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Anionic *N*-Fries Rearrangement of *N*-Carbamoyl Diarylamines to Anthranilamides. Methodology and Application to Acridone and Pyranoacridone Alkaloids

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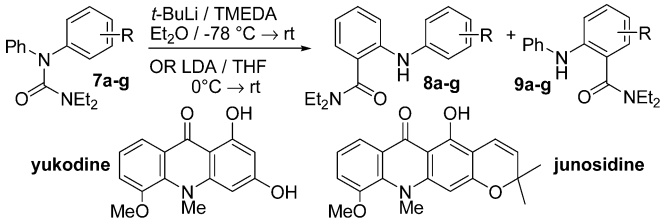
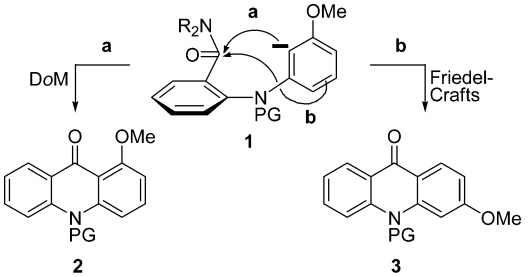
ABSTRACT



A general alkyllithium/LDA-mediated rearrangement of *N*-carbamoyl diarylamines 7a–g into the anthranilamides 8a–g and 9a–g (Table 1) is presented and applied to a regioselective efficient construction of acridone (17) and pyranoacridone (18) alkaloids (Scheme 4).

Recent efforts in our laboratories aim to develop new carbanionic aromatic chemistry which, by moderating the harsh conditions and circumventing rules of classical electrophilic substitution, offer complementary but also new, regioselective, and mild methods for the construction of polysubstituted aromatics, heteroaromatics, and their condensed counterparts.[1] To illustrate by a reaction that conceptually applies also for other heterocycles,[1g−j] the LDA-induced conversion **1** → **2** (Scheme 1), apparently driven by combined directed *ortho* metalation (D*o*M)[2] and Complex Induced Proximity Effect (CIPE),[3] is an anionic equivalent of the Lewis acid-catalyzed Friedel−Crafts reaction; the latter, if applied to **1**, provides the isomeric product **3** due to the strong EDG nature of the OMe group.[4,5] During the course of one of these studies,[1g] we uncovered an alkyllithium-mediated transformation of *N*-protected diarylamines **5** (Z = NAr, DMG = $CO_2{}^t$Bu) into *N*-aryl anthranilates **6a** (Scheme 2), constituting an *N*-analogue of the anionic *ortho*-Fries rearrangement of aryl *O*-carbamates, **5** (Z = O, DMG = $CONR_2$), into the salicylamides.[1a,6−8] We subsequently found that the corresponding rearrangement of the *N*-$CONEt_2$ derivative, **5** (Z = NAr, DMG = $CONEt_2$), into the anthranilamides **6b** proceeded with greater efficiency and

Scheme 1. Regiochemical Complementarity of Carbanion-Mediated and Lewis Acid-Catalyzed Cyclization Reactions



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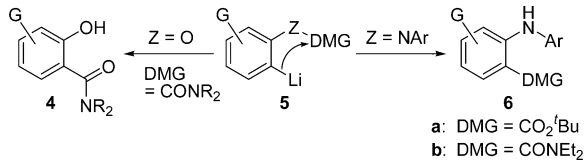
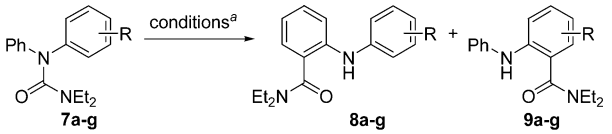
Scheme 2. Alkyllithium-Mediated Transformation of *N*-Protected Diarylamines into *N*-Aryl Anthranilates and *N*-Aryl Anthranilamides



regioselectivity. Herein we report on the scope and regioselectivity of this new version of the anionic *N*-*ortho*-Fries rearrangement,[9] show its link to further DoM chemistry, and demonstrate its application to the synthesis of acridone and pyranoacridone alkaloids.

