Tetrahedron Letters 61 (2020) 151944

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Facile synthesis of new functionalized 3,4-dihydro-2*H*-pyrroles using 2-isocyanoacetates

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ARTICLE INFO

Article history:
Received 18 March 2020
Revised 11 April 2020
Accepted 13 April 2020
Available online 16 April 2020

Keywords:
3,4-Dihydro-2*H*-pyrroles
2-Isocyanoacetates
(*E*)-2-Styrylbenzothiazole
Acrylonitriles

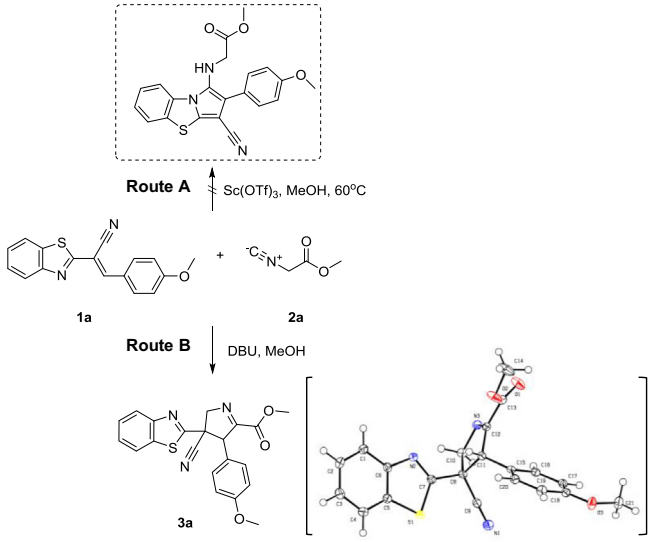
ABSTRACT

A one-step synthesis of novel functionalized 3,4-dihydro-2*H*-pyrroles from 2-isocyanoacetates and readily synthesized acrylonitriles is reported. The reaction proceeds smoothly under mild conditions with high efficiency. The structures of two representative structures, **3a** and **3m**, were confirmed by X-ray crystallographic analysis.

Introduction

Owing to their intrinsic properties as nucleophiles and electrophiles, isocyanides have been extensively applied in organic synthesis, particularly in the synthesis of nitrogen-containing molecules. Among them, isocyanides-based formal [4+1] annulation reactions have transpired as an efficient and direct protocol for the synthesis of various five-membered compounds [1]. We have also been involved in the construction of novel small libraries of *N*-heterocycles using Groebke-Blackburn-Bienaymé multicomponent reaction [2].

We envisioned that (*E*)-2-styrylbenzothiazole **1a** might also undertake the [4+1] intermolecular cyclization with isocyanides, however, no reaction occurred under the typical GBB reaction condition using $Sc(OTf)_3$ as a catalyst (route A, Scheme 1) [3]. However, we accidentally found that by using DBU as the promoter in this reaction, a new class of 3,4-dihydro-2*H*-pyrroles **3a** was obtained (route B, Scheme 1), the structure of compound **3a** was confirmed by single crystal X-ray diffraction analysis [4]. And to the best of our knowledge, this type of structure has not previously been reported. It is well-known that pyrrole and 2*H*-pyrrole are the ubiquitous cores in many natural products and small molecule chemotherapeutics, which possess diverse pharmacological properties [5]. Therefore, they are regarded as privileged structures by synthetic chemists because of widespread applications in medicinal chemistry and materials science. As such, a lot of effort has been spent developing practical methods for the synthesis of pyrrole units that incorporate appropriate functionality [5c,6].



Scheme 1. Synthetic approach to 3,4-dihydro-2*H*-pyrrole derivative **3a**.

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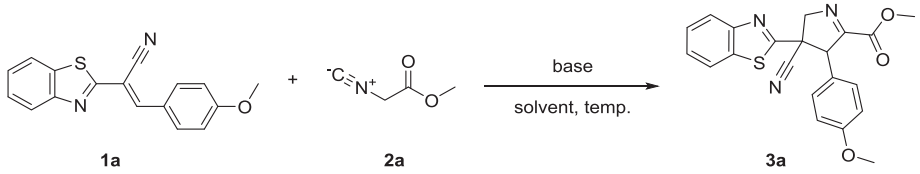
https://doi.org/10.1016/j.tetlet.2020.151944
0040-4039/

