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Acetic anhydride to the rescue: Facile access to privileged 1,2,3,4-tetrahydropyrazino[1,2-*a*]indole core via the Castagnoli-Cushman reaction

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ABSTRACT

Indole-fused cyclic anhydrides earlier deemed unreactive in the Castagnoli-Cushman reaction with imines have been rendered valid participant in this process. The new reaction format involves the use of respective indole-based dicarboxylic acids and *in situ* cyclodehydration of the latter by acetic anhydride. This finding validates a fundamentally new approach to synthesizing compounds based on the privileged 1,2,3,4-tetrahydropyrazino[1,2-*a*]indole core characterized by hitherto undescribed substitution pattern.

If a particular heterocyclic motif is frequently employed as a core scaffold in synthetic bioactive compounds, it is regarded as privileged [1] from drug design prospective. Hence, various synthetic methods to access such a heterocyclic system flexibly and conveniently from readily available precursors become particularly valuable. Recently, our attention was drawn to one such ring system, namely, 1,2,3,4-tetrahydropyrazino[1,2-*a*]indole which is prominently featured in synthetic compounds displaying diverse biological activities. These are eloquently exemplified by the small molecules endowed with such activities as analgesic (σ1 receptor modulator **1**) [2], antiviral ('indole-flutimide' **2**) [3], antiproliferative (**3**) [4] or acting as neurogenesis modulators (**4**) [5], phosphodiesterase inhibitors (**5**) [6], indoleamine-2,3-dioxygenase 1 inhibitors (longamide B analog **6**) [7] and non-covalent proteasome inhibitors ('indolo-phakellin' **7**) [8] (Fig. 1).

A brief survey of strategies typically employed to access the tricyclic core in question revealed that those normally rely on a stepwise grafting of the piperazine cycle onto the existing indole core while more convergent methods, particularly those involving multicomponent chemistry (except for an example of post-condensational modification of indole-containing Ugi reaction products [9]), are lacking in the literature. Recently, we established a one-step pathway to polysubstituted azole-fused piperazines via the Castagnoli-Cushman reaction [10–11] of a new type of cyclic anhydrides with imines [12]. This reaction successfully applied to pyrazole-containing cyclic anhydrides **8** (to give, after esterification, bicycles **9**) and should, in principle, be applicable to their indole counterpart **10a** which would offer a remarkably streamlined entry into 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles **11**. Unfortunately, involving anhydride **10a** in the Castagnoli-Cushman reaction failed as the latter delivered only an undiscernible mixture of products (Scheme 1). This was an unfortunate outcome as compounds **11** represent a rare substitution pattern around the privileged 1,2,3,4-tetrahydropyrazino[1,2-*a*]indole core, as evidenced by the SciFinder substructure search results summarized in Fig. 2.

Concomitantly with this work, we discovered that the recently described [13] variant of the Castagnoli-Cushman reaction (which involves the use of dicarboxylic acids as starting materials and *in situ* generation of the respective cyclic anhydride) can be the only workable format for the reaction when the cyclic anhydride employed as a starting material fails to react in the desired fashion [14]. Curious to see if the same approach would make the Castagnoli-Cushman reaction toward **11** more productive, we attempted to apply the *in situ* cyclodehydration protocol (involving the use of acetic anhydride as the dehydrating agent) to dicarboxylic acids **12a–c** synthesized as shown in Scheme 2. Herein, we describe our findings in this regard.

