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Anionic N-Fries Rearrangement of N-Alkyl-2-iodo Anilides Induced by Iodine–Magnesium Exchange: Application for Synthesis of Strained 1,2,3-Trisubstituted Indoles

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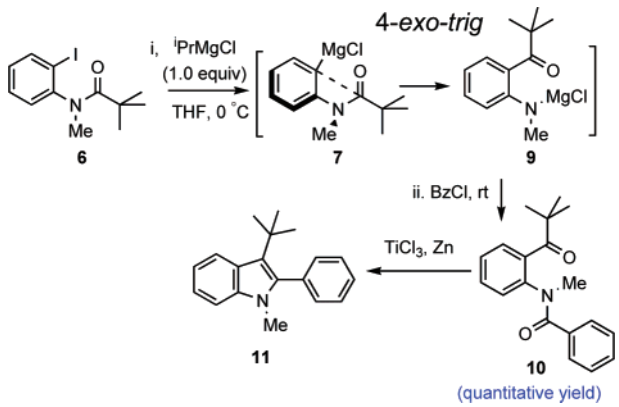
ABSTRACT



A superior, mild, high-yielding one-pot process for rapid access to oxo anilides has been developed that involves three cascade reactions: iodine–magnesium exchange, regiospecific ortho N-Fries rearrangement, and in situ trapping of the formed aniline anion. Coupled with McMurry cyclization, the two-step process allows ready synthesis of strained 1,2,3-trisubstituted indoles regioselectively.

The prevalence of the indole structural motif in numerous natural products and pharmaceutically active compounds is responsible for the tremendous amount of efforts in developing new methods for access to this heterocyclic system.[1] Although the classical Fischer indolization[2] still remains a general approach to indole compounds, it has a limited scope with respect to regioselectivity, an issue pertaining not only to the substituents on the aromatic ring of hydrazine but also to the enamine intermediates formed from ketones and hydrazines, which are highly dependent on the carbonyl substrates and reaction conditions. Consequently, several Pd-catalyzed indolization methods,[3] including those recently developed in this group,[4] are aimed to tackle these problems with respect to the chemo- and regioselectivity issues.

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(1) For a recent review of indole-containing natural products, see: (a) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155. (b) Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 175. For reviews on indole syntheses, see: (a) Sundberg, R. J., Ed. *Indoles*; Academic: London, 1996. (b) Sundberg, R. J. Pyrroles and their Benzo Derivatives: Synthesis and Applications. Katritzky, A. R., Rees, C. W., Eds.; Comprehensive Heterocyclic Chemistry, Vol. 4; Pergamon: Oxford, 1984; pp 313. (c) For a recent review on Fischer indole synthesis, see: Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 607.

(2) Fischer, E.; Jourdan, F. *Chem. Ber.* **1883**, *16*, 6.

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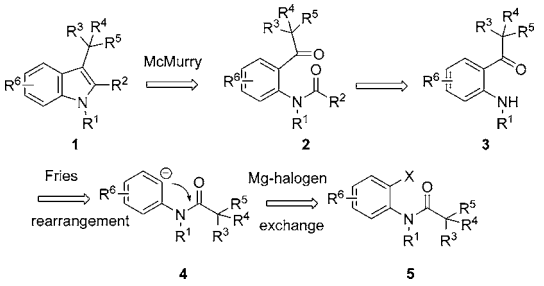
In our recent studies toward the synthesis of indole intermediates **1** containing a bulky quaternary carbon substituent at C3 (Scheme 1), we realized that there are few

Scheme 1. Synthetic Strategy to Strained 1,2,3-Trisubstituted Indoles

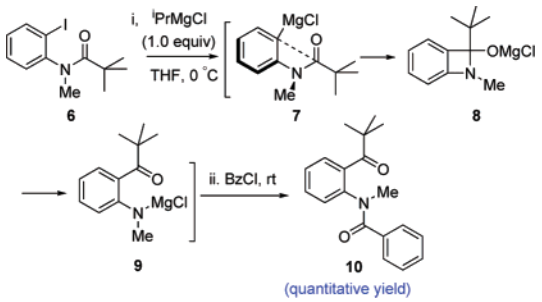


practical methods to introduce the bulky C3 substituent regioselectively. The cyclization of oxo anilides **2** via the McMurry reaction to afford the pyrrole ring has been reported;[5] however, the lack of an efficient method to prepare the oxo anilides **2** prompted us to develop a practical process for synthesis of these key intermediates.[6] Herein we report on the first high-yielding, one-pot process for rapid access to oxo anilides **2** via the sequence of anionic Fries rearrangement[7] induced by halogen−magnesium exchange of **5** and in situ amidation. Its application to the synthesis of strained 1,2,3-trisubstituted indoles is also described herein.

