

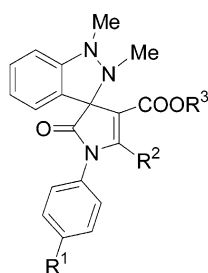
Translation of Pseudo-Cross-Conjugation into Chemistry: Cycloadditions of Mesomeric Betaines to the New Ring System Spiro[indazole-3,3'-pyrrole]

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R¹ = H, Cl, CF₃
R² = Me, COOMe, COOEt
R³ = Me, Et

Indazolium-3-amidates (X-ray analysis), readily available on trapping the N-heterocyclic carbene indazol-3-ylidene with isocyanates, underwent [3 + 2]-cycloadditions with activated triple bonds to spiro[indazole-3,3'-pyrroles]. A combination of NMR techniques such as heteronuclear single quantum coherence (HSQC), heteronuclear multiple bond correlation (HMBC), nuclear Overhauser enhancement spectroscopy (NOESY), and ¹H/¹⁵N correlations were applied to elucidate the structures of the cycloadducts.

Heterocyclic mesomeric betaines (HMB) are defined as neutral conjugated molecules that can exclusively be represented by dipolar canonical formulas in which both the negative and the positive charges are delocalized within a common π -electron system.¹ For decades, nomenclature (mesoion, ylide, sydnone, münchnone, inner salt) as well as adequate representation of these molecules was controversial. After first systematizations,²

a comprehensive classification of heterocyclic mesomeric betaines was proposed in 1985 by Ollis et al.¹ According to this classification, all heterocyclic mesomeric betaines can be divided into four classes on the basis of distinct types of conjugation present in these heteroaromatics. These are the classes of (i) conjugated mesomeric betaines (CMB), (ii) cross-conjugated mesomeric betaines (CCMB), (iii) pseudo-cross-conjugated heterocyclic mesomeric betaines (PCCMB), and (iv) 1,2-ylidic systems (N-ylides, N-oxides etc).¹ This classification undoubtedly lead to a profound understanding of the chemical, biological, and physical properties of individual members of this class of compounds,³ although very little information on PCCMB has been available to date. Conjugated mesomeric betaines (CMB) are by far the best investigated. Their characteristic capability to undergo 1,3-cycloadditions was applied in total syntheses of numerous alkaloids, for example, of ipalbidine,⁴ δ -coniceine,⁵ septicine,⁶ vallesamidine,⁷ lycopodine,⁸ onychine⁹ (via isomünchnones), allobohimbane,¹⁰ and lysergic acid⁷ (via isothiomünchnones). Cross-conjugated heterocyclic mesomeric betaines (CCMB) predominantly undergo 1,4-cycloadditions,¹¹ and this property was applied recently for the synthesis of the isoschizozygane alkaloid core.¹² The rich chemistry of CMB and CCMB contrasts with a remarkable lack of knowledge with respect to pseudo-cross-conjugated systems (PCCMB). In 1985, only three examples of PCCMB were known,¹ and except for two contributions by Potts¹³ no systematic investigations have been performed. Meanwhile it was recognized that PCCMB are relatively widespread in nature (homarine,¹⁵ nigellicine,¹⁶ and others¹⁴). Moreover it was found that pseudo-cross-conjugation is the condition for the formation of N-heterocyclic carbenes (NHC) by extrusion reactions^{17,18} and that in a reverse process