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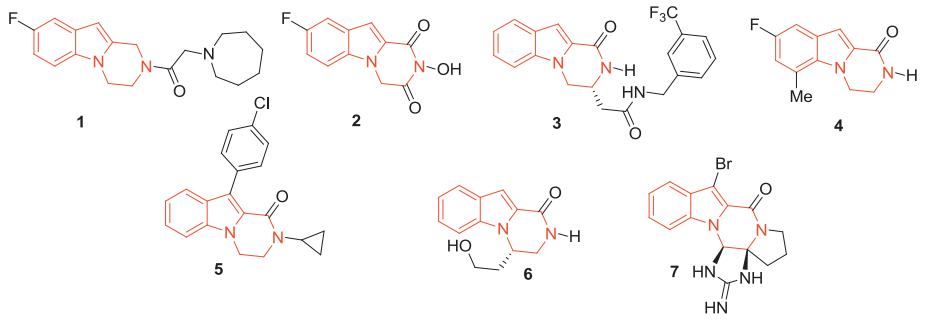
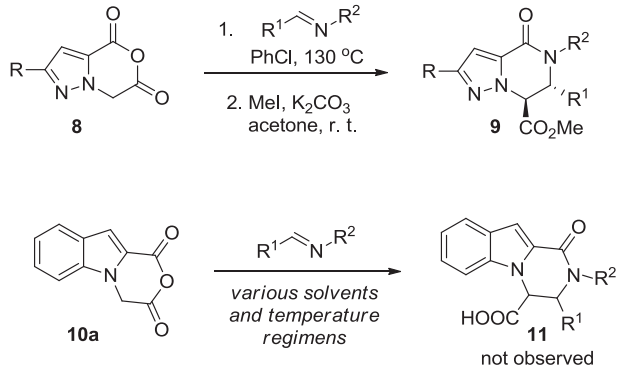


Fig. 1. Examples of bioactive compounds **1**–**7** containing the 1,2,3,4-tetrahydropyrazino[1,2-*a*]indole scaffold (highlighted).



Scheme 1. Recently described successful (**8** → **9**) and failed (**10a** → **11**) Castagnoli-Cushman reaction of azole-based cyclic anhydrides [12].

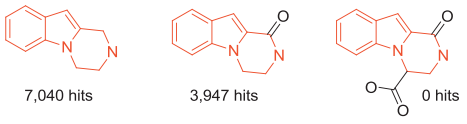
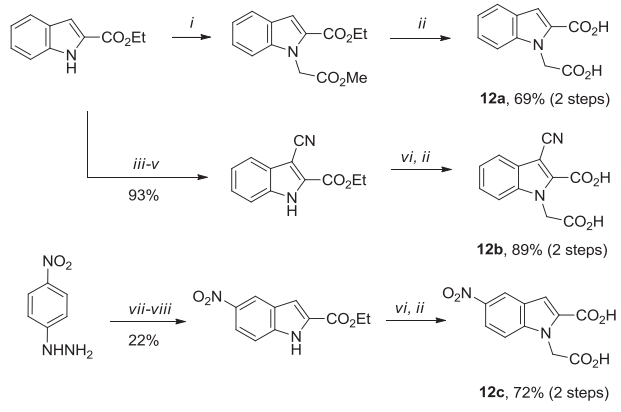


Fig. 2. Specific substitutions around the 1,2,3,4-tetrahydropyrazino[1,2-*a*]indole scaffold. Analyzed by SciFinder substructure search (hits with literature references only).



