An Anion-Induced Regio- and Chemoselective Acylation and Its Application to the Synthesis of an Anticancer Agent
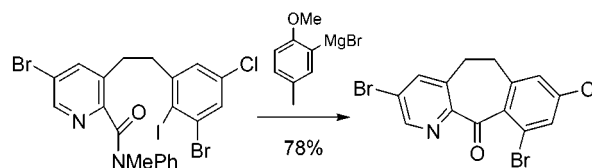
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ABSTRACT

An efficient Grignard- and organolithium-induced regio- and chemoselective anionic acylation is reported. A number of tricyclic ketones are prepared in good to excellent yields via this method. This method is complementary to the Frieldel–Crafts acylation for electron-deficient substrates. A novel anisole-based Grignard reagent was developed to effect the cyclization of sterically hindered substrates. This novel reagent has been successfully applied to the synthesis of Sch 66336, a candidate for oncologic treatment.

Sch 66336 is a potent farnesyl protein transferase inhibitor[1–2] and is currently in clinical trials for the treatment of several types of cancer. One of its synthetic challenges is the introduction of both the 3- and 10-bromo substituents in a convergent fashion. The initial synthesis[3] of Sch 66336 requires a total of seven steps for the sequential introduction of both the 3- and 10-bromo groups starting from the 8-chloroazaketone. These steps are nitration, reduction, and bromination for the introduction of the 3-bromo and nitration, reduction, bromination, and deamination for the 10-bromo group. For the convergent introduction of the 3-bromo group, we have developed and scaled up successfully an efficient palladium-catalyzed regioselective carbonylation.[4] Recent reports[5] on Grignard-induced cyclizations prompted us to disclose our results on the regioselective anionic acylation for the preparation of the 10-bromo-substituted azaketone.[6]

The synthetic strategy was to dissect the double benzylic chiral center and divide the molecule into a 3,10-dibromo-8-chloroazaketone, 1, and a lower part as shown in Figure 1. The azaketone 1 could be prepared from either a direct acylation of 2a or a directed regioselective cyclization of 2b. As expected, cyclization of 2a under Friedel–Crafts conditions generated an inseparable 1:1 mixture of two
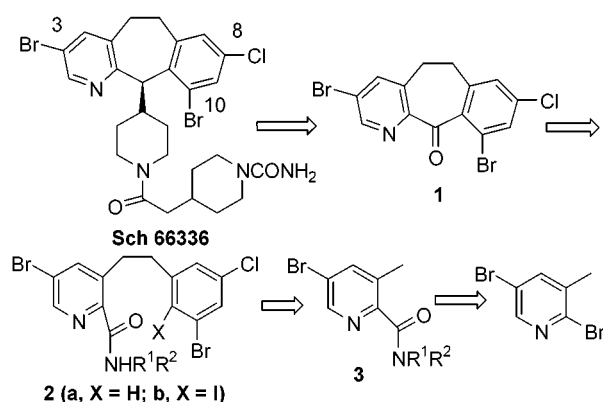

Figure 1. Retrosynthetic analysis.

(1) Barbacid, M, *Annu. Rev. Biochem.* **1987**, *56*, 779.
(2) Leonard, D. M. *J Med. Chem.* **1997**, *40*, 2971.

regioisomers, the 8-chloro-10-bromo and the 8-bromo-10-chloro azaketones. Thus, we turned our attention to an anionic "Friedel−Crafts" acylation by preactivating the 11-position with an iodo group.

Intramolecular anionic Friedel−Crafts equivalent reactions were first reported by Snieckus's group for the formation of tricyclic ketones.[7] The reported acylations are generally initiated by an amide-induced remote lithiation followed by an intramolecular addition of the newly formed anion to the amide group. This type of reaction cannot be applied directly to our synthesis as there are two nondiscriminative lithiation sites on the aromatic moiety in compound **2a**. Thus, it is necessary to regioselectively activate the 11-position. We postulated that a selective iodo−lithium or iodo−magnesium exchange of the 11-iodo substituent in **2b** followed by an intramolecular cyclization would afford the desired tricyclic ketone **1**. This assumption was supported by three very recent publications in which halogen−lithium and halogen−magnesium exchange-induced cyclizations are reported.[5] All these reported examples produced good yields for five- and six-membered heterocycles but poor yields for seven-membered rings. Furthermore, those substrates do not contain any other halogen groups that could compete with the desired iodo−metal exchange. Therefore, there are two key questions for our proposed reaction. (1) Can we achieve a selective activation of the iodo group at the hindered 11-positon? (2) Can we accomplish an effective subsequent cyclization to form the seven-membered ketones?