Result and discussion

These findings prompted us to turn our attention to optimizing the conditions for the efficient formation of this series of 3,4-dihydro-2*H*-pyrroles. The investigation was initiated with 2-(benzothiazol-2-yl)acrylonitrile (**1a**) and methyl isocyanoacetate (**2a**) as model substrates to optimize the reaction conditions, 2-(benzothiazol-2-yl)acrylonitrile (**1a**) and it's analogues were synthesized according to the method previously described [7]. The nature of the base was found to have a pronounced impact on the process. The reaction did not proceed in the absence of base (entry 1, Table 1). Among the organic bases, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) was shown to be more effective than DABACO and triethylamine (entries 2–5, Table 1). Moreover, among the different inorganic bases tested, potassium carbonate was the best base for this reaction, and the corresponding yield was enhanced up to 55% (entry 8, Table 1). Using weaker bases, such as sodium bicarbonate (entry 6, Table 1), or stronger bases, such as sodium hydroxide (entry 7, Table 1), no product was formed. Lower yield was observed when using 10% equimolar ratio of potassium carbonate (entry 10, Table 1), which indicated that an equimolar amount of base was required. Moreover, the decrease of the reaction yield was observed when the solvent was switched to non-polar or less polar solvents, such as THF, dichloromethane or DMF (entries 3, 11, 12 and 13, Table 1). In general, higher yields of the desired products were obtained at lower temperatures, the higher reaction temperature led to a significant decrease of reaction yield (60 °C, entry 14, Table 1). To our delight, the reaction yield was increased up to 84% when the temperature was decreased to 0 °C (entry 15, Table 1), and in most cases, the reaction was completed within several hours.

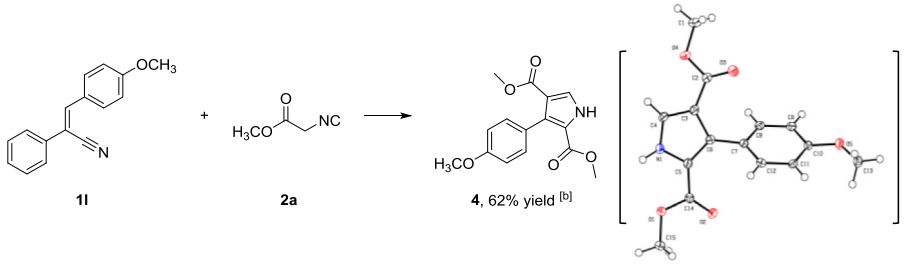
However, the reaction of 3-(4-methoxyphenyl)-2-phenylacrylonitrile (**1l**) with methyl isocyanoacetate (**2a**) under the same reaction condition only generated a trisubstituted pyrrole **4** in 62% yield. The identity of **4** was determined by spectral analysis and further confirmed by X-ray crystallographic analysis (Scheme 2) [4]. Similar findings were reported by Bullington and Samet as side-products in their synthesis [5d,8]. These results suggest that the cyclic 1-azadiene moiety is essential for the formation of 3,4-dihydro-2*H*-pyrrole ring. Based on the above preliminary results, a plausible mechanism for this process is proposed in Scheme 3. The formation of compound **4** presumably arises from initial Michael addition undergoing a retro-Michael with the leaving group being phenylacetonitrile (**A** → **B**). The resulting intermediate then reacted with isocyanoacetate again to obtain intermediate **C**, followed by a subsequent prototropic

Table 1
Optimization of reaction conditions.[a]

