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First domino radical cyclisation/Smiles rearrangement combination†

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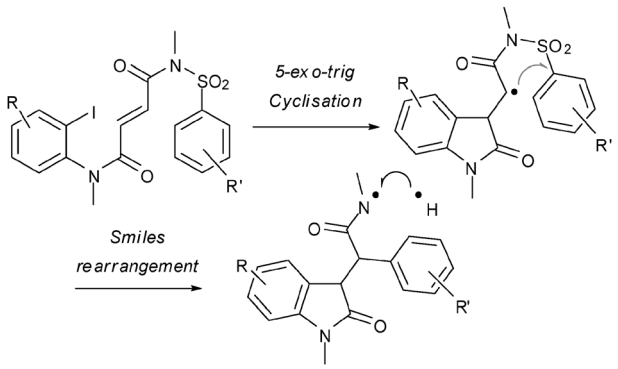
An unprecedented domino radical cyclisation–Smiles rearrangement process affording 3-(2′-aryl-*N*-methyl acetamido)indolin-2-ones is presented. Experimental rationalisation of this approach and description of an unexpected tricyclic core are also handled.

Smiles-type rearrangement is originally an intramolecular nucleophilic aromatic substitution,[1] which was first transposed to radical chemistry by Speckamp.[2] Later, Motherwell pointed out the importance of this rearrangement in the synthesis of biaryl derivatives.[3] Thus, radical Smiles rearrangement is triggered by free radical attack at the *ipso* position of sulfonates or sulfonamides followed by sulfur dioxide extrusion and final hydrogen abstraction. Its synthetic utility has been demonstrated by the preparation of stilbene derivatives,[4] fused [1,2-*a*]indoles,[5] 2-hydroxydiarylketones,[6] 2-arylethanols, 2-arylethylamines[7] or 3-arylpiperidines.[8] Recently, Zard *et al.* have evidenced an unusual radical Smiles rearrangement of *N*(α-xantyl)acetylaminopyridines proceeding *via* a spiro azetidinone intermediate.[9] As a versatile tool, Smiles rearrangement has recently been studied in multi-component reactions[10] or one-pot approaches.[11] However, to the best of our knowledge, only a few reports of domino strategy involving this rearrangement[12] are available and none in radical chemistry.

As part of our ongoing program dealing with the synthesis of complex indole-heterocycles by tandem reactions, we have recently described an efficient domino radical cyclisation approach affording 3-(2-oxopyrrolidin-3-yl)indolin-2-ones.[13] Based on these results, we were keen to investigate if a 5-*exo*-*trig* cyclisation could be combined with a radical promoted Smiles rearrangement. Herein, we report an original domino radical procedure combining, for the first time, Smiles rearrangement as a key step for the preparation of 3-(2′-phenyl-*N*-methylacetamido)indolin-2-ones (Scheme 1).

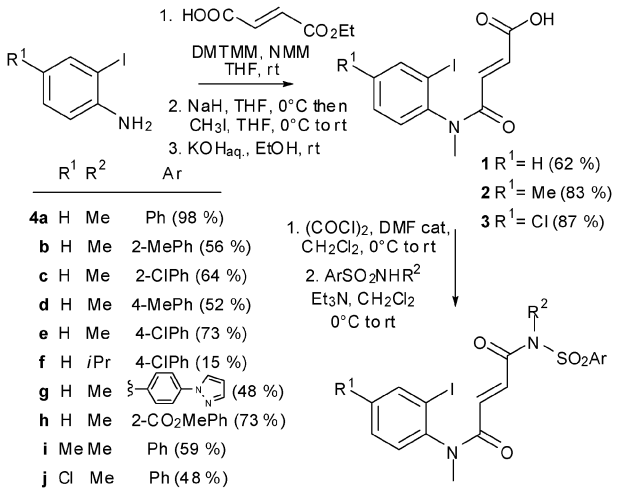
As depicted in Scheme 2, fumaric diamide-type starting materials were prepared through a straightforward approach.



Scheme 1 Our combined radical approach.

Carboxylic acid intermediates **1–3** were obtained by acylation of *o*-iodoanilines with fumaric acid ester in the presence of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) as a coupling agent, followed by *N*-methylation and subsequent saponification. An arylsulfonamide moiety was incorporated by reacting with the acid chlorides of **1–3** prepared with oxalyl chloride. In this way precursors **4a–j** were obtained in five steps in 10 to 61% yields.

