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A new and versatile synthetic route to 2-dimethylamino-3-alkyl and arylmethylene-2,3-dihydro-1*H*-isoindol-1-ones

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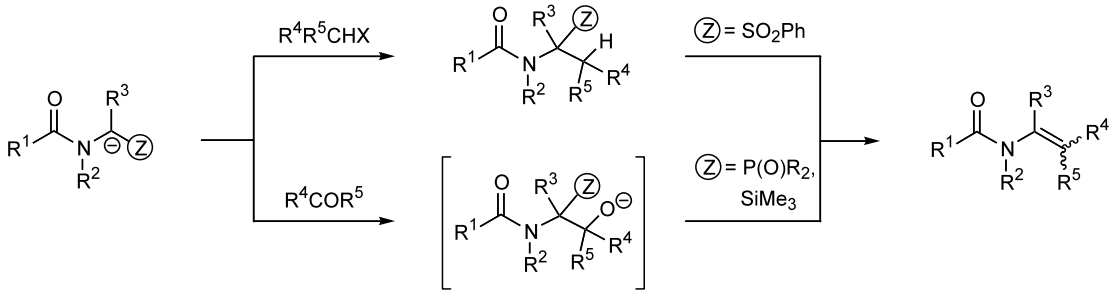
Abstract—A variety of 2-dimethylamino-3-alkyl and arylmethylene-2,3-dihydro-1*H*-isoindol-1-ones have been efficiently prepared from an appropriate 3-benzotriazolyl substituted parent model via a three-step sequence involving deprotonation, subsequent alkylation and ultimate elimination reaction induced by an acidic treatment.

3-(Alkyl and aryl)methylene-2,3-dihydro-1*H*-isoindol-1-ones **1**, **2** are a class of unsaturated compounds of growing interest in organic chemistry as reflected by recent articles dealing with their synthesis[1] and emphasizing their pharmaceutical and medicinal activities.[2] Moreover, they represent the core unit found in a number of isoindole derived families.[3] Accordingly, the synthesis of this heterobicyclic system has developed remarkably in recent years and this is also linked to the synthetic potential of compounds comprising the 3-methylenephthalimidine unit. Indeed such conjugated species have been recently involved in the elaboration of architecturally sophisticated naturally occurring substances, such as aristolactams[4] and isoindolobenzazepine alkaloids.[5] On the other hand, whereas considerable efforts have been devoted to synthesize a wide range of 2-alkyl or 2-aryl substituted isoindolinones, only a few papers report the preparation of their 2-amino substituted analogues. These compounds are accessible by different chemical processes including the replacement of oxygen in the corresponding phthalides[6] or the cyclisation of 2-alkynyl benzoic ester derivatives,[7] both by treatment with a suitable hydrazine. They may also be obtained by thermal rearrangement of phthalazinium ylides,[8] by carbonylation of *o*-palladation compounds,[9] or by condensation between a 2-aminophthalimide and a Grignard reagent.[10] However, these methods are rather restricted in scope, of low yielding and above all they suffer from the main drawback associated with they lack of universality and versatility. In order to obviate these limitations, it should be interesting to develop a more versatile methodology based upon the elaboration of the lactam ring followed by the creation of the exocyclic car-



Scheme 1.

Keywords: benzotriazole; carbanions; enamides; hydrazides; isoindolinones.