First, we studied this type of acylation with simpler substrates. These substrates were prepared via a lateral lithiation followed by alkylation with an appropriate electrophile. Some of the alkylated products prepared are summarized in Table 1. Lateral lithiation of *o*-toluic acid[8]

with *s*-BuLi followed by alkylation with 2-bromobenzyl-bromide gave the alkylated acid. The acid group was then converted to the corresponding amide **4** via an acid chloride. The other three examples in Table 1 were prepared starting with 3-methylpyridinic amides. Both *n*-BuLi and LDA worked well for the lateral lithiation of 3-methylpyridinic amides.[9] However, LDA is necessary for the lithiation of 5-bromo-3-methylpyridinic amide **8** because of the presence of the bromo group. In addition, a binary solvent system of methyl *tert*-butyl ether and THF was found to work best for entry 4 in order to minimize the de-iodonation side reaction. Since only tertiary amides are suitable for the anion-induced acylation, the secondary amides derived from **5** and **8** were further converted in good yields to their corresponding tertiary amides **6**, **7**, and **2b**, using NaH and MeI. Direct lithiation/alkylation of tertiary amides afforded the same products but in much lower yields.

The desired 2-iodo-3-bromo-5-chlorobenzyl bromide, **9**, was prepared in excellent overall yield by following the procedure in Scheme 1. Thus, bromination of 2-amino-5-
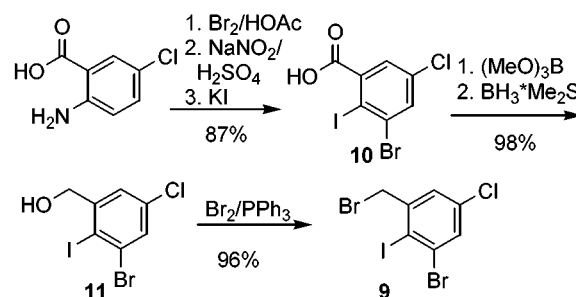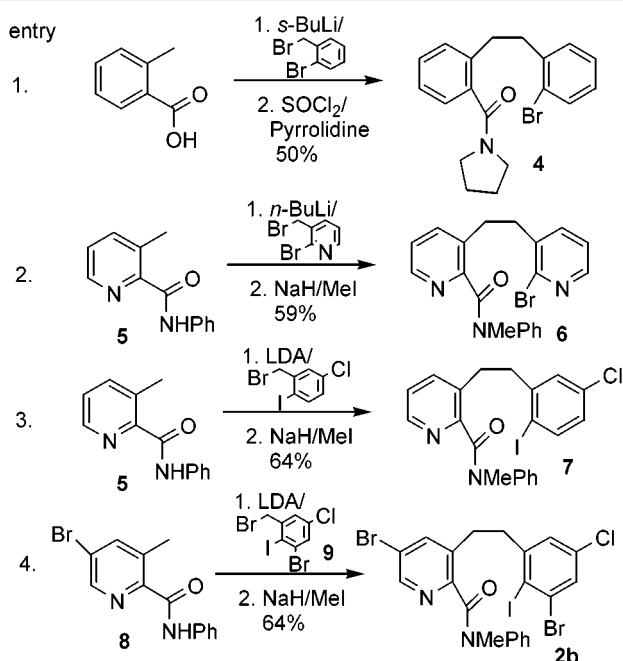
Scheme 1. Preparation of Benzyl Bromide **9**

chlorobenzoic acid followed by diazotization and iodide displacement afforded 2-iodo-3-bromo acid **10** in 87% yield. Reduction of the acid group with $(MeO)_3B$ and $BH_3−Me_2S$[10] gave the alcohol **11** in 98% yield. **11** was converted to the