Although Fries rearrangement of phenol-based carbamates, carbonates, benzoates, and pivalates, induced by the directed ortho lithiation, has been well reported,[8] the aniline version of anionic Fries rearrangement involving migration of the *N*-acyl group has been rarely documented[9] except for a few reports on the migration of phosphorus, sulfur, and silicon derivatives of anilines.[10] Furthermore, the chemo- and regioselectivities, as well as the cryogenic conditions (−78 °C), are issues often related to anionic Fries rearrangement induced by directed ortho lithiation. We envisoned that these issues could be circumvented by incorporating halogen−magnesium exchange[11] of 2-haloaniline (Scheme 1).

Our study began with the sequential magnesium−iodine exchange and the tandem anionic Fries rearrangement of *N*-pivaloyl-*N*-methyl-2-iodoanilide (**6**) (Scheme 2). When a

Scheme 2. Anionic Fries Rearrangement of *o*-(*N*,*N*-Methyl pivaloylamido)benzene Magnesium Chloride



solution of **6** in THF was treated with one equivalent of ^{i}PrMgCl at 0 °C, iodine−magnesium exchange occurred instantly, followed by pivaloyl migration in 3 min to afford *N*-methyl-2-pivaloyl-aniline in a quantitative yield. The migration was further evidenced by quenching an aliquot of the reaction mixture with D_2O, and finding no deuterium incorporation into the product, *N*-methyl-2-pivaloyl-aniline. The proton NMR spectrum of the isolated product featured four aromatic resonances at 7.89 (d), 7.33 (dd), 6.71 (d), 6.57 (dd) ppm as well as a doublet of the methyl group at 2.87 ppm with a coupling constant of 5.2 Hz. This evidence supported the formation of the acyl migration intermediate anion **9**. Furthermore, the intermediate anion **9** was easily trapped by addition of benzoyl chloride to afford quantitatively the oxo anilide **10** in one pot. Obviously, this is a very superior process, considering the excellent yield, mild reaction conditions, and the feature of three cascade reactions in one pot.

To elucidate the scope of this protocol, a variety of oxo anilides were prepared readily. The results are summarized in Table 1. Bulky admantane carbonyl group underwent N-Fries rearrangement under these conditions with excellent yields (entries 2, 3, Table 1). Other acyl groups which contain heteroatoms such as F, O, and N (entries 4−6, Table 1) were also able to migrate under the iodine−magnesium exchange conditions. The reaction conditions also tolerated the *N*-benzyl group (entry 7, Table 1). Presumably, in this case,

(3) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

(4) (a) Shen, M.; Li, G.; Lu, B. Z.; Hossain, A.; Roschangar, F.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2004**, *6*, 4129. (b) Liu, J. X.; Shen, M.; Zhang, Y. D.; Li, G.; Khodabocus, A.; Rodriguez, S.; Qu, B.; Farina, V.; Senanayake, C. H.; Lu, B. Z. *Org. Lett.* **2006**, *8*, 3573. (c) Lu, B. Z.; Zhao, W.; Wei, H.-X.; Dufour, M.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 3271.

(5) (a) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513. (b) Lenoir, D. *Synthesis* **1989**, 883. (c) Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215. (d) Fürstner, A.; Hupperts, A.; Seidel, G. *Org. Synth.* **1999**, *76*, 142.

(6) (a) Rees, C. W.; Storr, R. C.; Whittle, P. J. *Tetrahedron Lett.* **1976**, 4647. (b) Dyall, L. K. *Austr. J. Chem.* **1977**, *30*, 2669. (c) Grammaticakis, P. *C. R. Acad. Sci.* **1952**, *235*, 546.

(7) (a) Fries, K.; Finck, G. *Ber.* **1908**, *41*, 2447. (b) Fries, K.; Pfaffendorf, W. *Ber.* **1910**, *43*, 212. (c) Blatt, A. H. *Org. React.* **1942**, *1*, 342. (d) Effenberger, F.; Klenk, H.; Reiter, P. L. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 775.

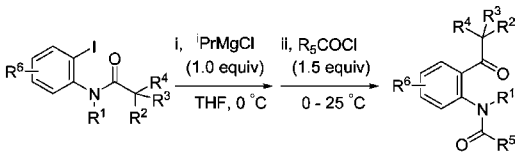
(8) (a) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935. (b) Hellwinkel, D.; Lämmerzahl, F.; Hofmann, G. *Chem. Ber.* **1983**, *116*, 3375. (c) Miller, J. A. *J. Org. Chem.* **1987**, *52*, 323. (d) Horne, S.; Rodrigo, R. *J. Org. Chem.* **1990**, *55*, 4520.