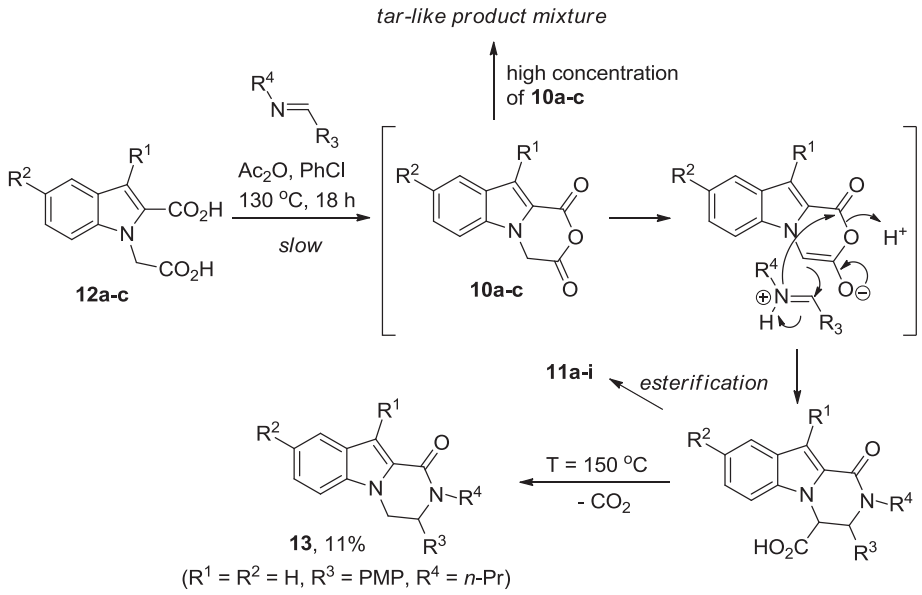
Scheme 2. Synthesis of dicarboxylic acids **12a–c** employed in this study. *Reagents and conditions:* i. $BrCH_2CO_2Me$, K_2CO_3, MeCN, reflux, 18 h; ii. NaOH, aq·THF, r. t., 18 h; iii. $POCl_3$, DMF, 0 °C to 60 °C; iv. NH_2OH·HCl, pyridine, EtOH, reflux, 15 h; v. MsCl, pyridine, 1,4-dioxane, reflux, 5 h; vi. $BrCH_2CO_2Me$, NaH, DMF,80 °C, 3 h; vii. CH_3COCO_2Et, AcOH, MeOH, r. t., 3 h; viii. polyphosphoric acid, *o*-xylene, 110 °C, 18 h.

The initial experiments involved the use of the earlier developed protocol, i. e. heating a solution of an imine and dicarboxylic acid **12a** in chlorobenzene at 150 °C in presence of an equimolar amount of acetic anhydride. To our delight, in this conditions, the desired product **11a** was detected in the reaction mixture by ^{1}H NMR analysis. However, a significant amount of decarboxylated product (such as **13**, structure shown in Scheme 3) was also detected. Lowering the reaction temperature to 130 °C significantly suppressed the formation of the decarboxylation product. Thus, these conditions were extended to the preparation of 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles **11a–i** (Table 1).

With the exception of compounds **11c** and **11d**, the reaction gave predominantly *trans*-configured products in low to moderate yields. The scope of the reaction appears to be limited to imines derived from aromatic aldehydes (R^3 = Ar) while the amine portion of the imine can be either aromatic or aliphatic. The high reaction temperature required for the reaction to proceed is indicative of the diminished reactivity of the intermediate cyclic anhydrides **10** (presumably formed in a low concentration via cyclodehydration by Ac_2O). This is in line with our previous observation of relatively low reactivity of pyrazole-including anhydrides **8** (*vide supra*). Irrespective of the reactivity of **10a–c**, the formation of tricyclic products **11** appears to be consistent with the reaction proceeding along the pathway of i. cyclodehydration of dicarboxylic acid **12**, ii. Mannich-type addition of the enolized anhydride **10** to protonated imine, iii. intramolecular aminolysis of the anhydride to give the observed product (isolated herein after esterification). The pivotal role, for the success of the reaction, of *in situ* cyclodehydration of **12a–c** (as opposed to employing anhydrides **10a–c** as reagents) is probably due to the low concentration of **10a–c** being maintained in this case during the course of the reaction. This may lead to the preferred interaction of **10a–c** with the imine component rather than the formation of the complex product mixture as discussed above (Scheme 3). Unfortunately, attempting to maintain concentration of **10a–c** low intentionally by a slow addition protocol did not produce compounds **11** either. So, it does appear that using acetic anhydride remains the only workable reaction format.