Table 1. Lateral Lithiation−Alkylation

(3) (a) Njoroge, F. G.; Taveras, A. G.; Kelly, J.; Remiszewski, S.; Mallams, A. K.; Wolin, R.; Afonso, A.; Cooper, A. B.; Rane, D. F.; Liu, Y.; Wong, J.; Vibulbhan, B.; Pinto, P.; Deskus, J.; Alvarez, C. S.; del Rosario, M.; Connolly, M.; Wang, J.; Desai, J.; Rossman, R. R.; Bishop, W. R.; Patton, R.; Wang L.; Kirschmeier, P.; Bryant, M. S.; Nomeir, A. A.; Lin, C. C.; Liu, M.; McPhail, A.; Doll, R. J.; Girijavallabhan, V.; Ganguly, A. K. *J. Med. Chem.* **1998**, *41*, 4890. (b) Njoroge, F. G.; Vibulbhan, B.; Wong, J. K.; White, S. K.; Wong, S.; Carruthers, N. I.; Kaminski, J. J.; Doll, R.; Girijavallabhan, V.; Ganguly, A. K. *Org. Lett.* **1999**, *1*, 1371.
(4) Wu, G.; Wong, Y.; Poirier, M. *Org. Lett.* **1999**, *1*, 745.
(5) (a) Iida, T.; Wada, T.; Tomimoto, K.; Mase, T. *Tetrahedron Lett.* **2001**, *42*, 4841. (b) Kondo, Y.; Asai, M.; Miura, T.; Uchiyama, M.; Sakamoto, T. *Org. Lett.* **2001**, *3*, 13. (c) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333.
(6) Part of the contents in this Letter are covered by our U.S. patent: 5,998,620, 1999.
(7) (a) Beaulieu, F.; Snieckus, V. *J. Org. Chem.* **1994**, *59*, 6508. (b) Familoni O. B.; Ionica, I.; Bower, J. F.; Snieckus, V. *Synlett* **1997**, 1081. (c) MacNeil, S. L.; Gray, M.; Briggs, L. E.; L, J. J.; Snieckus, V. *Synlett* **1998**, 419.
(8) Creger, P. L. *J. Am. Chem. Soc.* **1970**, *92*, 1396.
(9) (a) Clark, R. D.; Jahangir. *J. Org. Chem.* **1987**, *52*, 5378. (b) Schumacher, D. P.; Murphy, B. L.; Clark, J. E.; Tahbaz, P.; Mann, T. A. *J. Org. Chem.* **1989**, *54*, 2242.
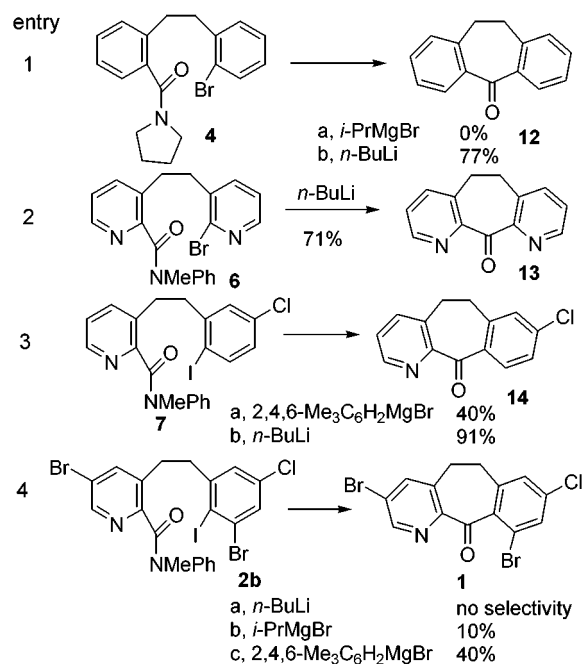(10) Lane, C. F.; Myatt, H. L.; Daniels, J.; Hopps, H. B. *J. Org. Chem.* **1974**, *39*, 3052.

corresponding benzyl bromide **9** in 96% yield by using Br_2 and PPh_3. The 2-bromo-3-bromomethylpyridine was prepared via a radical reaction[11] starting from 2-bromo-3-methyl-pyridine.

