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Unexpected isocyanide-based three-component bicyclizations for stereoselective synthesis of densely functionalized pyrano[3,4-*c*]pyrroles

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Abstract

A novel three-component bicyclization strategy for efficient synthesis of densely functionalized pyrano[3,4-*c*]pyrroles has been established from readily accessible 3-arylacrylic acids, dialkyl acetylenedicarboxylates and isocyanides. The reaction pathway involves Huisgen 1,3-dipole formation, Passerini-type reaction, Mumm rearrangement and oxo-Diels–Alder reaction sequence, resulting in continuous multiple bond-forming events including C–N, C–O and C–H bonds to rapidly build up molecular complexity.

Fused pyrroles are ubiquitous motifs in substantial naturally and non-naturally occurring compounds and can often serve as “privileged structures” in medical and pharmaceutical chemistry.¹ Among them, pyrano[3,4-*c*]pyrrole derivatives have been aroused interest owing to their biological activities.² With these attributes in mind, great efforts have been made by finding efficient synthetic methods for the construction of pyrano[3,4-*c*]pyrroles and their structural analogues. An extensive survey of the literature revealed that a few synthetic methods for forming functional pyrano[3,4-*c*]pyrroles have been developed, which involved transannulation of epoxides,³ annulation of cyclic substrates,⁴ and multi-step cyclization of acyclic precursors.⁵ Nevertheless, most of these approaches suffered from narrow substrate scope, multistep sequences, metal catalysts, and laborious workup. Therefore, the development of new and practical synthetic strategies, especially metal-free pathways, to

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access functionalized pyrano[3,4-*c*]pyrroles is highly desirable but full of challenge in pharmaceutical and fine chemical industries.

Isocyanide-based multicomponent reactions (IMCRs) have received considerable attention because of their multiple bond-forming events, inherent atom economy, and the excellent selectivity (including chemo-, regio-, and stereo-).⁶ As a branch of IMCRs, bicyclization reactions represent a uniquely powerful tool to access highly functionalized polycyclic structures of chemically and biomedically importance. These reactions not only feature annulation efficiency, extreme convergence and structural diversity and complexity but also avoid the isolation and purity of intermediates, thus minimizing the generation of waste.⁷ In recent years, the scientific community devotes much efforts in designing new isocyanide-based multicomponent bicyclizations toward various heterocycles.⁸ Of particular interest to us has been the exceptional reactivity of Huisgen 1,3-dipoles, generated in situ from the addition of isocyanide to electron-deficient alkynes, allowing the creation of complex and diverse drug-like small molecules.⁹ For instance, Nair et al. reported the [3+2] cycloaddition between activated styrenes and the zwitterion derived from isocyanide and dimethyl acetylenedicarboxylates (DMAD), furnishing substituted cyclopentadienes through a three-component reaction (Scheme 1a).¹⁰ To continue this project and our isocyanide-enabled transformations,¹¹ we found that when activated styrenes employed in the above report were replaced by 3-arylacrylic acids, the expected cyclopentadienes **5** were not observed (Scheme 1b). Instead, the reaction underwent an unexpected three-component bicyclization process to form densely functionalized pyrano[3,4-*c*]pyrroles with good to excellent yields and excellent stereoselectivity in atom- and step-economic manner (Scheme 1c). To the best of our knowledge, this protocol represents the first domino strategy encompassing a Huisgen 1,3-dipole formation, a Passerini-type reaction and an oxo-Diels–Alder reaction, which paves the way to the collection of pyrano[3,4-*c*]pyrroles through metal-free isocyanide-based bicyclizations. Herein, we would like to elaborate this interesting transformation.

Our initial investigations focused on the cascade bicyclization of (*E*)-4-(4-chlorophenyl)-4-oxobut-2-enoic acid (**1a**) with DMAD (**2a**) and *t*-butyl isonitrile (**3a**) for reaction condition optimization (Table 1). The reaction was conducted in a 1:1.2:1.2 molar ratio in *N,N*-dimethyl formamide (DMF) at 80 °C for 6 hours, delivering the unexpected product **4a** in a 63% yield. The higher yield was isolated using 1,4-dioxane as a reaction media (75% yield, entry 2). Exchanging 1,4-dioxane for acetonitrile (CH₃CN), the reaction gave a best outcome, affording the product **4a** in a 89% yield (entry 3). The use of toluene remarkably decreased the yield of **4a**. The more inferior result was observed when the reaction was carried out in dichloroethane (DCE). The other protonic solvents such as ethanol (EtOH) and acetic acid (HOAc) were met with little success. Next, the effect of reaction temperature was investigated. Lowering the temperature slightly to 60 °C proved to be infeasible, generating the 76% yield of **4a**, and the similar outcome was obtained with use of 100 °C.