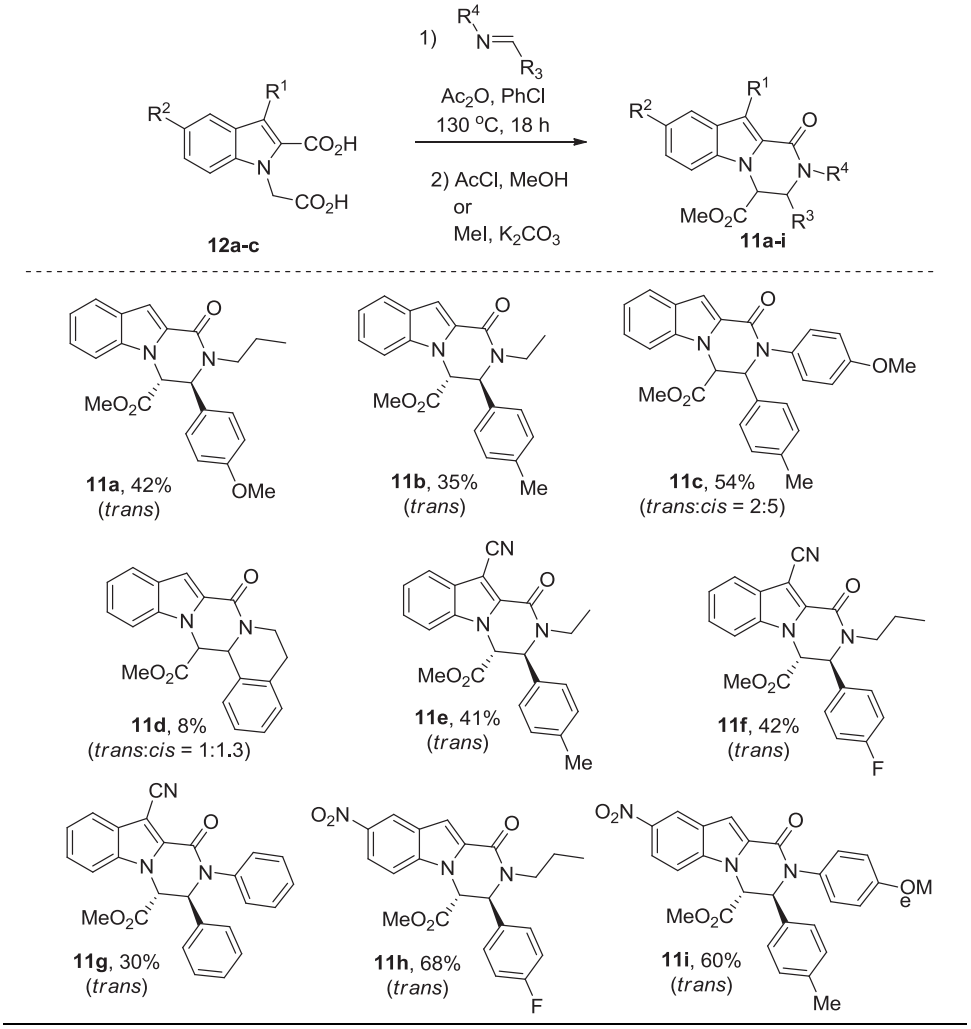
Interestingly, introduction of electron-withdrawing cyano group in position 3 of the indole ring (**12b**) did not significantly influence the outcome of the reaction while nitro group in position 5 of indole ring (**12c**) led to the noticeably higher yield of the reaction (*cf.* **11h–i**). The reasons for the observed difference remain to be elucidated.

In addition to the routine characterization data (^{1}H and ^{13}C NMR as well as high-resolution mass-spectrometry) which allow establishing the identity of the target compounds, we confirmed the connectivity and relative stereochemistry of selected Castagnoli-Cushman adducts containing the privileged 1,2,3,4-tetrahydropyrazino[1,2-*a*]indole scaffold with hitherto undescribed substitution pattern by single-crystal X-ray crystallography



Scheme 3. The desired course of the Castagnoli-Cushman reaction of dicarboxylic acids **12a–c,** its plausible mechanism and observable side-reactions.

Table 1
Products of the Castagnoli-Cushman reaction of dicarboxylic acids **12a–c** with imines.