Second, we studied the halogen−lithium and halogen−magnesium exchanges and the subsequent cyclization. Simple Grignard reagents such as *i*-PrMgBr failed to achieve halogen−magnesium exchanges for **4**, **6**, and **7**. This result confirms the previous report that *i*-PrMgBr works well only for electron-deficient aryl halides or alkenyl halides bearing an oxygen-containing functionality acting as a metal directing group.[12] Special reagents such as (*n*-Bu)$_3$MgLi are required for simple aryl bromide−magnesium exchanges.[5b]

For substrates **4**, **6**, and **7**, *n*-BuLi was found to be a very effective reagent for halogen−lithium exchanges. The completion of halogen−metal exchange was monitored by proton NMR after the reaction mixture was quenched with deuterium oxide. It is worth noting that the potential lateral lithiation of the benzylic positions did not take place under the reaction conditions. Furthermore, all the lithiated intermediates cyclized smoothly to produce the corresponding tricyclic ketones **12**,[13] **13**, and **14** in 77%, 71%, and 91% isolated yields, respectively. The formation of novel dipyridine-containing tricyclic ketone **13** (Table 2, entry 2) is

Table 2. Anion-Induced Regioselective Acylation

complementary to the Friedel−Crafts acylation for electron-deficient substrates. Tricyclic ketone **14** is a key intermediate for the synthesis of loratadine,[9b,14] a marketed allergy drug.

(11) Rebek, J.; Costello, T. *Heterocycles* **1984**, *22*, 2191.

(12) For reviews, see: (a) Rottlander, M.; Boymond, L.; Berillon, L.; Lepretre, A.; Varchi, G.; Avolio, S.; Laaziri, H.; Queguiner, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Chem Eur. J.* **2000**, *6*, 767. (b) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem.* **2000**, *112*, 4584; *Angew. Chem., Int. Ed.* **2000**, *39*, 4414.

Alkyl- and aryllithium reagents are not suitable for substrate **2b** as there is no useful chemoselectivity between iodo and bromo groups toward halogen−lithium exchanges. We then focused our attention on iodo−magnesium exchange. Simple Grignard reagents such as *i*-PrMgBr afforded a mere 10% of the desired azaketone **1**. PhMgBr gave ca. 10% of the product together with an intractable mixture, most likely due to the competitive addition to the amide group. Mesityl Grignard, a hindered reagent, was found to perform the iodo−magnesium exchange for both aryl iodides **7** and **2b**. However, the subsequent cyclization proceeded only in 40% solution yields for both substrates. The solution yield was determined by HPLC using an external purified standard. The major side product was the proton-quenched starting material.

To improve the yield, we examined the effect of the leaving group on the cyclization. A variety of amides were prepared and subjected to the iodo−magnesium exchange using mesityl Grignard, and their results are summarized in Table 3. Although, the exchange proceeded well for all

Table 3. Selection of Amide

entry	NR^1R^2	1:2a[a]	sol. yield[b]
1	$(MeOCH_2CH_2)_2NMe$	30:70	15%
2	pyrrolidinyl	28:72	22%
3	PhN_N	50:50	37%
4	PhNMe	63:37	40%
5	4-FPhNMe	63:67	40%
6	4-MeOPhNMe	40:60	30%

[a] The ratio was determined by ^{1}H NMR. [b] The solution yield was determined by HPLC.

amides, the ratio of cyclized ketone vs the proton-quenched byproduct (**1**:**2a**) varied from 0:100 to 63:37. Aryl amides gave much better ratios than the ratios of the alkyl ones. For example, PhNMe and 4-FPhNMe amides gave a 63:37 ratio of **1**:**2a** with 40% solution yields. Arylamines, the byproduct from the cyclization, stabilize anions better than alkyl ones and therefore are better leaving groups. Conversely, electron-donating groups such as 4-MeO in entry 6 destabilize the anion and therefore decrease both the ratio and the yield. The reason for the relatively good ratio obtained with piperazine derivatives (entry 3) was not very clear. PhNMe amide was selected for screening of different Grignard reagents because of its good results and easy preparation.