With these precursors in hand, we then turned our attention to the study of the domino radical cyclisation approach. In line with our preliminary results,[13] we initially investigated the reaction of **4a** using 2,2′-azoisobutyronitrile (AIBN) as initiator and *tris*(trimethylsilyl)silane (TTMSS)[14] (1.2 equiv.) as reducing agent in dry, degassed refluxing toluene (Table 1, entry 1).



	R¹	R²	Ar
4a	H	Me	Ph (98 %)
b	H	Me	2-MePh (56 %)
c	H	Me	2-ClPh (64 %)
d	H	Me	4-MePh (52 %)
e	H	Me	4-ClPh (73 %)
f	H	*i*Pr	4-ClPh (15 %)
g	H	Me	(48 %)
h	H	Me	2-CO₂MePh (73 %)
i	Me	Me	Ph (59 %)
j	Cl	Me	Ph (48 %)

Scheme 2 Synthesis of radical precursors (**4a–j**).

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† Electronic supplementary information (ESI) available: Experimental details, ^{1}H NMR and ^{13}C NMR spectra of all products and crystallographic data of **7e1**. CCDC 825601 (**7e1**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc15670a

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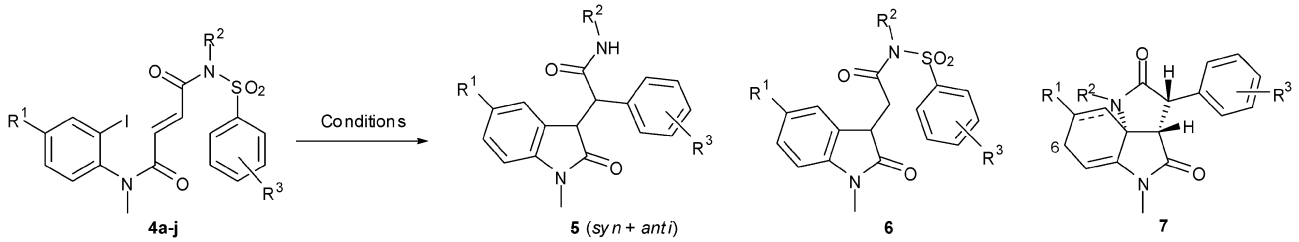
Table 1 Optimization of the reaction conditions for the radical cascade approach