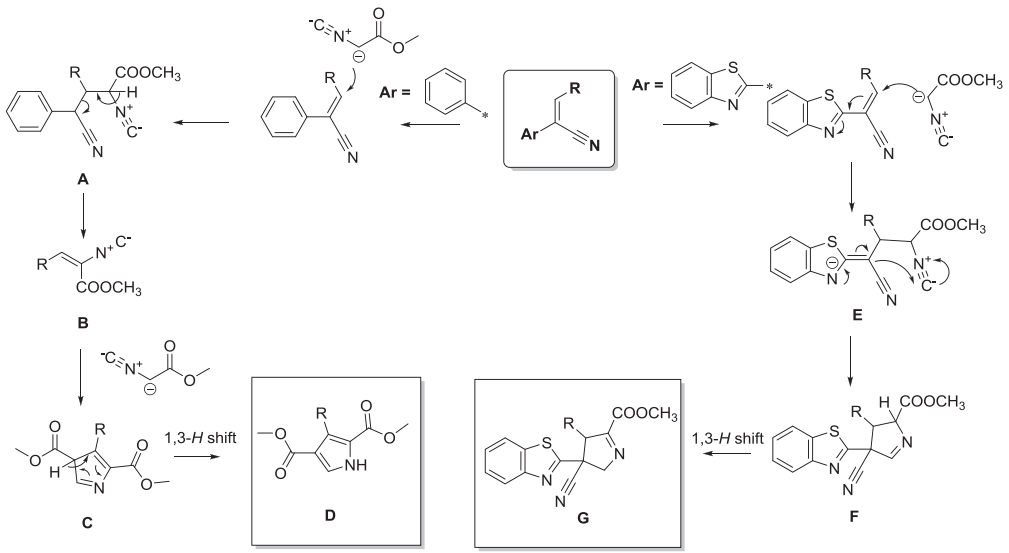


Entry	Base (mol%)	Solvent	Temp/°C	Yield (%)[b]
1	–	MeOH	60	0
2	DBU(100)	MeOH	25	42
3	DBU(100)	THF	25	24
4	DABCO(100)	MeOH	25	38
5	TEA(100)	MeOH	25	0
6	$NaHCO_3$(100)	MeOH	25	0
7	NaOH(100)	MeOH	25	0
8	K_2CO_3(100)	MeOH	25	55
9	Na_2CO_3(100)	MeOH	25	32
10	K_2CO_3(10)	MeOH	25	23
11	K_2CO_3(100)	THF	25	25
12	K_2CO_3(100)	CH_2Cl_2	25	15
13	K_2CO_3(100)	DMF	25	32
14	K_2CO_3(100)	MeOH	60	6
15	K_2CO_3(100)	MeOH	0	84

[a] Reaction conditions: **1a** (3.42 mmol, 1.0 equiv.), **2a** (1.1 equiv.), base (mol%), solvent (20 mL), 3 h.
[b] Isolated yield.



Scheme 2. Synthesis of **4**.[a] [a] Reaction conditions: **1l** (1.0 equiv.), **2a** (1.1 equiv.), K_2CO_3 (1.0 equiv.), MeOH (5 mL), 0 °C, 3 h. [b] Isolated yield.

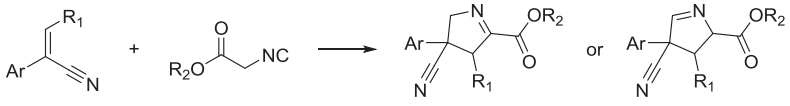


Scheme 3. The possible reaction mechanism of acrylonitriles and isocyanoacetate.

shift gives the final aromatic pyrrole ring **D**. Whereas the Ar group is benzothiazole, isocyanoacetate **2** would attack 2-styrylbenzothiazole first in the presence of a base to generate an intermediate **E**, which would undergo a rearrangement to furnish compound **F**, a subsequent 1,3-*H* shift gives the 3,4-dihydro-2*H*-pyrrole as product **G**.

With the optimized conditions in hand, we next examined a series of reactions between substrates **1a–m** and isocyanoacetates to establish the scope and limitations of this process. Substrates **1a–m** contain acrylonitrile moiety, since nitrile group is widely used in medicinal chemistry and nitrile-containing compounds comprise a substantial proportion in the therapeutic drugs [9]. The simplicity of a one-pot procedure is perfectly amenable to automation for combinatorial synthesis. Likewise, all the syntheses were performed on a parallel synthesizer (Radleys Discovery Technology, Carousel 12 Place Reaction Station) to give corresponding products. We first examined the reaction of substrates benzoxazole acrylonitrile (**1b**), *N*-methyl-benzimidazole acrylonitrile (**1c**) and 2-(pyridin-2-yl)acrylonitrile (**1d**), which showed less reactive compared with benzothiazole, gave the corresponding products (**3b–d**) in moderate yields (ranging from 45 to 60%; Table 2). Subsequently, reactions of various 2-styrylbenzothiazoles (**1a**, **1e–k**)