- (3) Schmidt, A. *Curr. Org. Chem.* **2004**, *8*, 653.
- (4) Sheehan, S. M.; Padwa, A. *J. Org. Chem.* **1997**, *62*, 438.
- (5) Straub, C. S.; Padwa, A. *Org. Lett.* **1999**, *1*, 83.
- (6) Padwa, A.; Sheehan, S. M.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 8648.
- (7) Marino, J. P.; Osterhout, M. H.; Padwa, A. *J. Org. Chem.* **1995**, *60*, 2704.
- (8) Padwa, A.; Brodney, M. A.; Marino, J. P., Jr.; Sheehan, S. M. *J. Org. Chem.* **1997**, *62*, 78.
- (9) Padwa, A.; Heidelbaugh, T. M.; Kueth, J. T. *J. Org. Chem.* **2000**, *65*, 2368.
- (10) Heidelbaugh, T. M.; Liu, B.; Padwa, A. *Tetrahedron Lett.* **1998**, *39*, 4757.
- (11) (a) Potts, K. T.; Rochanapruk, T.; Padwa, A.; Coats, S. J.; Hadjiarapoglou, L. *J. Org. Chem.* **1995**, *60*, 3795. (b) Padwa, A.; Coats, S. J.; Semones, M. A. *Tetrahedron* **1995**, *51*, 6651. (c) Padwa, A.; Coats, S. J.; Semones, M. A. *Tetrahedron Lett.* **1993**, *34*, 5405. (d) Kappe, T. *Heterocycles* **1984**, *21*, 358.
- (12) Padwa, A.; Flick, A. C.; Lee, H. I. *Org. Lett.* **2005**, *7*, 2925.
- (13) (a) Potts, K. T.; Murphy, P. M.; Kuehning, W. R. *J. Org. Chem.* **1988**, *53*, 2889. (b) Potts, K. T.; Murphy, P. M.; DeLuca, M. R.; Kuehning, W. R. *J. Org. Chem.* **1988**, *53*, 2898.
- (14) Schmidt, A. *Adv. Heterocycl. Chem.* **2003**, *85*, 67.
- (15) (a) Polychronopoulos, P.; Magiatis, P.; Skaltsounis, A.-L.; Tillequin, F.; Vardala-Theodorou, E.; Tzarbopoulos, A. *Nat. Prod. Lett.* **2001**, *15*, 411. (b) Nishitani, H.; Kikushi, S.; Okumura, K.; Taguchi, H. *Arch. Biochim. Biophys.* **1995**, *322*, 327. (c) Davis, A. R.; Targett, N. M.; McConnell, O. J.; Young, C. M. *Bioorg. Marine Chem.* **1989**, *3*, 85. (d) Berking, S. *Development* **1987**, *99*, 211.
- (16) Atta-ur-Rahman, Malik, S.; Cun-heng, H.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 2759.
- (17) Schmidt, A.; Beutler, A.; Habeck, T.; Mordhorst, T.; Snovydyvych, B. *Synthesis* **2006**, 1882.
- (18) (a) Schmidt, A.; Habeck, T.; Merkel, L.; Mäkinen, M.; Vainiotalo, P. *Rapid Commun. Mass Spectrom.* **2005**, *19*, 2211. (b) Schmidt, A.; Merkel, L.; Eisfeld, W. *Eur. J. Org. Chem.* **2005**, 2124.

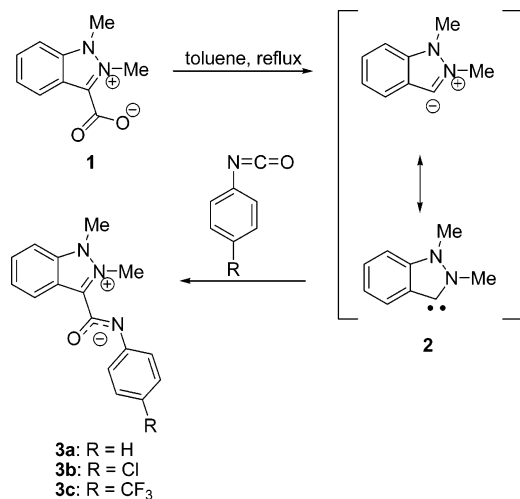
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[†] Institute of Organic Chemistry.

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(1) Ollis, W. D.; Stanforth, S. P.; Ramsden, C. A. *Tetrahedron* **1985**, *41*, 2239.