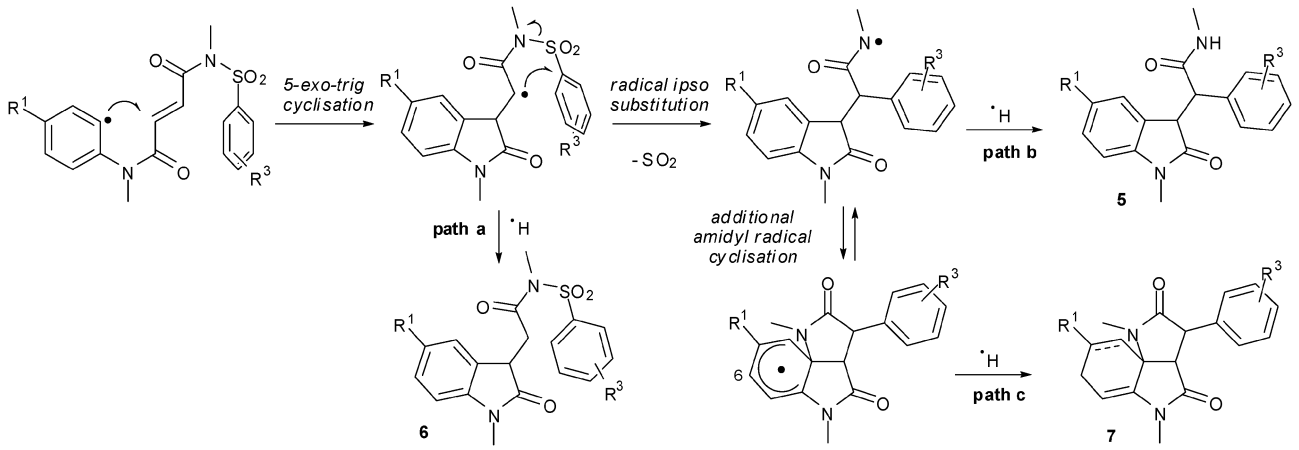


Entry	Cmpd	R^1	R^2	R^3	Reagents (equiv.) and conditions	**4** (rec. %)	**5** (yield %)	**6** (yield %)	**7**[a] (yield %)
1	**4a**	H	Me	H	TTMSS (1.2), AIBN (0.2), PhMe, 110 °C, 10 h	—	11	32	23
2	**4a**	H	Me	H	TTMSS (1.2), ACCN (0.2), octane, 126 °C, 10 h	23	28	20	13
3	**4a**	H	Me	H	TTMSS (1.2), ACCN (0.2 + 0.2), octane, 126 °C, 10 h	—	47	31	18
4	**4a**	H	Me	H	TTMSS (1.2) + ACCN (0.4) in decane[c], 174 °C, 5 h	23	42	3	—
5	**4a**	H	Me	H	TTMSS (1.2), ACCN (0.2 + 0.2), decane, 174 °C, 3 h	—	66	11	9
6	**4b**	H	Me	2-Me	TTMSS (1.2), ACCN (0.2 + 0.2 + 0.2[d]), decane, 174 °C, 4 h	—	62	—	—
7	**4c**	H	Me	2-Cl	TTMSS (1.2), ACCN (0.2 + 0.2 + 0.2[d]), decane, 174 °C, 6 h	—	59	Traces	—
8	**4d**	H	Me	4-Me	TTMSS (1.2), ACCN (0.2 + 0.2), decane, 174 °C, 4 h	Traces	64	13	—
9	**4e**	H	Me	4-Cl	TTMSS (1.2), ACCN (0.2 + 0.2 + 0.2[d]), decane, 174 °C, 3 h	—	68	—	7
10	**4f**	H	*i*Pr	4-Cl	TTMSS (1.2), ACCN (0.2 + 0.2 + 0.2), decane, 174 °C, 7 h	12	54	Traces	Traces
11	**4g**	H	Me	4-Pyraz.	TTMSS (1.2), ACCN (0.2 + 0.2 + 0.2[d]), decane, 174 °C, 4 h	11[e]	51	—	—
12	**4h**	H	Me	2-CO_2Me	TTMSS (1.2), ACCN (0.2 + 0.2), decane, 174 °C, 3 h	—	75	—	Traces
13	**4i**	Me	Me	H	TTMSS (1.2), ACCN (0.2 + 0.2 + 0.2), decane, 174 °C, 6 h	20	35	15	10[b]
14	**4j**	Cl	Me	H	TTMSS (1.2), ACCN (0.2 + 0.2 + 0.2[d]), decane, 174 °C, 5 h	—	55	8	5[b]
15	**4e**	H	Me	4-Cl	TTMSS (1.2)[f], AIBN (0.2 + 0.2), PhMe, 110 °C, 10 h	—	27	—	40

[a] Isolated as a mixture (4 : 1) of tetrahydro and dihydro products. [b] Dihydro product. [c] Addition of solution by a syringe pump over 1 h. [d] A third addition was required for complete conversion. [e] With an additional sulfonamide side product. [f] Slow addition (syringe pump) over 6 h.

After completion of the reaction, the crude mixture was washed with CH_3CN/hexane to separate silane derivatives and then carefully chromatographed to give the desired product **5a** in 11% yield. Two other products were also isolated. The first one **6a** resulted from the initial 5-*exo*-*trig* cyclisation followed by direct reduction. The second product **7a** was identified as a mixture of two tricyclic products derived from an unexpected process (Scheme 3).

After this successful domino radical cyclisation–Smiles rearrangement we optimised the reaction conditions by varying solvents, initiators, reagents and temperature. Since octane has been reported as an efficient and specific hydrogen donor toward highly reactive and electrophilic amidyl radicals,[9] further experiments were carried out in boiling octane. Under these conditions, exposure of **4a** to 2,2′-azocyclohexanecarbonitrile (ACCN), a liposoluble radical initiator, gave an increased yield (28%) of **5a** which was then improved to 47% with a second portion (0.2 equiv.) of the initiator (entries 2 and 3). Since SO_2 extrusion from an *N*-amidosulfonyl radical could be considered as the limiting step of the Smiles rearrangement[15] we speculated that higher temperature would accelerate this extrusion and therefore enhance the yield of the reaction. Combining high boiling point with hydrogen donating ability of aliphatic hydrocarbons, we selected refluxing decane (174 °C) for further experiments. In order to compensate the short half-life of the initiator and premature reduction of radical intermediates, the mixture of TTMSS and ACCN was added continuously to **4a** by a syringe pump. Under such conditions **5a** was obtained in 42% yield with some cyclised product (3%), but the reaction was incomplete (entry 4). Finally, the expected product **5a** was obtained in 66% yield by using 1.2 equiv. of TTMSS and



Scheme 3 Radical cyclisation/Smiles rearrangement pathway.

two-fold addition of ACCN in dry, degassed refluxing decane (entry 5).