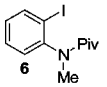
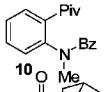
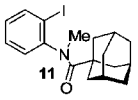
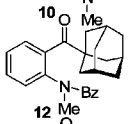
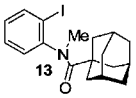
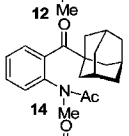
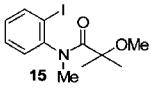
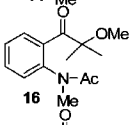
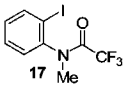
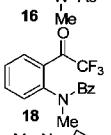
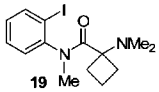
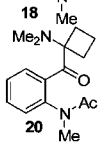
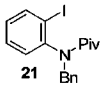
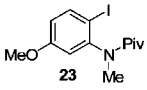
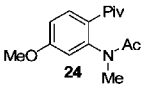
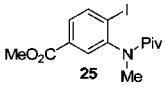
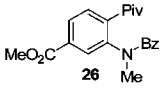
(9) Only two reports described migration of benzoyl and carbamoyl groups which are not within the scope of Fries rearrangement: (a) Horne, S.; Rodrigo, R. *Chem. Commun.* **1991**, 1046. (b) MacNeil, S.; Wilson, B. J.; Snieckus, V. *Org. Lett.* **2006**, *8*, 1133. For a recent paper on photochemically induced Fries rearrangement, see: Ferrini, S.; Ponticelli, F.; Taddei, M. *Org. Lett.* **2007**, *9*, 69.

(10) (a) Safer, S. J.; Closson, W. D. *J. Org. Chem.* **1975**, *40*, 889. (b) Hellwinkel, D.; Supp, M. *Chem. Ber.* **1976**, *109*, 3749. (c) Reference 8b. (d) Jardine, A. M.; Vather, S. M. *J. Org. Chem.* **1988**, *53*, 3983.

(11) For a review, see: Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.

Table 1. Anionic N−C Migration of Carbonyl Group[a]



entry	substrate	product	yield
1	 **6**	 **10**	100%
2	 **11**	 **12**	100%
3	 **13**	 **14**	95%
4	 **15**	 **16**	90%
5	 **17**	 **18**	74%
6	 **19**	 **20**	63%
7	 **21**	 **22**	98%
8	 **23**	 **24**	100%
9	 **25**	 **26**	78%

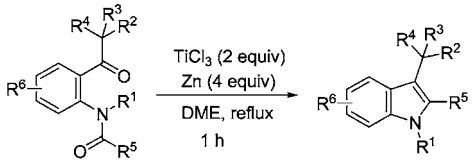
[a] All the substrates were prepared with high yields from corresponding 2-iodoanilines in an acylation−alkylation sequence.

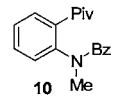
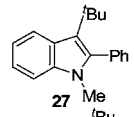
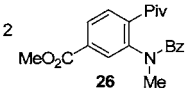
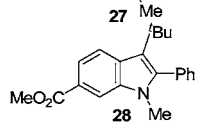
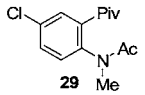
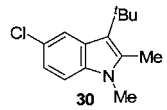
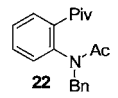
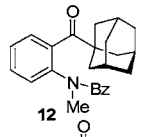
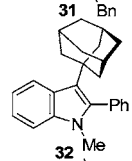
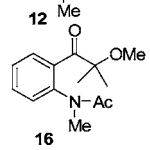
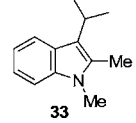
the iodine−magnesium exchange was able to surpass the potential deprotonation at the benzylic position. In the *N*-acylation step, both benzoyl chloride and acetic anhydride can be used as electrophiles toward the formed aniline anions.

Taking advantage of the fast iodine−magnesium exchange, the sequence was able to tolerate substitution on the aromatic ring of iodoanilines. Electron-donating groups such as methoxy had no effect on the reaction profile, giving the product **24** in a quantitative yield (entry 8, Table 1). Even in the presence of the labile methyl carboxylate functionality, the desired product **26** was obtained uneventfully, although the yield was compromised (entry 9, Table 1). It is noteworthy that the reaction of iodoaniline with *p*-cyano substitution resulted in a complex mixture.

