditions. The coupling product isocyanate **5** between trifluoroacetimidoyl chloride **4** and NaOCN was successfully detected by GC-MS in the presence or absence of a nickel catalyst (Scheme 4b). The positive result suggested that hydrazonoyl isocyanate might act as the key intermediate of the reaction, which was consistent with the assumption of our previous report.[6]

Considering the following observations, (1) the reaction was viable without any metal catalyst, (2) divalent nickel was used in the reaction in the absence of ligand, and (3) several Lewis acids, including $FeCl_3$, $Cu(OTf)_2$, $ZnCl_2$, and $Sc(OTf)_3$, all could promote the reaction, it is speculated that $NiCl_2$ serves as a Lewis acid to promote the reaction by activating the C═N and C═O double bonds. On the basis of the results of preliminary mechanistic investigations and the precedent literature,[6,8,17] a tentative mechanism is proposed as depicted in Scheme 5. Initially, the coordination of hydrazonoyl chloride

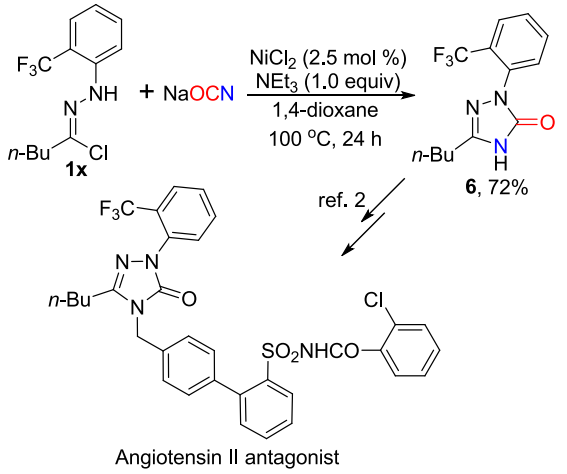
Scheme 5. Plausible Reaction Mechanism



1 with $NiCl_2$ formed nickel complex **A** to activate the C═N bond. Then, the intermolecular nucleophilic addition of cyanate anion into **A** led to the isocyanate intermediate **B** with the elimination of a NaCl byproduct. Finally, the $NiCl_2$- and NEt_3-promoted intramolecular nucleophilic addition of **B** and the subsequent hydrogen-transfer process afforded the 3*H*-1,2,4-triazol-3-one product **2** or **3**.[6,8] Of note, because of the key role of a base in the reaction and the easy generation of the nitrilimine intermediate from hydrazonoyl chloride in the presence of a base, we cannot totally exclude the possibility of a direct [3 + 2] cycloaddition reaction of *in-situ*-formed nitrilimine with sodium cyanate.[17]

The 2,4,5-trisubstituted-3*H*-1,2,4-triazol-3-one with an acidic sulfonamide moiety at the 2′-position of the biphenyl-4-ylmethyl side chain is defined as an orally active angiotensin II antagonist.[2] The core skeleton of angiotensin II antagonist **6** could be smoothly constructed in 72% yield by employing our developed protocol (Scheme 6), which underscores the promising application prospect of this methodology.

Scheme 6. Synthetic Applications



In summary, we have developed an atom-economical and sustainable strategy for the efficient preparation of 3*H*-1,2,4-triazol-3-ones via the nickel-promoted cascade annulation reaction of hydrazonoyl chlorides and sodium cyanate. Notable advantages include readily accessible starting materials, the use of an inexpensive nickel promoter, high efficiency, scalability, and NaCl as the sole harmless byproduct, which enable the great application prospect of this transformation. Further investigations toward the broader application scenarios of this protocol are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00568.

General comments, general procedure, analytic data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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