Pursuant of improvement of the anionic *N*-Fries rearrangement, and based on preliminary results from the *N*-BOC series,[8] the prototype *N*-carbamoyl diphenylamine **7a**[10] was subjected to standard *t*-BuLi/TMEDA conditions to afford product **9a** in excellent yield (Table 1, entry 1).[11] Application

Table 1. Anionic *Ortho N*-Fries Rearrangement of *N*-CONEt$_2$ Diarylamines **7a**−**g**



entry	R	product	conditions[a]	yield of **8**, %	yield of **9**, %
1	H	**8a/9a**	A		81
2	H	**8a/9a**	B		90
3	3-OMe	**8b/9b**	A	59	26[b]
4	3-OMe	**8b/9b**	B	6	90[b]
5	4-OMe	**8c/9c**	A	54	35
6	4-OMe	**8c/9c**	B	4	90
7	3,5-OMe	**8d/9d**	A	75	14
8	3,5-OMe	**8d/9d**	B	7	90
9	3-Cl	**8e/9e**	A		92[b]
10	3-Cl	**8e/9e**	B		94[b]
11	4-Cl	**8f/9f**	A		87
12	4-Cl	**8f/9f**	B		97
13	2-Ph	**8g/9g**	A	73	19
14	2-Ph	**8g/9g**	B	47	51

[a] Conditions: (A) 1. *t*-BuLi/TMEDA/−78 °C/Et$_2$O/1 h; 2. −78 °C → rt. (B) 1. LDA/0 °C/THF, 2. 0 °C → rt. [b] Migration to the 2-position occurs. No 6-substituted product was observed.

of these favorable conditions to a series of *N*-carbamoyl diarylamines **7b**−**g**, prepared in 49−94% yields by a Pd-catalyzed aryl amination protocol,[12] furnished migration products **8b**−**g** and **9b**−**g** in good to excellent yields and regioselectivities (Table 1, entries 3, 5, 7, 9, 11, and 13). In the absence of mechanistic studies for the anionic *ortho N*-Fries process,[11] including establishment of intramolecularity,[13] a rationale for the observed regioselectivities is speculative. However, noteworthy are the following points: (a) for **7b** (entry 3), regioselective migration occurs into the unsubstituted ring, which contrasts with that observed for an *N*,*N*-diisopropyl 3′-methoxybiphenyl-2 carboxamide;[14] (b) for **7e** (entry 9), migration takes place into the substituted

(1) (a) Anionic ortho-Fries: Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935−1937. (b) Vinylogous anionic ortho-Fries: Kalinin, A. V.; Miah, M. A. J.; Chattopadhyay, S.; Tsukazaki, M.; Wicki, M.; Nguen, T.; Coelho, A. L.; Kerr, M.; Snieckus, V. *Synlett* **1997**, *7*, 839−841. (c) 1,5-O→O CONEt$_2$ translocation: Chauder, B. A.; Kalinin, A. V.; Taylor, N. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **1999**, *38*, 1435−1438. (d) Remote anionic Fries: Wang, W.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 424−426. (e) 1,2 Wittig versus 1,5-O→O CONEt$_2$ translocation: Zhang, P.; Gawley, R. E. *J. Org. Chem.* **1993**, *12*, 3222−3223. (f) Carbamoyl Baker−Venkatarman reaction: Kalinin, A. V.; da Silva, A. J. M.; Lopes, C. C.; Lopes, R. S. C.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4995−4998. (g) Anionic Friedel−Crafts equivalents: To acridones: MacNeil, S. L.; Gray, M.; Briggs, L. E.; Li, J. J.; Snieckus, V. *Synlett* **1998**, *4*, 419−421. MacNeil, S. L.; Gray, M.; Briggs, L. E., Snieckus, V. In preparation. (h) To xanthones: Familoni, O. B.; Ionica, I.; Bower, J. F.; Snieckus, V. *Synlett* **1997**, *9*, 1081−1083. (i) To thiaxanthones: Beaulieu, F.; Snieckus, V. *J. Org. Chem.* **1994**, *59*, 6508−6509. (j) To phosphorinones: Gray, M.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1558−1560. (k) Anionic O→α- and *β*-vinyl carbamoyl translocation: Reed, M. A.; Chang, M. T.; Snieckus, V. *Org. Lett.* **2004**, *6*, 2297−2300.

(2) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933. (b) Hartung, C. G.; Snieckus, V. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 330−367.

(3) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206−2225.

(4) For a closely related example, see: Iwao, M.; Reed, N.; Snieckus, V. *J. Am. Chem. Soc.* **1982**, *104*, 5531−5533.

(5) For general effects of *m*-EDG on Friedel−Crafts chemistry, see: Taylor, R. In *Electrophilic Aromatic Substitution*; Wiley: New York, 1990; p 236. For examples, see: Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2553. Fu, J.-m.; Zhao, B.-p.; Sharp. M. J.; Snieckus, V. *Can. J. Chem.* **1994**, *72*, 227−236. Sharp, M. J. M.Sc. Thesis, University of Waterloo, 1986.