Next, with dicarbonyl compounds in hand, McMurry cyclization was carried out to generate indoles under standard McMurry conditions using $TiCl_3$ and zinc by refluxing in

Table 2. Synthesis of Strained 2,3-Disubstituted Indoles via McMurry Cyclization

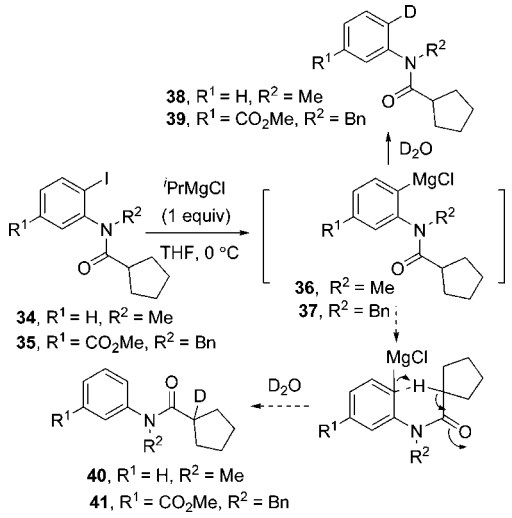


entry	substrate	product	yield
1	 **10**	 **27**	82%
2	 **26**	 **28**	81%
3	 **29**	 **30**	77%
4	 **22**	 **31**	68%
5	 **12**	 **32**	79%
6	 **16**	 **33**	54%

DME. The results are summarized in Table 2. Despite the bulky C2 and C3 substituents in the indole products, the reaction proceeded smoothly with good yields even in the presence of functional groups prone to reduction such as carboxylate (**26**), chloride (**29**), and benzyl (**22**) (entries 1−4, Table 2). Interestingly, when the acyl group at the C2 position of the oxo anilide was α-methoxydimethylcarbonyl (**16**), the ring cyclization was concomitant with reduction of the methoxy group to give C3 isopropyl indole product **33** (entry 6, Table 2). When the substrate containing trifluoroacetyl **18** was subjected to McMurry conditions, the reaction generated an intractable mixture.

In an effort to expand the scope of this N-Fries rearrangement, the iodoaniline **34** was examined. When it was reacted with ^{i}PrMgCl followed by quenching with D_2O, deuterium substitution was only observed at the position ortho to the aniline, suggesting that the α-proton of the amide remained intact. However, no acyl migration was observed (Scheme 3). More hindered substrate **35** was prepared, in attempt to facilitate the *N*-acyl migration by increasing the strain between the two substituents on the nitrogen atom. ^{1}H NMR of **35** showed clearly two split doublets of benzylic protons at 5.82 and 4.02 ppm, which is similar to the characteristics of substrate **21**, suggesting a rigid conformation of the benzyl

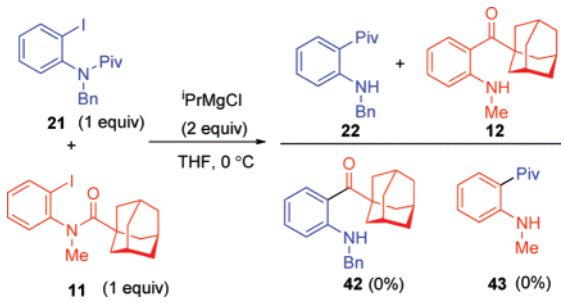
Scheme 3. Iodine−Magnesium Exchange of Anilides **34**, **35**



group due to steric hindrance. However, the reaction of **35** with ^{i}PrMgCl again stopped at the iodine−magnesium exchange stage without further acyl migration. Activation of the amide carbonyl by a variety of Lewis acids failed to facilitate the intramolecular nucleophilic attack. A similar result was observed with *N*-benzoyl 2-iodoanilide. No migration of the benzoyl group occurred. These results imply that the N-Fries rearrangement was limited to acyl groups with quaternary sp^3 α-carbon.

Mechanistically, the *N*-acyl migration reported herein proceeded in an intramolecular fashion, similar to the ortho O-Fries rearrangement. In a crossover experiment, an equimolar mixture of **11** and **21** was treated with two equiv of ^{i}PrMgCl. The reaction only afforded two corresponding migration products **12** and **22** with no trace amount of scrambled products **42** and **43** (Scheme 4). Presumably, the acyl migration proceeded through a transition state involving

Scheme 4. Cross-over Experiment of the N-Fries Rearrangement



a 4-*exo*−*trig* nucleophilic addition. Proton NMR of the starting *N*-alkyl 2-iodoanilides showed broadening or, in some cases, even splitting pattern for the two substituents attached to the nitrogen atom. The restricted rotation of the two groups suggested by this NMR feature indicated a strong steric interaction between the two groups, which could be the driving force of the migration.

In summary, we developed a superior one-pot process for rapid preparation of oxo anilides, involving iodine−magnesium exchange, regiospecific ortho N-Fries rearrangement, and in situ trapping of the formed aniline anion. The acyl groups capable of migration possess an sp^3 tertiary carbon center with carbon or heteroatom substituents. The acyl migration, coupled with acylation and McMurry cyclization, allows ready access to 1,2,3-trisubstituted indoles with tertiary carbon substituent at the C3 position.

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

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