(2) (a) Katritzky, A. R. *Chem. Ind.* **1955**, 521. (b) Ochiai, E. In *Aromatic Amine Oxides*; Elsevier: Amsterdam, 1967. (c) Katritzky, A. R.; Lagowski, J. M. In *The Chemistry of Heterocyclic N-Oxides*; Academic Press, New York, 1971. (d) Zugravesku, I.; Petrovanu, M. In *N-Ylide Chemistry*; McGraw-Hill: New York, 1976. (e) Ramsden, C. A. *J. Chem. Soc., Chem. Commun.* **1977**, 109.

SCHEME 1. Synthesis of Indazolium-3-amidates via an N-Heterocyclic Carbene


NHC can form PCCMB by trapping experiments.¹⁹ We describe here the first cycloaddition reactions of a PCCMB. For the first time these cycloadditions translate a theoretically predicted feature¹ of pseudo-cross-conjugation into chemistry. In addition, we present a single-crystal X-ray analysis of an indazoliumamidate.

1,3-Dimethylindazolium-3-carboxylate **1**, a model compound for the alkaloid nigellicin,¹⁶ was decarboxylated in toluene to generate the N-heterocyclic carbene **2**, which was trapped by interception with isocyanates.¹⁷ The resulting 1,3-dimethylindazolium-3-amidates **3a–c** were formed in good to excellent yields as yellow to orange compounds (Scheme 1).

The betaines **1** and **3a–c** are pseudo-cross-conjugated. Characteristic features of this type of conjugation are as follows. First, within the limits of the valence bond theory, Ollis et al.¹ postulated that the charges are effectively, but not exclusively, delocalized in separated parts of the common π -electron system as canonical formulas can be drawn that are electron sextet structures without internal electron octet stabilization (**I** in Figure 1). These canonical formulas delocalize the positive charge into the anionic partial structure and, undoubtedly, this method is not more than a means to recognize pseudo-cross-conjugation from the canonical formulas. Second, Potts and co-workers¹³ realized that the anionic partial structure of PCCMB is always isoconjugate with an odd, alternant hydrocarbon anion, as exemplified by **II** (Figure 1). In the sense of Dewar, cation and anion are joined by a union bond (u) through an unstarred position of the anionic partial structure. This atom, the carboxylate carbon atom of **1** and the central carbon atom of the NCO moiety of **3a–c**, is a nodal position of the highest molecular orbital (HOMO) of the molecule (**III**) and thus causes a charge-separated ground state of the molecule. A single-crystal X-ray analysis of the 4-trifluoromethylphenylamidate **3c** showed

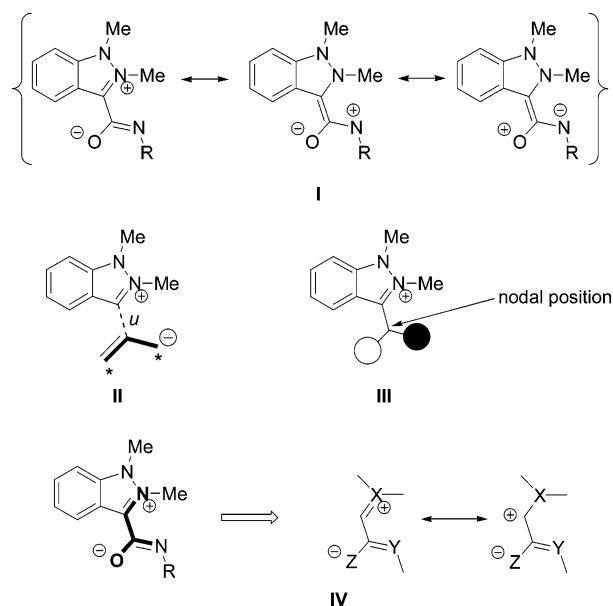


FIGURE 1. Characteristic features of “pseudo-cross-conjugation”.

an essentially planar amidate moiety ($\tau = 175.9^\circ$).²⁰ The phenyl ring is twisted by 31.9° , and the indazole ring is twisted by -37.8° from the plane of the amidate group. These findings are quite similar to benzanilide, the dihedral angles of which are -179.8° , -150.7° , and 32.5° , respectively. The bond length of the C1–C8 bond [crystallographic numbering, Figure 6 in the Supporting Information] was determined to be 151.1 pm and is in agreement to the definition of a union bond between these two π -electron systems. The CO bond length in the amidate group is 126.7 pm and is much larger than in amides (122.7 pm). Correspondingly, the CN bond of the amidate group is shortened (129.6 pm) in relation to benzanilide (136.2 pm).