(6) For other phenol- and aniline-based *ortho* anionic rearrangements, at times effected not by DoM but by metal−halogen exchange, see, inter alia: (a) ArOP(O)(OR)$_2$: Cambie, R. C.; Plamer, B. D. *Aust. J. Chem.* **1982**, *35*, 827−837 and references therein. Melvin, L. S. *Tetrahedron Lett.* **1981**, *22*, 3375−3376. Dhawan, B.; Redmore, D. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *61*, 183−187 and references therein. (b) ArOCOR: Hellwinkel, D.; Lämmerzahl, F.; Hofmann, G. *Chem. Ber.* **1983**, *116*, 3375−3405 and references therein. (c) ArOSiR$_3$: Billedeau, R. J.; Sibi, M. P.; Snieckus, V. *Tetrahedron Lett.* **1983**, *24*, 4515−4518. (d) ArN(R)P(O)(OR)$_2$: Jardine, A. M.; Vather, S. M. *J. Org. Chem.* **1988**, *53*, 3983−3985. (e) ArN(R)COR: Horne, S.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1991**, 1046−1048. Reference 7b. (f) ArN(R)SiR$_3$: ref 7b. (g) ArN(SO$_2$-Ph)Ar′: Hellwinkel, D.; Supp, M. *Chem. Ber.* **1976**, *109*, 3749−3766. Shafer, S. J.; Closson, W. D. *J. Org. Chem.* **1975**, *40*, 889−892. (h) For an analogous migration of *N*-acylphenothiazines, see: Hallberg, A.; Svensson, A.; Martin, A. R. *Tetrahedron Lett.* **1986**, *27*, 1959−1962.

(7) For an interesting migration in a thiophene 2-sulfonamide, see: Slocum, D. W.; Gierer, P. L. *J. Org. Chem.* **1973**, *38*, 4189−4192.

(8) Detailed studies will be the subject of a full paper. See also: MacNeil, S. L. M.Sc. Thesis, University of Waterloo, 1997.

(9) For reports on rearrangements of different *N*-groups, see refs 7d−h.

(10) For C-7 DoM chemistry of *N*-CONEt$_2$, 2-TMS-indole, see: Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003**, *5*, 1899−1902.

(11) For detailed optimization studies, see: Wilson, B. M.Sc. Thesis, Queen's University, 2004.

(12) See: (a) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215−7216. For reviews, see: (b) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131−209. (c) Hartwig, J. F. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 107−168.

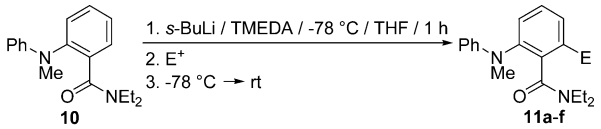
(13) The lack of *N*-deprotected products and products possessing two amide substituents, one at nitrogen and one at the ortho- or ortho′-position, which would arise by an *inter*molecular N → C carbamoyl migration, suggests but does not prove an *intra*molecular mechanism for the reaction.

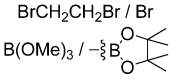
(14) Under LDA conditions, this compound gives 1-methoxyfluoren-9-one, the result of remote metalation−cyclization, see: Fu, J.-m.; Zhao, B.-p.; Sharp, M. J.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 1683−1685. For an indication of the generality of this reaction, see ref 3.

ring in agreement with the analogous in-between metalation of 3-chlorobenzamide,[2a] suggesting greater significance of the inductive effect of the chloro group; (c) an inductive effect of the chloro substituent may operate at longer distance, e.g., **7f** (entry 11); and (d) a presumed steric effect of the phenyl group for **7g** (entry 13) forces rearrangement to give mainly **8g** rather than a product of remote metalation−migration into the 2-Ph substituent as may be observed in the analogous biaryl *O*-carbamate series.[1d,15] Higher combined yields were obtained of the anthranilamides **8a**−**g** and **9a**−**g** compared to those observed for the anthranilates resulting from rearrangement of the corresponding *N*-Boc derivatives.[8] This may be due to the expected greater coordination effect of carbamoyl over Boc substitutents,[3] and the greater stability of **8a**−**g** and **9a**−**g** to nucleophilic attack of RLi reagents. Interestingly, the migration regiochemistry was found to be more predictable and thus much more synthetically useful when mediated by LDA (Table 1, entries 2, 4, 6, 8, 10, 12, and 14). Indeed, compounds **9a**−**g** were obtained in excellent yields and regioselectivities in all but one case (entry 14). Presumably, with LDA, the thermodynamic equilibrium existing between the two anions (leading respectively to **8a**−**g** and **9a**−**g**) is displaced toward the formation to that which is most stable (less basic) owing to its stabilization by two substituents (PhNCONEt$_2$ and R).