With the optimal conditions for this bicyclization process in hand, we then set out to explore the scope of the transformation by reacting various **1** with **2** and isocyanides **3** (Scheme 2). Upon repeating the reaction with *t*-butyl isocyanide **3a**, we are pleased to find that 3-arylacrylic acids **1** bearing electron-rich, electron-neutral, and electron-poor groups were well tolerated under the above conditions, delivering the collection of highly substituted

pyrano[3,4-*c*]pyrroles (**4b–4g**) with good to excellent yields of 59–83% and high diastereoselectivity (up to > 99:1 dr). Generally, electronic nature of substituents on the phenyl ring of **1** imposed an important impact on the reaction efficiency, the obtained chemical yields and diastereoselectivity. For instance, upon treatment of substrates **1** with electron-withdrawing groups like chloro (**1a**), the desired products **4a** was obtained in an 89% yield and 66.7:1 dr. In contrast, the presence of a methoxy group of substrate **1c** resulted in a 70% chemical yield and 4.5:1 dr. It is indicated that substrates **1** carrying electron-withdrawing groups showed the higher reactivity and selectivity than those with electron-donating counterparts. Next, various alkyl-, cycloalkyl-, and aryl-substituted isocyanides (**3b–3f**) were also selected to explore the feasibility of the bicyclization reaction. As we had expected, all the isocyanides were successfully engaged into these transformation, giving access to the corresponding pyrano[3,4-*c*]pyrroles derivatives with yields ranging from 59% to 93% and high diastereoselectivity (up to > 99:1 dr). Even if sterically encumbered 1,1,3,3-tetramethylbutyl (**3b**) and 1-adamantyl (**3c**) isocyanides were found to have no influence on the course of the reaction, with pyrano[3,4-*c*]pyrroles **4h–4p** afforded in 60–93% yields. Besides, the alkyl fragment in isocyanide moiety was alternated with an Ar group such as 4-bromophenyl, the target transformation was realized with the optimal conditions, as demonstrated by the formation of **4w** in an acceptable yield (69%) and 25:1 dr. Obviously, the current three-component bicyclizations can tolerate structurally diverse substrates with steric bulk and a different electronic nature, which provides a direct and practical protocol to form richly decorated pyrano[3,4-*c*]pyrroles. Most functionalities of resultant pyrano[3,4-*c*]pyrrole products offer a facile access to their further flexibly structural modifications. The structures of products **4** were fully characterized by their NMR spectroscopy and HRMS, and one case of **4b** was unambiguously determined by X-ray diffraction analysis (Figure 1).

In order to gain reasonable insight into the reaction mechanism, a hydrogen-deuterium exchange experiment was conducted. Treatment of **1a** with **2a** and **3a** in the presence of D₂O gave the deuterated pyrano[3,4-*c*]pyrrole **4a** in a 83% yield (Scheme 3). In this case, deuterium exchange was observed at 4 and 7a-protons of pyrano[3,4-*c*]pyrrole **4a**, suggesting that both protons would be involved intermolecular proton-transfer equilibrium.

Based on the experiment results and literature reports,^{9,12} a reasonable mechanism for the present bicyclization reaction is described in Scheme 4. The zwitterionic intermediate **A**, generated by the addition of isocyanide **3** into dialkyl acetylenedicarboxylate **2**, reacts with 3-arylacrylic acids **1** to yield 1,6-diene intermediate **B**, followed by Mumm rearrangement,¹³ leading to intermediate **C**. The great majority of **C** undergoes intramolecular oxo-Diels–Alder reaction,^{5c,d} affording the thermodynamically stable *cis* products **4** whereas the little amount of **C** is isomerized intermediate **C'**, which is converted into the kinetic *trans*-products **4'** via intramolecular oxo-Diels–Alder reaction.

