ONE-POT SYNTHESIS OF FUNCTIONALIZED PYRROLO[3,4-B]INDOLES VIA A TANDEM BARTON–ZARD AND FRIEDEL–CRAFTS APPROACH

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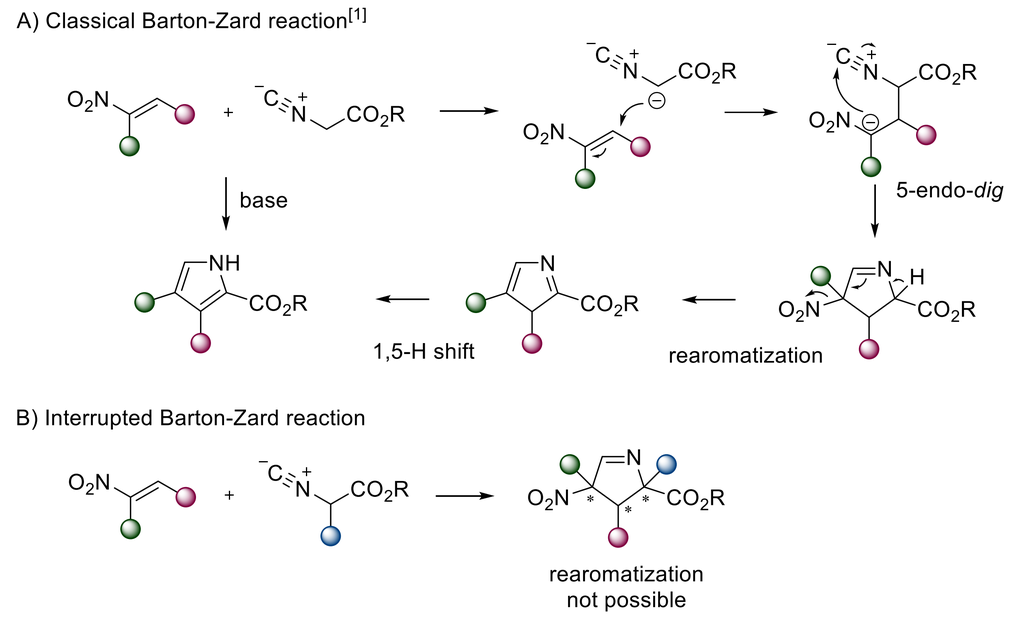
INTRODUCTION

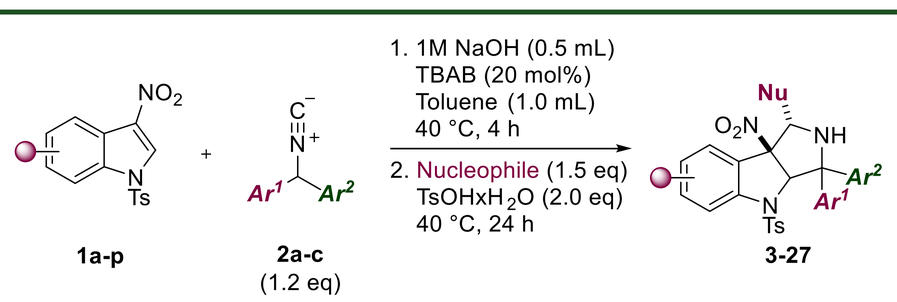
The Barton–Zard reaction provides a straightforward route to aromatic 2-carboxyl-3,4-disubstituted pyrroles via the reaction of electron-deficient alkenes, nitroarenes, or nitroindoles with *α*-isocyanoacetates under basic conditions.[1] However, when *α*-substituted isocyanoacetates are employed, the typical rearomatization step is disrupted, leading instead to the formation of non-aromatic polycyclic structures – a transformation known as the interrupted Barton–Zard reaction.[2] (**Scheme 1**)



Scheme 1. Classical vs. Interupted Barton-Zard reaction

RESULTS AND DISCUSSION

To date, only one example of such 3,3-diaryl-substituted polycyclic scaffolds has been documented, and solely as a postmodification.[3] Herein, we report a novel telescoped sequence combining the interrupted Barton–Zard reaction with a Friedel–Crafts alkylation for the direct synthesis of aryl-substituted hexahydropyrrolo[3,4-*b*]indole scaffolds. Under Brønsted base-mediated phase-transfer conditions, 3-nitroindoles (**1a–p**) react with benzophenone-derived isocyanides (**2a–c**), forming pyrrolo[3,4-*b*]indole intermediates that undergo *in situ* alkylation with aromatic and heteroaromatic nucleophiles under acidic conditions (**Scheme 2**).



Scheme 2. Developed cascade reaction for the synthesis of polycyclic pyrrolo[3,4-*b*] indole cores

3-nitroindoles

3, 75% yield
>20:1 d.r.
0.5 g scale: 68% yield

4, 48% yield
>20:1 d.r.

5, 61% yield
>20:1 d.r.

6, 51% yield
>20:1 d.r.

7, 34% yield
>20:1 d.r.

8, 46% yield
>20:1 d.r.

9, 56% yield
6.5:1 d.r.

10, 17% yield
10:1 d.r.

11, 22% yield
7:1 d.r.

12, 49% yield
>20:1 d.r.

nucleophiles

13, 30% yield
>20:1 d.r.

14, 56% yield
>20:1 d.r.

15, 34% yield
11:1 d.r.

16, 53% yield
11:1 d.r.

17, 73% yield
>20:1 d.r.

18, 40% yield
>20:1 d.r.

19, 23% yield
>20:1 d.r.

20, 55% yield
>20:1 d.r.

21, 44% yield
10:1 d.r.

22, 32% yield
1:1 d.r.

23, 18% yield
>20:1 d.r.

24, 70% yield (R=H)
25, 68% yield (R=Cl)

isocyanides

26, 59% yield
1:1 d.r.

27, 18% yield
1:1 d.r.

CONCLUSION

The reaction of 3-nitroindoles with *α*,*α*-diaryl-substituted methyleneisocyanides, followed by *in situ* addition of an aryl nucleophile, generally afforded the desired products as single diastereomers in moderate to good yields.[4] While the process tolerates most electron-deficient indoles and nucleophiles, it is highly sensitive to the structure of the isocyanide derivatives, with the dearomatization step representing the limiting stage of the cascade. Preliminary attempts under asymmetric conditions yielded racemic products in low yields; further optimization in this direction is currently underway in our group.

Our research group

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References

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[3] R. Dong, T. J. Han, L. Huang, G. J. Mei, Org. Chem. Front. 11 (2024) 3624–3629.
[4] J. Rešetar, K. Remar, A. Mikleušević, J. Suć Sajko, I. Bašić and M. Gredičak, Asian. J. Org. Chem. (2025), e00261.