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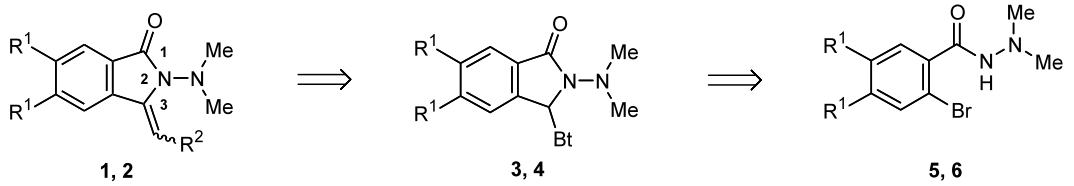
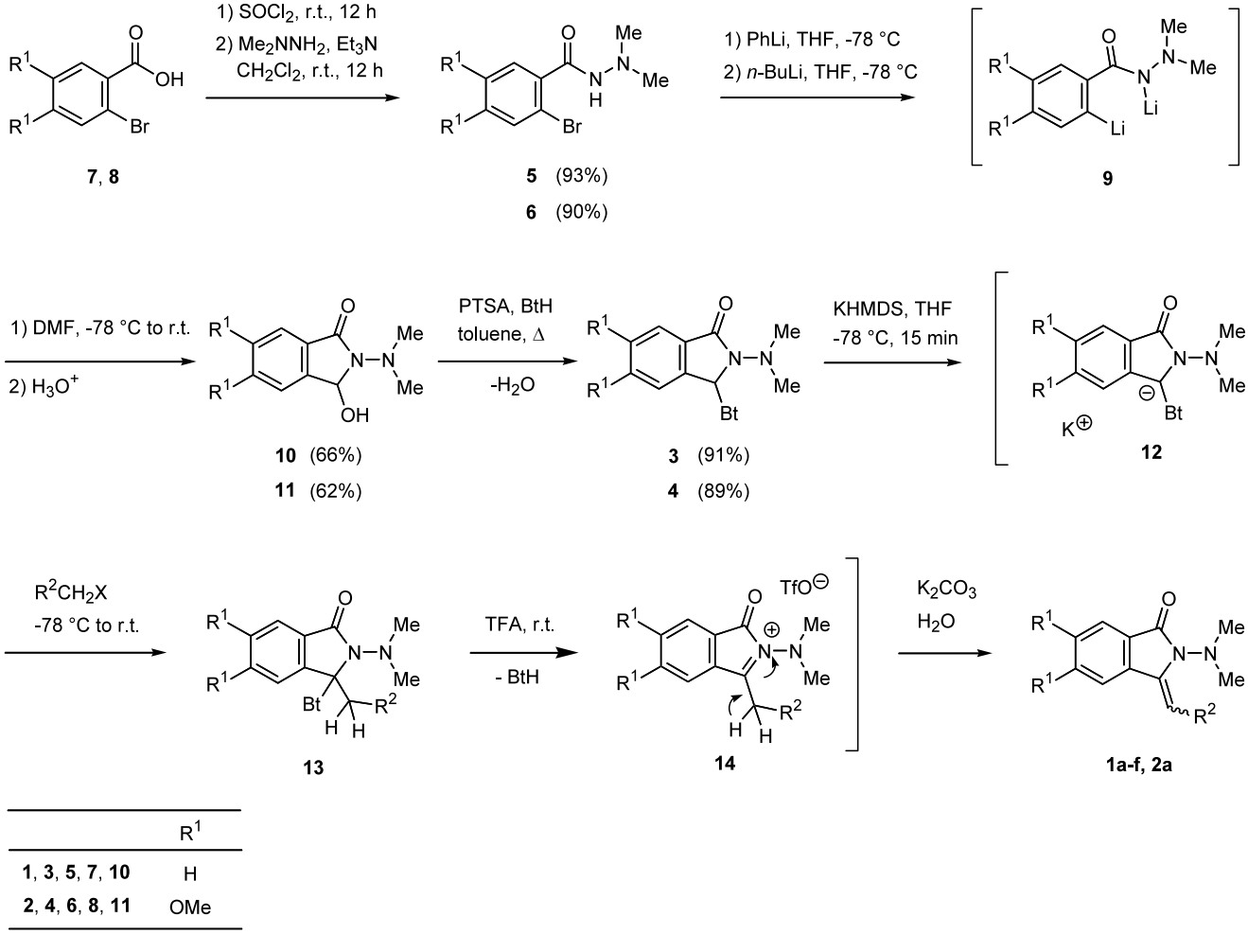
bon–carbon double bond. One of the most powerful synthetic approaches to *N*-substituted-*N*-acylenamines involves the condensation between an α-aminocarbanionic species connected to a stabilising group (Z) with electrophiles structurally dependent of the final elimination step (Scheme 1). Thus, alkyl halides have been employed with sulfonated carboxamides[11] ($Z=SO_2Ph$), whereas carbonyl compounds have been indifferently used with phosphorylated[12] or sililated[13] carboxamides ($Z=P(O)R_2$ or $Z=SiMe_3$). However, these methods are mostly efficient with benzylic or allylic type alkyl halides or with nonenolizable aldehydes or ketones, respectively.

We wish to report in this paper a new simple and versatile synthetic approach to 2-dimethylamino-3-alkyl or arylmethylene isoindolinones **1**, **2**, which relies upon the same synthetic principle, but which is based upon the assistance of a new type of auxiliary. Crucial to the success of our strategy was, therefore, the ability to identify a group that was sufficiently robust to survive the projected metallation step and yet was labile enough to promote the formation of the fragile exocyclic carbon–carbon bond under mild conditions. This dual requirement and recent results obtained in the area of α-aminocarbanion chemistry[14] prompted us to incorporate a benzotriazolyl group in the parent bicyclic



Scheme 2.



	R^1
1, **3**, **5**, **7**, **10**	H
2, **4**, **6**, **8**, **11**	OMe

Scheme 3.