As an alternative and enhanced regioselective route to the products of anionic *ortho N*-Fries rearrangement into the more highly substituted ring, compounds **9b**,**d**,**e** (Table 1), representing 6-substituted anthranilamides of potential pharmaceutical value,[16] the D*o*M chemistry of the readily prepared *N*-methyl derivative **10** was pursued (Table 2). In

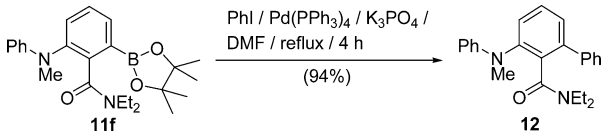
Table 2. D*o*M Route to Anthranilamides **11a**−**f**



entry	E^+ / E	Product	yield, %
1	MeI / Me	**11a**	98
2	DMF / CHO	**11b**	91
3	TMSCl / TMS	**11c**	97
4	Cl_3CCCl_3 / Cl	**11d**	99
5	$BrCH_2CH_2Br$ / Br	**11e**	99
6	$B(OMe)_3$ / 	**11f**	85

the event, standard metalation of **10** followed by quench with an archetypical group of electrophiles furnished excellent yields of products **11a**−**f** including those (Table 2, entries 1, 2, and 5) which, due to sensitivity to the alkyllithium and lithium amide conditions, could not be obtained by the Fries rearrangement (Table 1). To illustrate further potentially useful transition metal catalyzed chemistry of some products (**11d**−**f**; entries 4−6), the boropinacolate **11f**, derived from the crude boronic acid by in situ treatment with pinocol (see Supporting Information), was submitted to the typical Suzuki−Miyaura cross coupling conditions and afforded compound **12** (Scheme 3), representing an interesting bi-

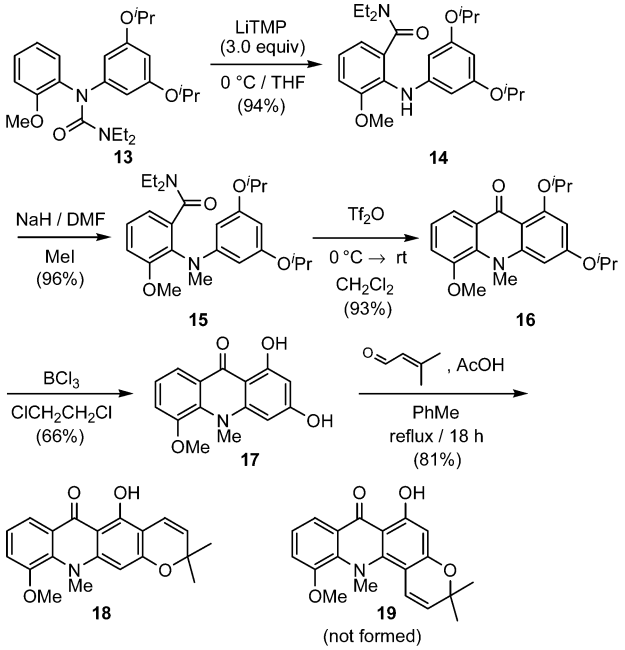
Scheme 3. Synthesis of Anthranilamide **12** by Suzuki-Miyaura Cross Coupling



arylamine−biaryl framework that invites further metalation chemistry.

To enhance further appreciation of the *N*-Fries rearrangement concept, syntheses of the highly oxygenated acridone, yukodine (**17**), and pyranoacridone, junosidine (**18**) (Scheme 4), were undertaken. The route toward yukodine (**17**) and

Scheme 4. Total Synthesis of Yukodine (**17**) and Junosidine (**18**)



junosidine (**18**),[17] originally isolated from *Citrus junos*,[18] was initiated from the *N*-carbamoyl diarylamine **13**, readily prepared in three steps and 90% overall yield with use of key Buchwald C−N bond cross coupling technology.[19] Treatment with an excess of LiTMP[20] resulted in a highly regioselective (single isomer by ^{1}H NMR) and quantitative

(15) For other synthetic applications, see James, C. A. Ph.D. Thesis, University of Waterloo, 1998.