(13) Olah, G. A.; Mathew, T.; Farnia, M.; Prakash, G. K. S. *Synlett* **1999**, 1067.

(14) Medichem S. A. U.S. Patent: 6,084,100, 2001.

Finally, we prepared a number of Grignard reagents in order to improve the cyclization yield. The fact that the bulkier aryl Grignard gave better results led us to speculate that a stepwise electron transfer mechanism may be operating. First, the iodo-Gringard exchange takes place and transfers only one electron to the hindered 11-position. If the one-electron species has a relatively long half-life, it will add to the carbonyl group of the amide, leading to a cyclic ketone. If the rate of the second electron transfer is faster than that of the cyclization, an inactive anionic intermediate will form, resulting in a proton-quenched product. Therefore, the longer the Grignard holds the magnesium, the longer the half-life of the one-electron species and the better the cyclization yield. Evidence was observed previously for one-electron involvement in the reaction of alkyllithium and aryl iodide.[15] Bulkier Grignard reagents such as mesitylMgBr may slow the second electron transfer. Introduction of magnesium-coordinating substituents ortho to the MgBr group should be more effective in slowing down the second electron-transfer process.
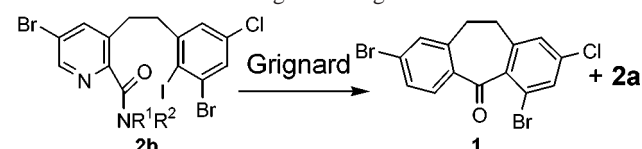
To test our theory, we prepared 2,4,6-$(MeO)_3$PhMgBr since it contains two coordination sites ortho to MgBr. To our delight, this reagent worked exceptionally well for substrate **2b** and produced almost exclusively the cyclized ketone **1** with a 60% solution yield as shown by entry 3 in Table 4. The requirement of a long reaction time and excess reagent indicated a strong bidental coordination of the MgBr and a slow iodo−magnesium exchange. Next, we prepared a Grignard reagent (entry 4) with only one coordination site by replacing one of the MeO groups with a methyl. This monodental Grignard induced the cyclization smoothly in only 20 min with a 98:2 ratio of **1:2a** and a 65% isolated yield. We then removed the methyl group and prepared four additional monodental anisole-based Grignard reagents. All of the four reagents worked very well for the cyclization as shown in entries 5, 6, 7, and 8 in Table 4. These results also suggested that the coordination played a more important role than the steric hindrance.
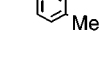
2-MeO-5-MePhMgBr (entries 8 and 9) was selected for optimization on the basis of its good result and easy preparation. Further studies revealed that addition of 30% dioxane improves that solution yield from 66% to 78%. A simple workup procedure[16] was also developed to give **1** in 64−67% isolated yield. With this development, we were able to establish a convergent synthesis of Sch 66336.

(15) For a review of the mechanism, see: Bailey, W. F. Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1.

(16) After completion, the reaction mixture was poured into water and the product was extracted with *t*-BuOMe. The organic layer was washed with water and concentrated. Addition of *t*-BuOMe precipitated **1** as off-white solid.

Table 4. Selection of Grignard Reagent

entry	Grignard (eq.)	temp C	time	1:2a	sol. yield
1	*i*-PrMgBr (1.1)	-50	30 min	15:85	10%
2	[structure] (1.5)	-15	2 h	63:37	40%
3	[structure] (4.0)	-20	8 h	98:2	60%
4	[structure] (1.2)	-20	20 min	98:2	65%
5	[structure] (1.1)	-20	20 min	98:2	68%
6	[structure] (1.5)	-20	20 min	98:2	70%
7	[structure] (1.5)	-20	20 min	98:2	66%
8	[structure] (1.3)	-20	30 min	98:2	66%
9	[structure] (1.3) (+30% dioxane)			98:2	78%

In summary, we have developed an efficient anion-induced regio- and chemoselective acylation. We have also introduced the anisole-based reagents for the cyclization of sterically hindered substrates and applied them successfully to the synthesis of an advanced intermediate for an anticancer agent. This method is complementary to the Friedel−Crafts acylation for electron-deficient aromatic rings.

Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via Internet at http://pubs.acs.org.

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