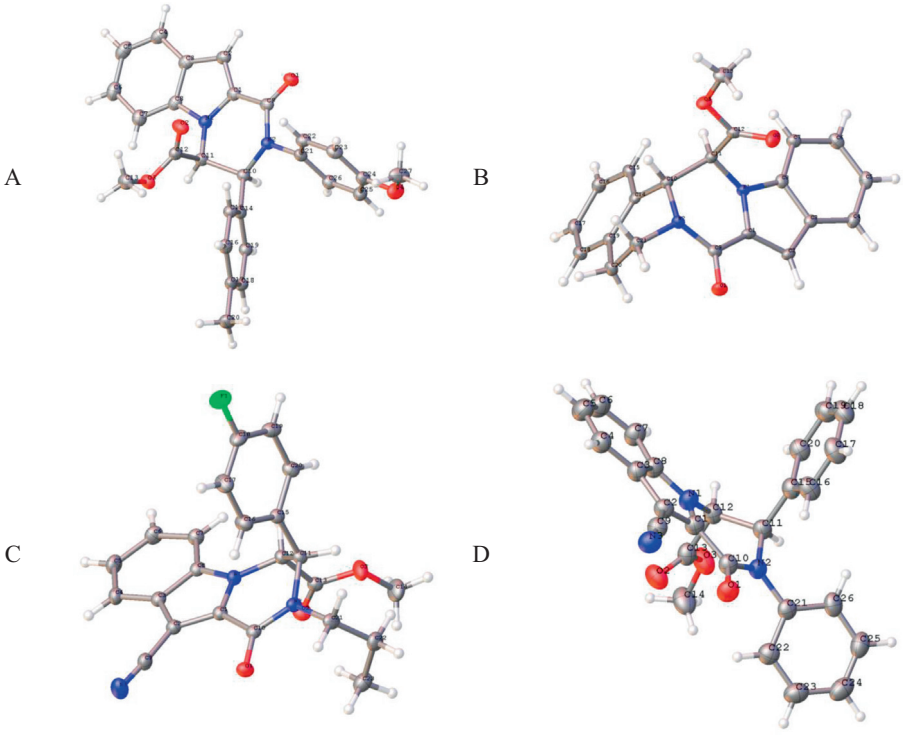


Fig. 3. X-ray crystal structures of selected compounds prepared in this work: (A) **11c** (*cis*) – CCDC 1856908; (B) **11d** (*trans*) – CCDC 1856911; (C) **11f** (*trans*) – CCDC 1857123; (D) **11g** (*trans*) – CCDC 1857122.

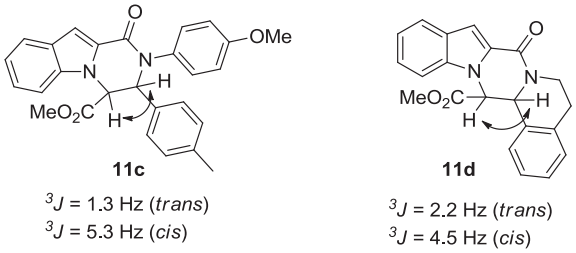


Fig. 4. Vicinal coupling constants as a criterion for relative stereochemistry assignment.

(Fig. 3). Because we managed to get the crystals of either *trans*- or *cis*-configured tricyclic products in those cases when both isomers were formed (**11c** and **11d**), it allowed establishing the straightforward ^{1}H NMR criteria for assigning the relative stereochemistry. Indeed, in line with previous observations [12], the vicinal coupling constant (^{3}J) between the methine protons of the piperidone ring is noticeable smaller (by 2–4 Hz) for the *trans*-isomer compared to that in the *cis*-isomer (Fig. 4).

In summary, we have described a remarkable case of restoring the desired reactivity of novel heterocycle-including cyclic anhydrides in the Castagnoli-Cushman reaction by applying the recently developed format of the reaction involving *in situ* cyclodehydration of the respective precursor discarboxylic acids. The latter protocol allowed preparing compounds based on a privileged 1,2,3,4-tetrahydropyrazino[1,2-*a*]indole scaffold in one step (followed by esterification) from simple precursors in a fundamentally new fashion.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.08.049.

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