Third, the distinct classes of heterocyclic mesomeric betaines possess characteristic dipole increments, which can be dissected from the canonical formulas.¹ Among them, the masked dipole **IV**, which is present in **1** and **3a–c**, is characteristic for pseudo-cross-conjugated mesomeric betaines.¹ To date, to the best of our knowledge this characteristic dipole type has never been verified by cycloaddition reactions. Reaction of the amidate **3a** with diethyl acetylenedicarboxylate in acetonitrile at room temperature indeed gave the spiro[indazole-3,3'-pyrrole] **4a** in 81% yield as yellow compound. Similarly, the 4-chlorophenylamidate **3b** and the 4-trifluoromethylphenylamidate **3c** underwent cycloadditions to the spiro compounds **4b** and **4c** in good yields, respectively. Reaction with dimethyl acetylenedicarboxylate gave **4d** and **4e**. Ethyl-2-butinecarboxylate resulted in the formation of **4f** in 66% yield, but the reaction afforded higher temperatures (Scheme 2).

Structure elucidation was accomplished as follows: We first performed H–H correlation spectroscopy (COSY), heteronuclear single quantum coherence spectroscopy (HSQC), and nuclear Overhauser enhancement spectroscopy (NOESY), which allowed unambiguous peak assignments. The ¹H and ¹³C NMR peak assignments of **4f** are presented in Figure 2 as an example.

(19) (a) Duong, H. A.; Tekavec, T. N.; Arif, A. M.; Louie, J. *Chem. Commun. (Cambridge)* **2004**, 112. (b) Holbrey, J. D.; Reichert, W. M.; Tkatchenko, I.; Bouajila, E.; Walter, O.; Tommasi, I.; Rogers, R. D. *Chem. Commun. (Cambridge)* **2003**, 28. (c) Ishiguro, K.; Hirabayashi, K.; Nojima, T.; Sawaki, Y. *Chem. Lett.* **2002**, 796. (d) Kuhn, N.; Steimann, M.; Weyers, G.; Henkel, G. *Z. Naturforsch.* **1999**, *54b*, 434. (e) Kuhn, N.; Fahl, J.; Fawzi, R.; Maichle-Mossmar, C.; Steimann, M. *Z. Naturforsch.* **1998**, *53b*, 720. (f) Katritzky, A. R.; Faïd-Allah, H. M. *Synthesis* **1983**, 149. (g) Schönherr, H.-J.; Wanzlick, H.-W. *Chem. Ber.* **1970**, *103*, 1037. (h) Schössler, W.; Regitz, M. *Chem. Ber.* **1974**, *107*, 1931.

(20) Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-627932. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax (+44)1223–336-033; e-mail deposit@ccdc.cam.ac.uk].

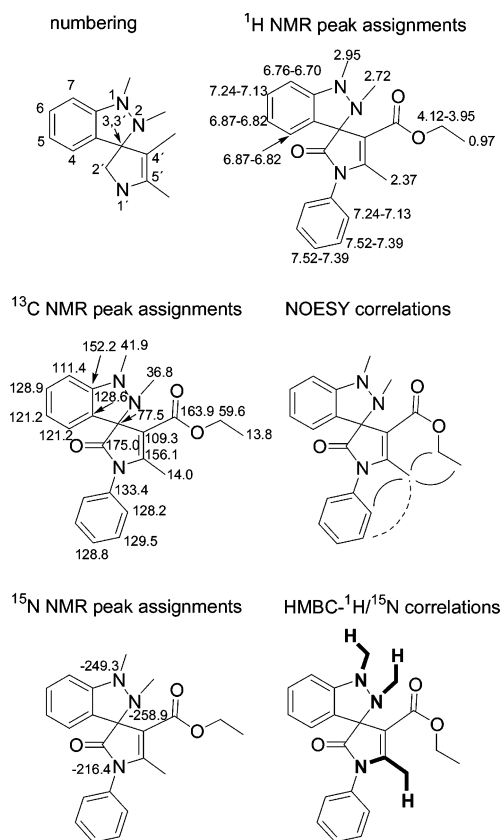
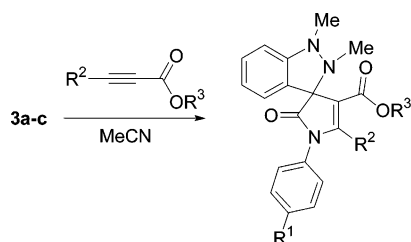