(16) An important example is GF120918, an acridone 1-carboxamide that has been identified as an optimized inhibitor of multidrug resistance (MDR), see: (a) Ward, K. W.; Azzarano, L. M. *J. Pharmacol. Exp. Ther.* **2004**, *310*, 703−709. (b) Hyafil F.; Vergely C.; Du Vignaud P.; Grand-Perret T. *Cancer Res.* **1993**, *53*, 4595−602.

N-Fries rearrangement to the anthranilamide **14**, which, upon standard methylation, provided compound **15**. Unfortunately, attempts to incorporate a second anionic step to **16** in this total synthesis with LDA, LiTMP, and alkyllithium reagents resulted only in the formation of complex mixtures of products.[11,21] Hence, resorting to more classical methods, treatment of **15** with Tf_2O[22] smoothly gave the acridone, which upon selective deisopropylation,[23] furnished, with similar efficiency, yukodine (**17**).[24]

The synthetic work was concluded by adaptation of a convenient procedure for chromene ring construction[25] to afford junosidine (**18**) in 81% yield. The route proceeds in nine steps and 33% overall yield from commercially available 1-chloro-3,5-dimethoxybenzene and constitutes the first total synthesis of this natural product uncontaminated by its naturally occurring angular regioisomer, 5-methoxynoracronycine (**19**).[26]

In summary, we have disclosed results on a new anionic *ortho N*-Fries rearrangement of *N*-CONEt$_2$ diarylamines to anthranylamides, **7** → **8**, **9,** which leads to products **8b**−**d**,**g** and **9a**−**f** with good to excellent regioselectivity and in synthetically useful yields (Table 1); an alternate, highly regioselective route to 6-substituted anthranylamides, **10** → **11**, has also been developed (Table 2). Furthermore, a link of the *N*-Fries migration to sequential D*o*M and Suzuki−Miyaura cross coupling chemistry (**11f** → **12**) has been established (Scheme 3) and its application to an efficient synthesis of acridone and pyranoacridone alkaloids has been demonstrated (Scheme 4). In combination with the reliable preparative route to diarylamines by Buchwald−Hartwig C−N coupling technology,[27] the *N* → C 1,3-carbamoyl migration, particularly when linked to D*o*M tactics, allows regioselective construction of 6-substituted anthranilic acid derivatives which may be inaccessible by alternative methods and generally offers further enrichment of carbanionic chemistry for the regioselective elaboration of polysubstituted aromatics.

Acknowledgment. NSERC Canada is acknowledged for consistent support of our synthetic programs. We thank Matthew Gray and Laura Briggs for preliminary experiments. S.M. was an NSERC Postgraduate Fellow (1994−1998), Queen's Graduate Fellow (1998−1999), and OGS (Science & Technology) recipient (1999−2000).

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For a comprehensive review on the isolation, structural elucidation, synthesis, biochemistry, and biological activities of these and other naturally occurring acridones, see: Skaltsounis, A. L.; Mitaku, S.; Tillequin, F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 2000; Vol. 54, pp 259−377.

(18) (a) Takemura, Y.; Uchida, H.; Juichi, M.; Omura, M.; Ito, C.; Nakagawa, K.; Ono, T.; Furukawa, H. *Heterocycles* **1992**, *34*, 2123−2130. (b) Juichi, M.; Inoue, M.; Sakiyama, K.; Yoneda, M.; Furukawa, H. *Heterocycles* **1987**, *26*, 2077−2079.

(19) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413.

(20) LiTMP was found to yield superior results to LDA for this particular transformation. See ref 12.

(21) The di-OMOM ether corresponding to **15** also led to complex product mixtures. For sensitivity of MOM derivatives to strong bases, see ref 16.

(22) Charette, A. B.; Chua, P. *Synlett* **1998**, 163.

(23) Sala, T.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2593−2598.

(24) A sample was found to be identical with the natural product by comparison of NMR and other spectroscopic and physical data. For yukodine, see ref 19a, for junosidine, see ref 19b.

(25) Chauder, B. A.; Lopes, C. C.; Lopes, R. S. C.; da Silva, A. J. M.; Snieckus, V. *Synthesis* **1998**, 279.

(26) Juichi, M.; Inoue, M.; Kuniko, A.; Furukawa, H. *Heterocycles* **1986**, *24*, 1595−1597.

(27) Buchwald−Hartwig conditions typically afford products in higher yields, under milder conditions, than classical Ullmann conditions. For a direct comparison involving *N*-phenyl-4-methoxyaniline, see: Anémian, R.; Morel, Y.; Baldeck, P. L.; Paci, B.; Kretsch, K.; Nunzi, J.-M.; Andraud, C. *J. Mater. Chem.* **2003**, *13*, 2157−2163.