These optimised conditions were then successfully applied to 2-tolyl **4b** and 2-chlorophenyl **4c** sulfonamide-type precursors leading to the corresponding oxindoles **5b** and **5c** in 62% and 59% yields, respectively (entries 6 and 7). In both cases a third portion of ACCN (0.2 equiv.) was needed to complete the reaction. We were pleased to find that *p*-methyl **4d** or *p*-chloro **4e** substituted sulfonamide analogs under the same conditions gave oxindoles **5d** or **5e** in 64 and 68% yields, respectively (entries 8 and 9). Under these conditions, only a few amount of tricyclic product **7e** was isolated. 4-Pyrazolo substituted derivative **4g** afforded the prospected oxindole **5g** in a slightly lower yield (51%) probably due to the lower migration ability of the diaryl group (entry 11).

Next we examined the influence of R^1 and R^2 groups on the radical domino process. An *N*-isopropyl group containing analog **4f** led to an almost equimolar *syn–anti* mixture of **5f** in 54% yield along with some starting material (entry 10). Treatment of *p*-toluidine analog **4i** gave a complex mixture of products (entry 13), while the *p*-chloro counterpart **4j** smoothly afforded the expected **5j** in 55% yield together with monocyclic **6j** (8%) and tricyclic **7j** (5%) products (entry 14).

In connection with optimisation studies we focused our attention on the so-called tricyclic products **7a** and **7e** obtained as an unseparable mixture (4 : 1). Spectroscopic analyses (MS, NMR) evidenced a partially reduced oxindole moiety. Fortunately in the 4-chlorophenyl series the major derivative **7e1** was isolated in a pure crystalline form (entry 9). X-Ray analysis of **7e1** confirmed its unique tricyclic structure with a tetrahydro-oxindole skeleton bearing an additional pyrrolidone moiety with a *cis* relative configuration between the ring junction and aryl substituted carbon (Fig. 1). Minor compounds (**7a2** and **7e2**) could be identified as dihydrooxindole analogs by comparison of NMR and MS data. These results supported that only one of the two intermediate diastereomers (30 : 70 to 50 : 50 ratio, ^{1}H NMR determination) cyclised[16] by addition of the amidyl radical on the ring junction of the oxindole moiety.[17] A tricyclic radical intermediate underwent successive reductions affording the tetrahydro-oxindole derivative as the major product (Scheme 3, path c).[18] Minor dihydro compounds may result from the reduction at C6 of the indolinone ring probably owing to the steric hindrance of TTMSS. In the series of substituted iodoanilines the exclusive formation of dihydro derivatives **7i** and **7j** may also be explained by the more accessible C6 carbon to reducing agents. In order to promote the final stages of our domino process a solution of TTMSS was slowly added to a mixture of **4e** and AIBN in boiling toluene. These conditions enabled to increase to 40% the chemical yield of tricyclic products **7e** (entry 15).

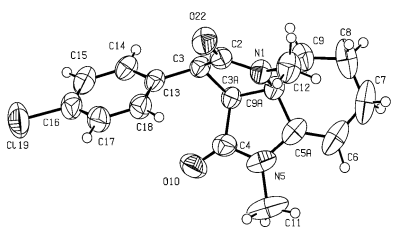


Fig. 1 ORTEP view and atom labeling of **7e1**.

With the aim to extend our domino process to the synthesis of complex indole-heterocycles, we were pleased to find that the ester containing precursor **4h** gave exclusively the corresponding oxindole derivative **5h** in very good yield (entry 12). This compound could be considered as a useful intermediate toward indolo[2,3-*b*]quinoline-type derivatives by simple functional group transformations.

In conclusion, these preliminary results demonstrated the efficiency and potentiality of our original domino radical cyclisation–Smiles rearrangement approach and could open an access toward various azaheterocycles of biological interest. Moreover, we observed an unprecedented domino radical cyclisation–Smiles rearrangement–radical cyclisation sequence affording tricyclic di(tetrahydro)oxindoles **7**. Optimisation and mechanistic studies of this procedure are in due course.

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