FIGURE 2. Structure elucidation by a combination of HSQC, HMBC, HH-COSY, and NOESY NMR techniques.

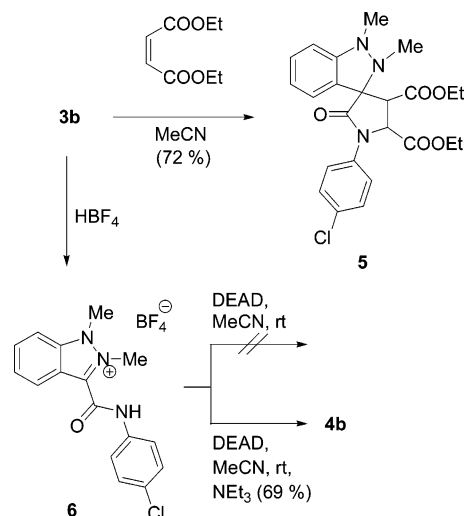
SCHEME 2. 1,3-Dipolar Cycloadditions of Indazolium-3-amidates



- 4a:** R¹ = H, R² = COOEt, R³ = Et (81 %)
4b: R¹ = Cl, R² = COOEt, R³ = Et (73 %)
4c: R¹ = CF₃, R² = COOEt, R³ = Et (66 %)
4d: R¹ = Cl, R² = COOMe, R³ = Me (72 %)
4e: R¹ = CF₃, R² = COOMe, R³ = Me (54 %)
4f: R¹ = H, R² = Me, R³ = Et (66 %)

The resonance frequency at $\delta = 77.5$ ppm in the ¹³C NMR spectra was assigned to the spiro carbon atom. This was supported by a heteronuclear multiple bond coherence (HMBC) measurement, as interactions between 4-*H* and the signal at $\delta = 77.5$ ppm were detected. The latter-mentioned resonance frequency also correlates with the singlet of the methyl group at N2. In addition, the ¹H/¹⁵N correlation of **4f** enabled a peak assignment of the ¹⁵N NMR signals, which are as shown in Figure 2. All resonance frequencies are in the characteristic region of N_{sp³}-hybridized nitrogen atoms, and this finding proves the ring closure reaction via the *N*-atom of the amidate moieties of **3a–c**, and, consequently, the formation of a pyrrole ring. Thus, the formation of indazole-3,3'-furans by attack of the

SCHEME 3. Cycloaddition with Diethyl Maleate



oxygen atom of the amidates to the triple bond was excluded from consideration, although furans with exocyclic imine groups are known.²¹ The regiochemistry of **4f** was finally elucidated by a NOESY spectrum. As the methyl group attached to C-5' of the pyrrole ring correlates with the ortho-hydrogen atoms of the phenyl substituent at N-1', we can unambiguously conclude that the regioisomer **4f** was formed. To the best of our knowledge, spiro compounds **4a–f** are the first representatives of a new ring system.