In conclusion, we developed a novel, metal-free isocyanide-enabled three-component bicyclizations that offered a facile and practical pathway to access a wide range of densely functionalized pyrano[3,4-*c*]pyrroles in a high diastereoselective and convergent manner. The present transformation involved Huisgen 1,3-dipole formation, Passerini-type reaction,

and Mumm rearrangement as well as oxo-Diels–Alder reaction sequence, resulting in the formation of two new ring and six new chemical bonds including C–N, C–O and C–H bonds. This protocol also features flexible structural modification, excellent atom economy, high synthetic efficiency, and mild reaction conditions. A further investigation on evaluating biological activity of these resultant compounds is currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Notes and references

- (a) Domagala A, Jarosz T, Lapkowski M. *Eur. J. Med. Chem.* 2015; 100:1760.(b) Estévez V, Villacampa M, Menéndez J-C. *Chem. Soc. Rev.* 2010:4402. [PubMed: 20601998] (c) Gupton J-T. *Top. Heterocycl. Chem.* 2006; 2:53.(d) Thompson R-B. *Faseb J.* 2001; 15:1671. [PubMed: 11481212]
- (a) Charvat, T-T.; Chu, H.; Krasinski, A.; Lange, C-W.; Leleti, M-R.; Powers, J-P.; Punna, S.; Sullivan, T-J.; Ungashe, S. *PCT Int. Appl. WO 2011035332 A1.* 2011. (b) Caronna S, Lamartina L, Petruso S, Sprio V, Caruso A, Felice A. *Heterocycles.* 1989; 29:1065.
- (a) Madhushaw R-J, Li C-L, Shen K-H, Hu C-C, Liu R-S. *J. Am. Chem. Soc.* 2001; 123:7427. [PubMed: 11472176] (b) Shen K-H, Lush S-F, Chen T-L, Liu R-S. *J. Org. Chem.* 2001; 66:8106. [PubMed: 11722212]
- (a) Gupta A-K, Ila H. *Junjappa, H. Synthesis.* 1988:284.(b) Hassan M-A, Kady M, Abd Mohay A-A. *Indian J. Chem. Sect. B.* 1982; 21B:372.
- (a) Carlin R-B, Carlson D-P. *J. Am. Chem. Soc.* 1957; 79:3605.(b) Gowrisankar S, Lee K-Y, Kim J-N. *Tetrahedron.* 2006; 62:4052.(c) Murray W-V, Mishra P-K, Turchi I-J, Sawicka D, Maden A, Sun S. *Tetrahedron.* 2003; 59:8955.(d) William V-M, Pranab K-M, Sengen S, Amy M. *Tetrahedron Lett.* 2002; 43:7389.
- (a) Zhu, J.; Wang, Q.; Wang, M-X. *Multicomponent Reactions in Organic Synthesis.* Wiley-VCH; Weinheim: 2015. (b) Müller, TJJ., editor. *Science of Synthesis, Multicomponent Reactions I.* New York: Georg Thieme Verlag KG, Stuttgart; 2014. (c) Nenajdenko, V., editor. *Isocyanide Chemistry.* Wiley-VCH Verlag GmbH & Co. KGaA; 2012.
- For selected reviews, see: Domling A, Wang W, Wang K. *Chem. Rev.* 2012; 112:3083. [PubMed: 22435608] Kaim L, Grimaud L. *Eur. J. Org. Chem.* 2014:7749. Gijs K, Eelco R, Orru R-V. *Beilstein J. Org. Chem.* 2014; 10:544. [PubMed: 24605172] Vlaar T, Maes B-U, Ruijter E, Orru R-V. *Angew. Chem. Int. Ed.* 2013; 52:7084. Rotstein B-H, Zaretsky S, Rai V, Yudin A-K. *Chem. Rev.* 2014; 114:8323. [PubMed: 25032909] Brauch S, Van Berkel S-S, Westermann B. *Chem. Soc. Rev.* 2013; 42:4948. [PubMed: 23426583]
- (a) Tian Y, Tian L, He X, Li C-J, Jia X, Li J. *Org. Lett.* 2015(b) Jia S, Su S, Li C, Jia X, Li J. *Org. Lett.* 2014; 16:5604. [PubMed: 25313935] (c) Su S, Li C, Jia X, Li J. *Chem. Eur. J.* 2014; 20:5905. [PubMed: 24700458]
- (a) Yavari I, Moradi L. *Helv. Chim. Acta.* 2006; 89:1942.(b) Yavari I, Esnaashari M. *Synthesis.* 2005:1049.(c) Yavari I, Djahaniani H. *Tetrahedron Lett.* 2005; 46:7491.(d) Siddiqui IR, Srivastava A, Shamim S, Srivastava A, Shireen, Waseem M-A, Abumhdi A-A, Rahila, Srivastava A, Rai P, Singh R-K. *Asian J. Org. Chem.* 2013; 2:519.(e) Shaabani A, Ghadari R, Sarvary A, Rezayan A-H. *J. Org. Chem.* 2009; 74:4372. [PubMed: 19397302] (f) Zhao L-L, Wang S-Y, Xu X-P, Ji S-J. *Chem. Commun.* 2013; 49:2569.(g) Adib M, Sheikhi E, Kavooosi A, Bijanzadeh HR. *Tetrahedron.*