Table 1. Enehydrazides **1a–f**, **2a** prepared

1, **2**	R^1	R^2	R^2X	(Isomer) mp (°C)	Yield (%) (*E*/*Z*)
1a	H	H	MeI	Oil[18]	93
1b	H	Me	EtI	(*E*) oil (*Z*) 76–77	90 (25/75)
1c	H	Et	*n*-PrI	(*E*) oil (*Z*) 71–72	91 (25/75)
1d	H	*n*-Pr	*n*-BuI	(*E*) oil (*Z*) 68–69	90 (20/80)
1e	H	*n*-Pent	*n*-HexI	(*E*) oil (*Z*) oil	88 (15/85)
1f	H	Ph	BnBr	(*E*) oil[19] (*Z*) 99–100[20]	94 (10/90)
2a	OMe	H	MeI	Oil	91

lactams **3**, **4**. We anticipated that the target exocyclic enehydrazides **1**, **2** should be accessible from the parent 3-benzotriazolyl-isoindolinones **3**, **4** synthesized from the 2-bromohydrazides **5**, **6** (retrosynthetic Scheme 2). On the other hand, we decided to especially focus our study on the synthesis of 2-dimethylamino substituted model compounds, because this group has been recently reported to display favourable properties towards deprotonation[15] and could act as a protecting group of the lactam ring.[14e] For this purpose, the benzoic acids **7**, **8** were first converted into their corresponding *N*,*N*-dimethyl hydrazides **5**, **6** via a classical Schotten–Baumann reaction (Scheme 3). According to a procedure reported by McCombie and co-workers,[16] the dilithiated species **9** generated by sequential treatment of 2-bromohydrazides **5**, **6** with phenyllithium and *n*-butyllithium[17] were then quenched with dimethylformamide to afford the 3-hydroxy isoindolinones **10**, **11**. In order to introduce the benzotriazolyl group into our model compounds, the hemiaminals **10**, **11** were treated with a catalytic amount of *p*-toluene sulfonic acid in the presence of benzotriazole to deliver the target 3-substituted bicyclic lactams **3**, **4** in good yields. Compounds **3**, **4** were exposed to potassium hexamethyldisilazide (KHMDS, 1.1 equiv.) to induce the formation of the benzylic α-aminocarbanions **12**, which were then allowed to react with an array of alkyl halides to afford the alkylation products **13**. Treatment of adducts **13** with trifluoroacetic acid gave rise to the transient iminium salts **14**, which finally furnished the bicyclic enhydrazides **1a–f**, **2** after neutralisation with potassium carbonate (Table 1).

In conclusion, we have developed a new, concise and versatile synthesis of polysubstituted 2-dimethylamino-3-alkyl and arylmethylene-2,3-dihydro-1*H*-isoindol-1-ones from easily accessible starting materials. Undoubtedly, this new methodology may be broadened to the elaboration of a wide variety of *N*-acyl enamines.

Acknowledgements

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18. Selected data for compound **1a**: oil;[9] ^{1}H NMR ($CDCl_3$, TMS) δ ppm: 2.97 (s, 6H, NMe_2), 5.13 (d, $J=0.8$ Hz, 1H), 5.24 (d, $J=0.8$ Hz, 1H), 7.43 (dt, $J=7.4$, 1.3 Hz, 1H, H_{arom}), 7.52 (dt, $J=7.4$, 1.4 Hz, 1H, H_{arom}), 7.60 (td, $J=7.4$, 1.0 Hz, 1H, H_{arom}), 7.73 (td, $J=7.4$, 1.0 Hz, 1H, H_{arom}). ^{13}C NMR ($CDCl_3$, TMS) δ ppm: *C* 165.9 (CO), 140.4, 134.5, 128.8, *CH* 132.0, 129.4, 122.7, 120.2, CH_2 89.9, CH_3 43.9. *m*/*z* (%): 188 (M^+, 27), 146 (34), 145 (100). IR (KBr) 1709 (CO).
19. Selected data for compound **1f** (*E*): oil; ^{1}H NMR ($CDCl_3$, TMS) δ ppm: 2.99 (s, 6H, NMe_2), 6.86 (s, 1H), 7.40–7.70 (m, 6H, H_{arom}), 7.79 (td, $J=7.4$, 1.1 Hz, 1H, H_{arom}), 7.92 (dt, $J=7.7$, 1.1 Hz, 1H, H_{arom}), 7.99 (dt, $J=7.7$, 1.1 Hz, 1H, H_{arom}). ^{13}C NMR ($CDCl_3$, TMS) δ ppm: *C* 165.6 (CO), 136.5, 134.9, 131.5, 129.4, *CH* 132.0, 129.9, 128.8, 127.0, 126.8, 122.8, 119.3, 107.7, CH_3 43.0.
20. Selected data for compound **1f** (*Z*): mp 99–100°C; ^{1}H NMR ($CDCl_3$, TMS) δ ppm: 3.07 (s, 6H, NMe_2), 7.03 (s, 1H), 7.32–7.48 (m, 8H, H_{arom}), 7.79 (d, $J=7.8$, 1H H_{arom}). ^{13}C NMR ($CDCl_3$, TMS) δ ppm: *C* 165.0 (CO), 135.4, 133.9, 133.0, 129.4, *CH* 131.4, 129.3, 130.0, 128.4, 127.5, 122.7, 122.6, 111.4, CH_3 43.7. *m*/*z* (%): 264 (M^+, 26), 220 (100), 219 (71). IR (KBr) 1702 (CO).