We next treated 4-chloroamidate **3b** with diethyl maleate and obtained the spiro[indazole-3,3'-pyrrolidine] derivative **5** as a mixture of diastereoisomers that could not be separated by chromatographic means. The compound displays all characteristic properties as outlined in Figure 2. In agreement with the formation of diastereomers, eight signals of the CH groups of the pyrrolidine ring between 42.7 and 56.3 ppm were detected in the ¹³C distortionless enhancement by polarization transfer (DEPT)-135 and HMBC NMR spectra. Under analogous conditions, no reaction was observed between **3b** and *N*-phenyltriazoline-2,4-dione or diethyl azodicarboxylate. Furan-2,5-dione gave a mixture of yet unidentified products. In a control experiment, we protonated the amidate **3b** to the corresponding indazoliumamide tetrafluoroborate **6** and tried the cycloaddition with diethyl acylenedicarboxylate. No reaction was observable after 1 h at room temperature. Addition of 1 equiv of triethylamine, however, resulted in a spontaneous formation of the cycloadduct **4b** in 69% yield (Scheme 3). The cycloaddition thus unambiguously proceeds via the pseudo-cross-conjugated heterocyclic mesomeric betaine.

In summary, we can conclude that the class of pseudo-cross-conjugated heterocyclic mesomeric betaines is indeed a class of its own and displays its characteristic chemistry in comparison to the other classes of mesomeric betaines.

Experimental Section

Typical Procedure for Cycloadditions: Preparation of Diethyl 1,2-Dimethyl-2'-oxo-1'-phenyl-1,2-dihydrospiro[indazole-3,3'-1*H*-pyrrole]-4',5'-dicarboxylate **4a.** 1,2-Dimethyl-1*H*-indazolium-3-(*N*-phenyl)amidate **3a** (50 mg, 0.19 mmol) was suspended

(21) (a) Oshita, M.; Yamashita, K.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 761. (b) Chatani, M.; Oshita, M.; Tobisu, M.; Ishii, Y.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 7812.

in 3 mL of acetonitrile. Then diethyl acetylenedicarboxylate (0.03 mL, 0.19 mmol) was added, whereupon the color of the suspension changed from yellow to dark red and violet. After the mixture was stirred for 12 h at room temperature, the solvent was evaporated in vacuo, and the residue was chromatographed (silica gel; petrol : EtOAc = 5:1). The cycloadduct was isolated as a yellow solid, yield 67 mg (0.15 mmol, 81%), mp 132–133 °C. ^1H NMR (CDCl_3) δ 7.49–7.36 (m, 3H), 7.30–7.25 (m, 3H), 6.99–6.97 (m, 1H), 6.95–6.82 (m, 1H), 6.79–6.72 (m, 1H), 4.21 (q, 2H, $^3J = 7.1$ Hz, CH_2), 4.14–4.03 (m, 2H, CH_2), 2.97 (br s, 3H, CH_3), 2.78 (br s, 3H, CH_3), 1.11 (t, 3H, $^3J = 7.1$ Hz, CH_2), 1.05 (t, 3H, $^3J = 7.1$ Hz, CH_3); ^{13}C NMR (CDCl_3) δ 174.3, 161.3, 160.7, 152.3, 147.4, 133.5, 129.6, 129.4, 128.9, 128.4, 127.0, 126.6, 121.6, 111.7, 110.7, 77.3, 62.7, 60.5, 41.9, 37.1, 13.8, 13.7; IR (KBr) 3455, 2975, 1749, 1696, 1159, 759 cm^{-1} ; EIMS (70 eV) 435 (M^+ , 33%), 405 ($\text{M} -$

C_2H_5 , 31%), 333 ($\text{M} - \text{CO}_2\text{Et} - 2\text{CH}_3$, 100%). HR-ESI-MS calcd for $\text{C}_{24}\text{H}_{26}\text{N}_3\text{O}_5$: 436.1872. Found: 436.1875. Anal. Calcd for $\text{C}_{24}\text{H}_{25}\text{N}_3\text{O}_5$: C, 66.19, H 5.79, N 9.65. Found: C, 66.06, H, 4.80, N, 9.38.

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Supporting Information Available: Experimental details, spectroscopic data, NMR spectra, X-ray data, molecular drawings, and the CIF file of **3c**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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