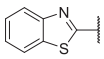
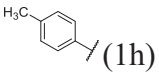
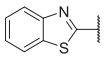
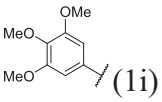
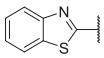
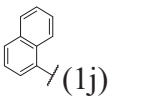
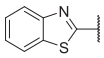
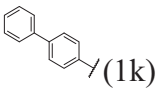
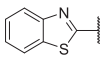
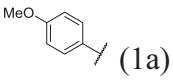
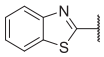
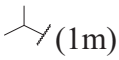
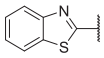
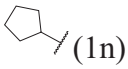
Table 2
Synthesis of **3b–n** under optimized conditions.[a]



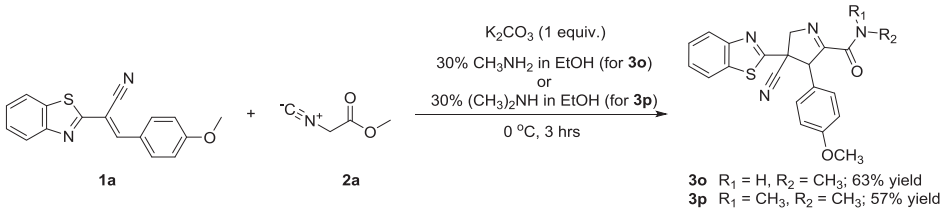
Entry	Ar	R_1	R_2	Product, yield (%)[b]
1	(1b)	MeO	Me–	**3b**, 51
2	(1c)	MeO	Me–	**3c**, 45
3	(1d)	MeO	Me–	**3d**, 60
4		Br (1e)	Me–	**3e**, 50
5		Cl (1f)	Me–	**3f**, 56
6		Cl, Cl (1g)	Me–	**3g**, 85

(*continued on next page*)

Table 2 (*continued*)

Entry	Ar	R_1	R_2	Product, yield (%)[b]
7			Me–	**3h**, 50
8			Me–	**3i**, 70
9			Me–	**3j**, 51
10			Me–	**3k**, 52
11			Et–	**3l**, 77
12			Me–	**3m**, 78
13			Me–	**3n**, 64

[a] Reaction conditions: **1a–n** (1.0 equiv.), **2a–b** (1.1 equiv.), K_2CO_3 (1.0 equiv.), MeOH, 0 °C, 3 h.
[b] Isolated yields.



Scheme 4. Synthesis of **3o**–**p**.[a] [a] Reaction conditions: **1a** (1.0 equiv.), **2a** (1.1 equiv.), K_2CO_3 (1.0 equiv.), 30% CH_3NH_2 or $(CH_3)_2NH$ alcohol solution, 0 °C, 3 h.

with methyl isocyanoacetate (**2a**) and ethyl isocyanoacetate (**2b**) were investigated (Table 2, entries 4–11). All reactions worked well to produce the expected products **3e**–**l** in moderate to good yield (50–85% yields). While measuring the ^{1}H NMR, we observed that compounds bearing the aliphatic substituents as R_1 group (**3m**–**n**) showed different NMR spectral profile. The core structure of compound **3m** turned out to be 3,4-dihydro-2*H*-pyrrole-4-carbonitrile identified by X-ray crystallographic analysis [4], which is the valence-bond isomer of the aryl substituted series (**3a**–**l**). Possible reason is that aliphatic substituents stabilized the intermediate **F** which does not undergo further 1,3-*H* shift process (Scheme 3).

Moreover, we were pleased to find that under the same reaction condition, the use of 30% methylamine or dimethylamine alcohol solution as the solvent for *in situ* ammonolysis of methyl isocyanoacetate **2a**, the amide products **3o** and **3p** was obtained with decent yields (Scheme 4).

Conclusion

In summary, we have developed an efficient method for the sequential synthesis of new functionalized 3,4-dihydro-2*H*-pyrrole derivatives, which were characterized by means of ^{1}H NMR, ^{13}C NMR, HRMS and X-ray. Easily accessible starting materials, metal catalyst-free conditions, good yields are the main advantages of this method. Meanwhile, biological activities of this rarely described class of compounds are currently under investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by the National Science & Technology Major Project "Key New Drug Creation and Manufacturing Program", China (grant no.: 2014ZX09508001), the National Natural Science Foundation of China (grant nos.: 81473130, 81473092).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151944.

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