- 2010; 66:9263.(h) Alizadeh A, Rostamnia S, Zhu L-G. Synthesis. 2008:1788.(i) Alizadeh A, Oskueyan Q, Rostamnia S, Ghanbari-Niaki A, Mohebbi AR. Synthesis. 2008:2929.(j) Alizadeh A, Oskueyan Q, Rostamnia S. Synthesis. 2007:2637.
10. Nair V, Menon R-S, Beneesh P-B, Sreekumar V, Bindu S. Org. Lett. 2004; 6:767. [PubMed: 14986970]
11. (a) Ma G-H, Jiang B, Tu X-J, Ning Y, Tu S-J, Li G. Org. Lett. 2014; 16:4504. [PubMed: 25140818] (b) Ma G-H, Tu X-J, Ning Y, Jiang B, Tu S-J. ACS Comb. Sci. 2014; 16:281. [PubMed: 24588380] (c) Gao Q, Zhou P, Liu F, Hao W-J, Yao C, Jiang B, Tu S-J. Chem. Commun. 2015; 51:9519.(d) Pan Y-Y, Wu Y-N, Chen Z-Z, Hao W-J, Li G, Tu S-J, Jiang B. J. Org. Chem. 2015; 80:5764. [PubMed: 25919002]
12. For selected reviews for Passerini-type reactions, see: Alvim HGO, da Silva Junior EN, Neto BAD. RSC Adv. 2014; 4:54282. Liu Z-Q. Curr. Org. Chem. 2014; 18:719. Kazemizadeh AR, Ramazani A. Curr. Org. Chem. 2012; 16:418. Klein JC, Williams DR. Li JJ. Name Reactions for Homologations. 2009:765–785.
13. (a) Ramozzi R, Morokuma K. J. Org. Chem. 2015; 80:5652. [PubMed: 25974627] (b) Medeiros GA, da Silva WA, Bataglioni GA, Ferreira DAC, de Oliveira HCB, Eberlin MN, Neto BAD. Chem. Commun. 2014; 50:338.(c) La Spisa F, Feo A, Mossetti R, Tron GC. Org. Lett. 2012; 14:6044. [PubMed: 23150900] (d) Cheron N, Ramozzi R, Kaim LE, Grimaud L, Fleurat-Lessard P. J. Org. Chem. 2012; 77:1361. [PubMed: 22225432]

Figure 1.
X-ray Structure of **4b**.

Nair's work

This work

Scheme 1.
Cascade bicyclizations toward pyrano[3,4-*c*]pyrroles

Scheme 2.

Scope of the bicycloaddition reaction. Yields (isomers) of isolated products based on substrates **1** after column chromatography on silica gel are given. The dr value was confirmed by ^1H NMR. **1** (0.5 mmol), **2** (0.6 mmol) and **3** (0.6 mmol), CH_3CN (4.0 mL), at 80°C for 6.0 hours.

Scheme 3.
Hydrogen-deuterium exchange experiment

Scheme 4.
Plausible mechanism

Table 1Optimization of reaction conditions^a

Entry	Solvent	T/°C	Yield ^b /%
1	DMF	80	63
2	1,4-Dioxane	80	75
3	CH ₃ CN	80	89
4	Toluene	80	58
5	DCE	80	35
6	EtOH	80	10
7	HOAc	80	ND
8	CH ₃ CN	60	76
9	CH ₃ CN	100	80

^a Reaction conditions: (*E*)-4-(4-chlorophenyl)-4-oxobut-2-enoic acid (**1a**, 0.5 mmol), dimethyl but-2-ynedioate (**2a**, 0.6 mmol) and *t*-butyl isocyanide (**3a**, 0.6 mmol), solvent (4.0 mL), 6.0 hours.

^b Isolated yields.